

# Fertility2017

5-7 JANUARY 2017

Edinburgh International  
Conference Centre (EICC)

 #fertility2017

## CONFERENCE HANDBOOK

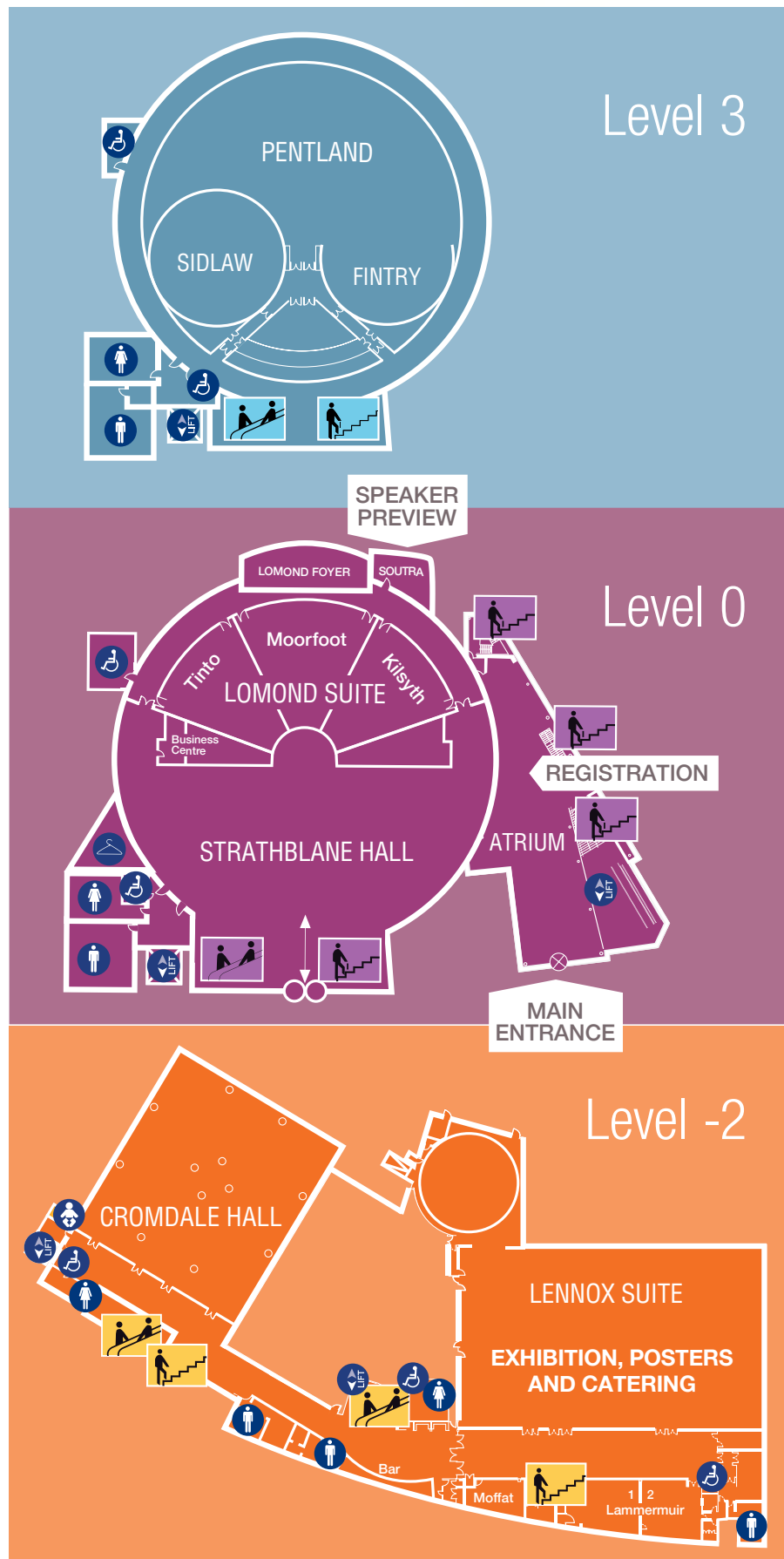
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## VENUE PLAN



VENUE PLAN

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AND BIOGRAPHIES

POSTER  
PRESENTATIONS

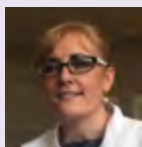
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## CHAIR'S WELCOME



A warm welcome to Edinburgh and to the International Conference Centre for Fertility 2017. This is the tenth joint Fertility meeting organised by the Association of Clinical Embryologists (ACE), the British Fertility Society (BFS) and the Society for Reproduction and Fertility (SRF). As always, we have attempted to organise an exciting scientific programme which appeals to scientists, clinicians, embryologists, nurses and counsellors. I hope you agree there is something for everyone.

The theme for Fertility 2017 is the Ovary with plenary sessions on Developmental and environmental impacts on the ovary, Oocytes, and Ovarian function/dysfunction. There will also be 3 eponymous lectures: The Anne McLaren Memorial Lecture, the Howard Jacobs Lecture and the Bob Edwards Memorial Lecture. These, together with the Update sessions, will allow renowned experts to present their latest data in a wide range of topics of interest to delegates.

Fertility 2017 is set to be the most successful yet, having an unprecedented number of abstract submissions and delegates registered. Consequently, competition to present in the parallel, short oral communication sessions was immense. We are also in the fortunate position to have a large number of high quality abstracts being presented during the poster sessions.

The social events are an integral part of Fertility 2017 providing delegates with an excellent opportunity to network and discuss science. This year we are taking a break from the usual football tournament and instead have organised ten pin bowling followed by a meal. The venue for dinner on Thursday evening is the Caves where you will experience the historic 18th Century South Bridge Vaults. Finally, on Friday the conference dinner will be held at the Conference Centre and followed by a traditional Ceilidh band.

Organising Fertility 2017 has very much been a team effort and I would particularly like to thank members of the joint Programme Committee who have worked diligently to prepare what I hope you will agree is an outstanding scientific programme. I would also like to thank the Conference organisers, Profile Productions and the many sponsors and exhibitors.

It is a pleasure to welcome you to the Fertility 2017 conference and the beautiful city of Edinburgh. I hope you find the meeting both enjoyable and scientifically rewarding.

**Dr Franchesca Houghton**

*Fertility 2017 and SRF Programme Committee Chair  
University of Southampton*

## ACKNOWLEDGEMENTS

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## CONFERENCE PROGRAMME

### Wednesday 4 January

|       |                                  |
|-------|----------------------------------|
| 17.00 | Ten pin bowling at Fountain Park |
| 19.00 | After at Akva!                   |

### Thursday 5 January

08.00 **Registration, refreshments, exhibition and poster presentations**

#### PLENARY SESSION - Developmental and environmental impacts on the ovary

PENTLAND

|       |   |
|-------|---|
| 09.15 | Chair's welcome<br><i>Dr Franchesca Houghton, Fertility 2017 Programme Chair and Associate Professor in Stem Cells and Developmental Biology, University of Southampton</i>   |
| 09.25 | Development of the ovary and rescue after chemotherapy<br><i>Prof Blanche Capel, Professor of Cell Biology, Duke University Medical Centre, USA</i>   |
| 09.55 | How the environment affects ovarian function and the oocyte<br><i>Dr Roger Sturmey, Senior Lecturer in Reproductive Medicine, Hull York Medical School</i>  |
| 10.25 | Replenishing the adult ovarian follicular population: Isolation and characterisation of germ line stem cells from adult women<br><i>Prof Evelyn Telfer, Personal Chair in Reproductive Biology, University of Edinburgh</i> |

11.05 **Exhibition, refreshments and attended poster presentations of odd numbered posters**

#### PLENARY SESSION - The Anne McLaren Memorial Lecture

PENTLAND

Chair: *Dr Tony Michael, Director of Taught Programmes (Biological & Chemical Sciences) and Reader in Reproductive Biology, Chair, Society of Reproduction and Fertility*

The role of sister germ cells in oocyte differentiation  
*Dr Allan Spradling, Department of Embryology, Carnegie Institution for Science/ HHMI, Baltimore, USA*

13.00-13.45 SRF AGM

FINTRY

13.00 **Lunch, exhibition and poster presentations**

#### 14.15-15.45 SHORT PAPER SESSIONS A

##### A1 Emerging strategies in ART

FINTRY

Chair: *Dr James Nicopollous, Consultant Gynaecologist, The Lister Hospital, London and Dr Yacoub Khalaf, Guy's and St Thomas' Hospital*

|       |  |
|-------|--|
| 14.15 | Multilocus genetic risk scores for poor ovarian response - <i>Joaquin Ll cer, Instituto Bernabeu Biotech, Spain</i>  |
| 14.30 | For women undergoing double embryo transfer on day five, the addition of a poor quality embryo may have a detrimental effect on assisted reproduction outcome - <i>Alison Richardson, University of Nottingham</i>   |
| 14.45 | A second injection of kisspeptin-54 safely improves oocyte maturation during in vitro fertilisation therapy in women at high risk of ovarian hyperstimulation syndrome - <i>Ali Abbara, Imperial College London</i>  |
| 15.00 | Progesterone assay concentrations to guide whether to proceed to a fresh embryo transfer or to freeze all suitable embryos are insufficiently reliable - <i>Jennifer Lyon, GCRM, Glasgow</i>   |
| 15.15 | The clinical value of time-lapse as an efficacious embryo selection tool: A systematic literature review and meta-analysis of 45 studies involving 28876 embryos - <i>Stephanie Yip, Imperial College London</i>   |
| 15.30 | Intralipid infusion does not result in improved live birth rates in women with recurrent implantation failure undergoing IVF treatment and is associated with an increased risk of congenital fetal malformations: a double blinded randomised controlled trial - <i>Islam Gamaleldin, University of Bristol</i> |

##### A2 Sperm integrity and function

MOORFOOT

Chair: *Prof Allan Pacey, Editor, Human Fertility and Prof Chris Barrett, University of Dundee*

|       |  |
|-------|--|
| 14.15 | SRF/SRB Exchange paper:<br>Cellular samurais and sperm: Katnal2 is an essential regulator of microtubules in haploid male germ cells and sertoli cells - <i>Jessica Dunleavy, Monash University, Australia</i> |
| 14.30 | Does exposure to cisplatin impair survival and proliferation of spermatogonial stem cells in prepubertal mouse testis? - <i>Frederica Lopes, University of Edinburgh</i>                                       |



# CONFERENCE PROGRAMME

|       |  |
|-------|--|
| 14.45 | Effect of electronic-cigarette flavourings on (I) human sperm motility, chromatin integrity in vitro and (II) mice testicular function in vivo - <i>Helen O'Neill, UCL</i>   |
| 15.00 | Sperm DNA quality in Hr6b (Ubiquitin-conjugating enzyme) Knockout Mice: DNA damage study - <i>Sheena Lewis, Queen's University Belfast</i>   |
| 15.15 | DNA sequence analysis of the sperm HALO provides evidence for sequence-specific compartmentalisation of chromatin in the mature spermatozoon nucleus - <i>Adel Binhurahem, University of Leeds</i>                     |
| 15.30 | As defined by sperm chromatin integrity, a complementary relationship exists between sperm affinity for hyaluronic acid and sedimentation properties in density gradients - <i>Forough Torabi, University of Leeds</i> |

## A3 Social challenges of infertility

KILSYTH

Chair: *Isabel Traynor, Nurse Manager, Glasgow Royal Infirmary and British Fertility Society Executive Committee*

|       |   |
|-------|---|
| 14.15 | Kisspeptin modulates sexual and emotional processing in men - <i>Waljit Dhillon, Imperial College London</i>  |
| 14.30 | Addressing the needs of orthodox Jewish couples seeking fertility treatment - <i>Katie Best, Gateshead Fertility Unit</i>   |
| 14.45 | Does egg sharing, in which women donate half of their eggs reduce the chances of success compared to women having self-funded IVF/ISCI cycles? - <i>Shabana Bora, Lister Fertility Clinic</i> |
| 15.00 | Fertility preservation for young persons undertaking gender reassignment; management considerations for the clinical embryologist - <i>Charlotte Taylor, Bourn Hall Clinic</i>                |
| 15.15 | The role of a clinical nurse specialist in managing a successful donor sperm programme - <i>Denise Kerslake, Jessop Fertility, Sheffield Teaching Hospitals NHS Foundation Trust</i>          |
| 15.30 | Surrogacy - why, where and how? A study of cycles conducted between 2012 and 2015 - <i>Lucy Richardson, Herts and Essex Fertility Centre</i>  |

## A4 Predicting embryo growth and development

SIDLAW

Chair: *Helen Priddle, Embryology Laboratory Manager, CRGW and Ellen Armstrong, Association of Clinical Embryologists Executive Committee*

|       |  |
|-------|--|
| 14.15 | Blastocyst contraction pattern as a potential predictor of embryo chromosomal content - <i>Xavier Vinals, The Centre for Reproductive &amp; Genetic Health</i>                               |
| 14.30 | The developmental potential of mosaic embryos - <i>Samer Alfarawati, Reprogenetics UK</i>  |
| 14.45 | Comparing euploidy rates of blastocysts cultured in the embryoscope to conventional incubators - <i>Reena Gupta, CARE Fertility</i>  |
| 15.00 | Impact of double cryopreservation and biopsy on PGD cycle outcome - <i>Yaser Dajani, Assisted Conception Unit Guy's Hospital</i>   |
| 15.15 | First clinical application of a novel ultra-rapid comprehensive chromosome screening technique - <i>Katharina Spath, Reprogenetics UK</i>  |
| 15.30 | Haploid parthenotes and normally fertilised embryos have differential response to ammonia exposure in vitro - <i>Guruprasad Kalthur, Kasturba Medical College, Manipal University, India</i> |

## A5 Hormones in female reproduction

TINTO

Chair: *Dr Bob Robinson, Lecturer, University of Nottingham and The Society of Reproduction and Fertility*

|       |   |
|-------|---|
| 14.15 | Evidence for TGF $\beta$ regulation of cell cycle genes in granulosa cells of primordial follicles - <i>Sofia Granados-Aparici, The University of Sheffield</i>   |
| 14.30 | Effect of bone morphogenetic protein-15 (BMP15) on gonadotropin-stimulated synthesis of hyaluronan and progesterone in porcine ovarian follicle - <i>Eva Nagyova, Institute of Animal Physiology and Genetics, Academy of Sciences of the Czech Republic</i>                              |
| 14.45 | British Fertility Society/AFS Exchange paper: Clomiphene, metformin, letrozole, tamoxifen or combined clomiphene-metformin for polycystic ovary syndrome - a systematic review and individual participant data network meta-analysis - <i>Rui Wang, University of Adelaide, Australia</i> |
| 15.00 | Prostaglandin effects to myometrial and leiomyoma cells in vitro through microRNA profiling - <i>Myoungseok Han, Dong-A University, Department of Obstetrics and Gynecology, South Korea</i>  |
| 15.15 | The impact of DHEA on endometrial receptivity - <i>Douglas Gibson, The University of Edinburgh</i>  |
| 15.30 | Dynamic changes in gene expression and signalling during early placental development in the horse - <i>Amanda de Mestre, The Royal Veterinary College, London</i>   |

15.45 **Exhibition, refreshments and poster presentations**

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### 16.30-18.00 UPDATE SESSION 1

**BFS Update** **Controversies in reproductive medicine** **PENTLAND**  
Chair: Dr Jane Stewart, Newcastle Fertility Centre & Secretary, British Fertility Society and Dr Tommy Tang, Consultant Gynaecologist, Belfast Health and Social Care Trust

16.30 Managing unexplained infertility - evidence vs expectations - Prof Siladitya Bhattacharya, Director, Institute of Applied Health Sciences, University of Aberdeen

17.00 IUI vs IVF - Dr Madelon Van Wely, Centre for Reproductive Medicine, Amsterdam, Netherlands

17.30 Speaker tbc

**ACE Update** **Advancing our knowledge of embryo selection** **SIDLAW**  
Chair: Prof Daniel Brison, Honorary Professor of Clinical Embryology and Stem Cell Biology, Scientific Director of the Department of Reproductive Medicine and Co-Director NW Embryonic Stem Cell Centre (NWESCC) and Karen Schnauffer, Liverpool Association of Clinical Embryologists

16.30 Embryo selection: What evidence is required, and do we even need it? - Dr Sebastiaan Mastenbroek, Assistant Professor & Clinical Embryologist, Centre for Reproductive Medicine, Academic Medical Centre, Amsterdam

17.00 The zinc spark as a novel marker of oocyte and embryo quality - Dr Nan Zhang, Postdoctoral Fellow, Woodruff Lab, Northwestern University, Canada

17.30 Embryo biomarkers - Kirstine Kirkegaard, Department of Clinical Medicine, Aarhus University, Denmark

**SRF Update** **Endometrial and embryo dialogue** **FINTRY**  
Chair: Dr Robert Abayasekara, Director of Studies, Medicine & Veterinary Medicine, Fitzwilliam College, Cambridge

16.30 Extrinsic and intrinsic regulation of pregnancy establishment in ruminants - Prof Tom Spencer, Professor of Reproductive and Developmental Biology, University of Missouri, USA

17.00 Prostaglandin F2α in embryo-maternal interactions in the pig - Dr Agnieszka Wacławik, Associate Professor, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland

17.30 Predicting recurrent implantation failure in IVF - Prof Nick Macklon, Professor of Obstetrics and Gynaecology, University of Southampton

**Nursing Update** **Challenges in reproductive medicine** **KILSYTH**  
Chair: Alison McTavish, Unit Manager, ACRM and Dr Amanda Jefferys, Consultant Gynaecologist, Subspecialist in Reproductive Medicine, University Hospitals Bristol NHS Trust

16.30 Dilemmas for couples considering egg donation treatment - Ruth Wilde, Senior Fertility Counsellor, Complete Fertility Southampton

17.00 Prediction and prevention of miscarriage - Prof Arri Coomarasamy, Director of Tommy's National Centre for Miscarriage Research, University of Birmingham

17.30 Screening for viruses and effect of positive results on fertility storage and treatment - Andrew Drakeley, Consultant Gynaecologist, Hewitt Fertility Centre, Liverpool

18.00-19.00 Poster presentations and welcome reception

18.30-19.15 **Ferring symposium** **LAMMERMUIR**  
Debate: Will personalised medicine contribute significantly to improving success rates in IVF?  
Chair: Dr Nick Raine-Fenning, Associate Professor of Reproductive Medicine & Surgery, University of Nottingham  
For: Dr Stuart Lavery, Consultant Gynaecologist, Honorary Senior Lecturer, Imperial College and Director, IVF Hammersmith  
Against: Prof Charles Kingsland, Clinical Director, Liverpool Women's Hospital

19.30 Supper at The Caves - an evening of history, folk music, and networking

# CONFERENCE PROGRAMME

## Friday 6 January

08.10 **Registration, refreshments, exhibition and poster presentations**

08.15-09.00 **Merck symposium: Pre-treatment optimisation – uterus and sperm** LAMMMERMUIR  
*Prof Christopher Barratt, Head of the Reproductive Medicine Group, University of Dundee and Dr Tarek El-Toukhy, Consultant in Reproductive Medicine and Surgery and Pre-implantation Genetic Diagnosis (PGD), Guy's and St Thomas' Hospital, London*

**PLENARY SESSION - Oocytes** PENTLAND

09.10 Chair's welcome  
*Dr Valentine Akande, Bristol Centre for Reproductive Medicine & British Fertility Society*

09.20 Why is aneuploidy so common in oocytes and why does it increase with a woman's age?  
*Prof Keith Jones, Head of Biological Sciences, Professor of Cell Biology, Principal Investigator, University of Southampton*

09.45 Meiosis in mammalian oocytes  
*Dr Christian Ottoloni, School of Biosciences, University of Kent*

10.10 Can we stop ovarian ageing?  
*Prof Helen Picton, Head of Division of Reproduction and Early Development, Leeds Institute of Cardiovascular and Metabolic Medicine*

10.35 **Exhibition, refreshments and attended poster presentations of even numbered posters**

**The Howard Jacobs Lecture** PENTLAND  
*Chair: Prof Adam Balen, University of Leeds and Chair, British Fertility Society*

11.20 Ovarian stimulation for infertility treatment: Past, present and future  
*Prof Bart Fauser, Visiting Professor and Senior Consultant in Reproductive Medicine, The Bridge Centre*

12.10 British Fertility Society Honorary Fellowships

12.20-13.00 **BFS AGM** FINTRY

12.20 **Lunch, exhibition and poster presentations**

13.30-15.00 **SHORT PAPER SESSIONS B**

**B1 Maturing a good egg** KILSYTH  
*Chair: Prof Helen Picton, Head of Division of Reproduction and Early Development, Leeds Institute of Cardiovascular and Metabolic Medicine and Belinda Lo, PHD Student, University of Oxford, Early Career Rep Society of Reproduction and Fertility*

13.30 Sub-populations of oogonial stem cells can be isolated from the adult human ovary - *Yvonne Clarkson, The University of Edinburgh*

13.45 Characterisation of P-body formation during bovine oogenesis - *Jianping Lu, University of Leeds*

14.00 Functional analysis of the oocyte specific imprinting regulator KHDC3L in bovine oocytes and embryos - *Erika Berenyi, University of Leeds*

14.15 Mitochondrial indices of ovine oocyte maturation in-vitro - *Keerthi Gnanaprabha, University of Leeds*

14.30 Mitochondrial markers associated with maternal age during ovine oocyte maturation in vitro - *Chutima Topipat, Reproduction and Early Development, University of Leeds*

14.45 RNA-Seq profiling of bovine cumulus-oocyte transcript abundance after treatment with cAMP modulators - *Eduardo Montanari Razza, Institute of Biosciences, University of São Paulo State (UNESP, Brazil)*

**B2 The ART of sperm** TINTO  
*Chair: Jason Kasraie, Chair-elect, Association of Clinical Embryologists and Rebecca Swann, Pre-Registrant Clinical Embryologist, Oxford Fertility*

13.30 Novel prognostic factors for sperm retrieval in patients with non-obstructive azoospermia undergoing microdissection testicular extraction (mTESE) - *Seraphina Rong Luo, Hammersmith Hospital*

13.45 Improving art outcome following unexplained total failed fertilisation - *Sarah Martins da Silva, Reproductive and Developmental Biology, School of Medicine, University of Dundee*

14.00 The clinical value in assessing sperm total aneuploidy rate in couples undergoing failed intracytoplasmic sperm injection (ICSI) and its correlation with semen parameters - *Timothy Bracewell-Milnes, Imperial College London*

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- 14.15 Profiling the intracellular calcium dynamics in single spermatozoa and their association with IVF fertilisation success - *Mark Kelly, University of Dundee*
- 14.30 Sperm preparation and egg activation for bovine intracytoplasmic sperm injection (ICSI) - *Judith Gomez-Martinez, University of Nottingham*

### B3 Fertility preservation

FINTRY

Chair: *Prof Richard Anderson, Head of Section, Obstetrics and Gynaecology, The University of Edinburgh*

- 13.30 Investigating the role of somatic cells in follicle dysregulation observed in a mouse model of premature ovarian insufficiency using the reaggregated ovary technique - *Sairah Sheikh, University of Oxford*
- 13.45 Ethanolic extract of *Moringa oleifera* leaves attenuate cyclophosphamide-induced testicular toxicity by improving endocrine functions - *Guruprasad Nayak, Kasturba Medical College, Manipal University, India*
- 14.00 Human fetal testis xenografting as a model for developing fertility preservation strategies for prepubertal boys - *Marsida Hutka, The University of Edinburgh*
- 14.15 Can tyrosine kinase signalling protect the ovary from cisplatin-induced damage? - *Agnes Stefansdottir, The University of Edinburgh*
- 14.30 Development of a survey to assess interest in fertility preservation among children and adolescents with cancer: The cancer and reproductive health (CAREh) in kids and teens survey - *Nikoletta Panagiotopoulou, Aberdeen Maternity Hospital*
- 14.45 A nationwide UK survey on female fertility preservation prior to cancer treatment - *Yazan Abdallah, Manchester IVF*

### B4 Predicting embryo growth and development 2

SIDLAW

Chair: *Prof Tom Fleming, Professor of Developmental Biology, University of Southampton, Treasurer, Society for Reproduction and Fertility, University of Southampton and Kacie Thomson, Imperial College London and Early Career Rep, Society for Reproduction and Fertility*

- 13.30 A method to a fully automated evaluation of bovine blastocyst images based on artificial intelligence - *Marcelo Nogueira, São Paulo State University, Brazil*
- 13.45 Oliana Strings: Useful marker of embryo viability - *Ranya Derrick, Imperial College London*
- 14.00 Healthy baby born after preimplantation genetic diagnosis of mitochondrial DNA disease utilising next-generation sequencing - *Katharina Spath, Reprogenetics UK, University of Oxford*
- 14.15 Prostaglandin F2 $\alpha$  regulates adhesion of HTR8/SVneo trophoblast cell line - *Monika Baryla, Institute of Animal Reproduction and Food Research of Polish Academy of Science, Olsztyn, Poland*
- 14.30 Hyaluronic acid: An anti-angiogenic shield for the post-implantation embryo - *Ron Hadas, The Weizmann Institute of Science, Israel*
- 14.45 Does the additional transfer of a poor quality blastocyst affect clinical outcome? - *Shreena Taylor, Chelsea and Westminster Hospital*

### B5 Optimising health outcomes

MOORFOOT

Chair: *Dr Virginia Bolton, Treasurer, British Fertility Society, Consultant Clinical Embryologist, Guy's and St Thomas' Hospital and Dr Tony Rutherford, Consultant in Reproductive Medicine & Gynaecological Surgery, IVI UK*

- 13.30 An ectopic pregnancy cannot be excluded...Or can it? - *Alison Richardson, University of Nottingham*
- 13.45 Live birth rates following the transfer of atypically fertilised embryos in an IVF/ICSI setting - *Victoria Berry, University of Bristol*
- 14.00 Can the transfer of a genetically affected embryo after PGD ever be justified? Questions of autonomy and welfare of the child in a case report of the transfer of an embryo affected by osteogenesis imperfecta - *Georgios Christopoulos, IVF Unit, Hammersmith Hospital*
- 14.15 Slow release insemination versus conventional IUI: Initial results from a multi-centre trial - *Bryan Woodward, IVF Consultancy Services*
- 14.30 Multivariate analysis examining the association between infertility, assisted reproduction and pregnancy outcomes in a single centre tertiary referral obstetric unit - *Eimer O'Malley, Coombe Women and Infants University Hospital, Dublin*
- 14.45 Development of a universal method for the preimplantation diagnosis of  $\beta$ thalassaemia and sickle-cell anemia using a novel next generation sequencing approach: A new paradigm for PGD - *Nada Kubikova, University of Oxford, Reprogenetics UK*

15.00 **Exhibition, refreshments and poster presentations**



# CONFERENCE PROGRAMME

|                       |   |                 |
|-----------------------|---|-----------------|
| 15.45-17.15           | <b>UPDATE SESSION 2</b>   |                 |
| <b>BFS Update</b>     | <b>Emerging evidence and new approaches to management</b>   | <b>SIDLAW</b>   |
|                       | Chair: Dr Marco Gaudoin, Medical Director, Glasgow Centre for Reproductive Medicine   |                 |
| 15.45                 | Premature ovarian insufficiency - Lisa Webber, Consultant Gynaecologist, University College London Hospitals  |                 |
| 16.15                 | Infertility, fertility treatment and risk of cancer - Prof Alistair Sutcliffe, Professor of General Paediatrics, Institute of Child Health, London  |                 |
| 16.45                 | Preparing for gender transition - Dr James Barrett, Clinical Lead and Consultant in Adult Gender Dysphoria Medicine, Charing Cross Gender Identity Clinic   |                 |
| <b>ACE Update</b>     | <b>Emerging technologies</b>  | <b>PENTLAND</b> |
|                       | Chair: Dr Stephen Troup, Scientific Director, Hewitt Fertility Centre, Liverpool and Dr Roger Sturme, Senior Lecturer in Reproductive Medicine, Hull York Medical School  |                 |
| 15.45                 | Is spending the first few days of life in a test tube good for your health? The EpiHealth project - Prof Daniel Brison, Honorary Professor of Clinical Embryology and Stem Cell Biology; Scientific Director of the Department of Reproductive Medicine; and Co-Director NW Embryonic Stem Cell Centre (NWESCC) |                 |
| 16.15                 | Mechanisms of lineage specification in human embryos and stem cells - Kathy Niakan, Group Leader, Francis Crick Institute   |                 |
| 16.45                 | What can we learn from the embryo in its first 14 days? - Sanna Vuoristo, Postdoctoral Scientist, University of Cambridge   |                 |
| <b>SRF Update</b>     | <b>Infectious threats to reproduction</b>   | <b>FINTRY</b>   |
|                       | Chair: Dr Richard Lea, Reader & Associate Professor, University of Nottingham and Olivier Sandra, Research Scientist, INRA, France  |                 |
| 15.45                 | Consequences of bluetongue and schmallenberg on ruminant reproduction - Prof Peter Mertens, Professor of Virology University of Nottingham, The School of Veterinary Medicine and Science, University of Nottingham   |                 |
| 16.15                 | Pathogenesis of enzootic abortion and identification of immune correlates of protection - Prof Gary Entrican, Principal Research Scientist, The Moredun Foundation and Honorary Professor, University of Edinburgh and University of Glasgow  |                 |
| 16.45                 | Role of chlamydial infection in early pregnancy failure - Prof Andrew Horne, Professor of Gynaecology and Reproductive Sciences and Honorary Consultant Gynaecologist, University of Edinburgh  |                 |
| <b>Nursing Update</b> | <b>Reproductive endocrinology</b>   | <b>KIKSYTH</b>  |
|                       | Chair: Carrie Lomax, Nurse Manager, Bristol Centre for Reproductive Medicine and Debbie Evans, Director of Clinical Services, Herts and Essex Fertility Centre and British Fertility Society  |                 |
| 15.45                 | New concepts in PCOS - Prof Adam Balen, Leeds Centre for Reproductive Health and Chair, British Fertility Society   |                 |
| 16.15                 | Thyroid disease and reproductive problems - Dr Ephraim Yasmin, Consultant in Reproductive Medicine and Surgery, University College London Hospitals   |                 |
| 16.45                 | Pitfalls of ovarian reserve assessment - Prof Richard Fleming, Honorary Professor of Reproductive Medicine (Retired), University of Glasgow   |                 |
| 17.30-18.15           | <b>Finox Biotech symposium: From science to practice. Challenging myths</b>   | <b>TINTO</b>    |
|                       | Changing the stimulation dose in mid-cycle has no scientific basis - Prof Richard Fleming, Honorary Professor of Reproductive Medicine (Retired), University of Glasgow   |                 |
|                       | Introduction of the FORWARD grant - Prof Julian Jenkins, Finox Biotech  |                 |
|                       | DHEA study, winner of the FORWARD grant - Prof Roy Homburg, Head of Research, Homerton University Hospital  |                 |
| 19.30                 | Conference dinner and ceilidh, EICC<br>Awards presented throughout evening  | <b>CROMDALE</b> |
| 12.30-17.00           | <b>SCHOOLS ENGAGEMENT PROGRAMME</b>   |                 |
|                       | <b>Everything you need to know about fertility but are afraid to ask!</b>   |                 |
|                       | BFS, ACE and SRF supported by the Scottish Government host a schools session for S5 and S6 pupils from all over Scotland to enable them to experience and learn about the basics of reproductive healthcare, lifesciences and understand the career opportunities awaiting them                                 |                 |

## CONFERENCE PROGRAMME

### Saturday 7 January

08.45 **Registration, exhibition, refreshments and poster presentations**

#### PLENARY SESSION

PENTLAND

- 09.10 Chair's welcome  
*Stephen Harbottle, Chair, Association of Clinical Embryologists*
- 09.15 **Bob Edwards Memorial Lecture**  
What we know, what we think we know and what we don't know  
*Prof Gerald Schatten, Professor of Cell Biology and Physiology, University of Pittsburgh, USA*
- 10.00 Debate: Is it all about the hype? Mild stimulation has better outcomes than controlled ovarian hyperstimulation  
Chair: *Dr Jane Stewart, Newcastle Fertility Centre & Secretary, British Fertility Society*  
For - *Prof Geeta Nargund, Medical Director, CREATE Fertility & Consultant Gynaecologist, Reproductive Medicine Services, St George's Hospital London*  
Against - *Prof Siladitya Bhattacharya, Director, Institute of Applied Health Sciences, University of Aberdeen*
- 10.35 An update on NHS funding - *Susan Seenan, Chief Executive, Fertility Network UK*

10.45 **Exhibition, refreshments and poster presentations**

#### 11.30-13.00 UPDATE SESSION 3

##### BFS Update General update session

SIDLAW

Chair: *Prof Enda McVeigh, Consultant, University of Oxford and Dr Raj Mathur, Consultant Gynaecologist, Central Manchester Foundation Trust*

- 11.30 Environmental factors and infections that affect sperm quality - *Prof Allan Pacey MBE, Professor of Andrology, University of Sheffield*
- 12.00 Use of SPRMs in fertility and gynaecology - *Prof Hilary Critchley, Professor of Reproductive Medicine, University of Edinburgh*
- 12.30 Better information = better care - *Peter Thompson, Chief Executive, Human Fertilisation & Embryology Authority*

##### ACE Update Pre-implantation genetics

PENTLAND

Chair: *Dr Dagan Wells, Director, Reprogenetics UK Ltd*

- 11.30 Innovations in PGD of single gene disorders: The karyomapping revolution - *Prof Alan Handyside, Consultant in Pre-implantation Genetics, The Bridge Centre and Visiting Professor, University of Leeds*
- 12.00 PGS using next-generation methodologies: A review of the clinical evidence - *Dr Tony Gordon, Laboratory Director, Genesis Genetics*
- 12.30 Should all IVF patients undergo preconception 'carrier' screening? - *Alexander Bisignano, CEO, Recombine*

##### SRF Update Influence of reproduction on lifetime health

FINTRY

Chair: *Prof Colin Duncan, Professor of Reproductive Medicine and Science, University of Edinburgh, The Society of Reproduction and Fertility and Dr Adam Watkins, Research Fellow, Aston University and The Society of Reproduction and Fertility*

- 11.30 One carbon metabolism: Linking nutritional biochemistry to epigenetic programming of long-term development - *Prof Kevin Sinclair, Professor of Developmental Biology, University of Nottingham*
- 12.00 Testosterone and health in ageing men - *Prof Ilpo Huhtaniemi, Professor of Reproductive Endocrinology, Imperial College London*
- 12.30 Prenatal steroids programme metabolic dysfunction in sheep - *Dr Mick Rae, Edinburgh Napier University*

##### Nursing Update Female reproductive organs

KILSYTH

Chair: *Helen Kendrew, Matron, Bath Fertility Centre*

- 11.30 Management of ovarian cysts in fertility patients - *David Ogutu, Consultant Obstetrician and Gynaecologist, North Middlesex University Hospital and Fertility Specialist, Herts and Essex Fertility Centre (HEFC)*
- 12.00 Ultrasound screening prior to fertility treatment - *Prof Nick Raine-Fenning, Clinical Associate Professor and Reader in Reproductive Medicine and Surgery, University of Nottingham*
- 12.30 The uterus and the window of implantation - *Prof Siobhan Quenby, Director, Biomedical Research Unit in Reproductive Health, Professor of Obstetrics, University of Warwick, and Honorary Consultant at University Hospital Coventry and Warwickshire NHS Trust*

## CONFERENCE PROGRAMME

13.00-13.45 ACE AGM

PENTLAND

13.00 **Lunch, exhibition and poster presentations (final session)**

14.15 Close of exhibition

### PLENARY SESSION - Ovarian function/dysfunction

PENTLAND

14.15 Chair's welcome

*Prof Adam Balen, University of Leeds & Chair, British Fertility Society*

14.20 Predicting the menopause through genetics - *Dr Anna Murray, Associate Professor, University of Exeter Medical School*

14.45 What can we learn about the oocyte from cumulus cell gene expression? - *Prof Tom Adriaenssens, Vrije Universiteit, Brussels*

15.10 Latest understanding in the control of GNRH secretion - *Prof Richard Anderson, Head of Section, Obstetrics and Gynaecology, University of Edinburgh*

15.35 Closing remarks and introduction to Fertility 2018

15.45 Close of conference

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PROGRAMME

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## CONFERENCE INFORMATION

### Access

The EICC is fully accessible by wheelchair to all public areas by ramp or lift. If you have any special access requirements, specifically in the auditorium, then do please let a member of the organising team know. Alternatively, you may ask any member of staff at the EICC.

### Admission to conference sessions

Admission to conference sessions is strictly by badge only. Please ensure you are in your seat at least five minutes prior to the start of each session and that any phones or other electronic devices are switched off or turned to silent.

### App

The free conference app is available to download by visiting the app store on your device and searching for 'FERTILITY 2017'. The app contains all the information in this handbook so you can access everything you need to know about the conference at any time, easily and quickly. If you are using an iPad, please ensure you search under the iPhones tab only.

### Attendee list

A full list of participants is available from the registration desk.

### Badges

In the interests of security, please make sure that your name badge is clearly visible at all times. If you lose your badge, please ask staff at the registration desk for a replacement as soon as possible. We would be grateful if you would return your badge to registration at the end of the conference for recycling.

### Certificates of attendance

Certificates will be emailed to delegates within two weeks of the conference taking place. The certificate will reflect days attended.

### Cloakroom

There is a cloakroom for general use in the main foyer of the EICC; this service is provided at no charge to all participants. Additional space will be made available for luggage on Saturday. The cloakrooms are attended by a member of EICC staff at all times; please note, however, that items are left at your own risk.

### Conference presentations

Presentations from the conference will be available to download from [www.fertilityconference.org](http://www.fertilityconference.org) after the conference (subject to agreement by speakers).

### Emergencies

In the event of an emergency please contact a member of staff from Profile Productions or a member of the EICC security staff, who you will see throughout the building. In all other instances, please dial 999.

### Exhibition

The exhibition is an integral part of this conference and the support of all the organisations at the event is greatly appreciated. Please take your time to visit the exhibition in Lennox Suite.

### Hearing loop

The EICC has hearing loops in all breakout rooms, please turn your aid to T to access the service.

### Lunch and refreshments

Complimentary lunch and refreshments will be served in the exhibition hall during the breaks as indicated on the programme. There are several catering points available so please use them all to avoid congestion. Water coolers are also located around the EICC.

### Poster presentations

Posters will be on display in Lennox Suite for the duration of the conference. Please refer to the poster section in this handbook or the app for full details of all the presentations.

### Peoples poster prize

We are asking delegates to vote for their favourite poster by text message or by completing a voting slip. Please ask at registration for further details. Voting will close on Friday 6 January at 16.00. The prize will be presented at the conference dinner on Friday evening.

### Prayer room

If you require a quiet space to pray, we have allocated a room for your use. Please speak to the registration staff who will direct you.

### Registration desk

If you have any enquiries please make your way to the registration desk in The Atrium where the team from Profile Productions will always be at hand. Official opening times are:

|                     |               |
|---------------------|---------------|
| Wednesday 4 January | 15.00 – 19.00 |
| Thursday 5 January  | 08.00 – 19.30 |
| Friday 6 January    | 08.10 – 18.30 |
| Saturday 7 January  | 08.15 – 16.00 |

### Security

In the interests of security, EICC security personnel will be located in different areas of the EICC. Should you wish to report anything please talk to one of the security staff or contact a member of the conference team at the registration desk.

### Speaker preview and lounge

The speaker preview room is located in the Soutra room adjacent from registration. Speakers are kindly asked to visit the preview room at least two hours prior to their session to upload their presentation and check it through with the technical team. Refreshments will be available.

### Twitter

Delegates are strongly encouraged to Tweet ideas, debate and chat or to send comments at #Fertility2017 during the conference.

### Wi-Fi

Connecting to the free EICC Wi-Fi network: Click on EICC network and enter your details in your browser.

### Social and networking programme

#### Welcome reception

The welcome reception will be held in the exhibition hall on Thursday 5 January from 18.00-19.00. Free for all to attend, delegates are encouraged to take this excellent opportunity to meet with exhibitors, Society representatives and colleagues.

#### The Caves

After the welcome reception on Thursday evening, why not join delegates at this unique and exclusive venue for a fun evening of networking, traditional entertainment and to also learn about the rich history of Edinburgh's' secret underground city. Tickets are £30 which includes a drinks reception, supper and entertainment. A limited number of tickets are available from registration.

#### Conference dinner and Ceilidh

The conference dinner will be held at the EICC in the Cromdale Hall on Friday 6 January at 19.30. Enjoy a champagne reception followed by a three-course dinner with wine, and live ceilidh band to dance away the evening. A limited number of tickets are available from the registration desk at £65.

Thursday 5 January

### Development of the ovary and rescue after chemotherapy

During formation of the ovary, the somatic gonad progenitor cells enter mitotic arrest, upregulate *Foxl2*, and initiate differentiation as granulosa cells. Surprisingly, descendants of fetal granulosa cells contribute to a specific population of follicles in the medulla of the ovary that initiate growth after birth. Granulosa cells that populate adult primordial follicles derive from the ovarian surface epithelium perinatally, and immediately enter mitotic arrest to establish the ovarian reserve. Quiescent follicles are likely maintained by repressive signals from the growing follicles in each estrus cycle.

During chemotherapy, many granulosa cells in growing follicles undergo cell death. Loss of repressive signals from growing follicles may lead to activation and exhaustion of the ovarian reserve, resulting in infertility and collapse of ovarian function. However, if a fraction of a healthy ovary is grafted onto the ovary of a chemo-treated host, both fertility of the host and ovarian function are rescued. Current experiments aim to understand the damage caused by chemotherapy and the mechanisms involved in rescue by the graft.



#### Prof Blanche Capel

*Professor of Cell Biology, Duke University Medical Centre, USA*

Blanche Capel is a James B. Duke Professor of Cell Biology at Duke University Medical Center. Her graduate training was in mouse genetics and stem cell biology with Beatrice Mintz at Fox Chase Cancer Center, followed by postdoctoral research in the Lovell-Badge laboratory at NIMR, Mill Hill, London, leading to the discovery of *Sry*, the male sex-determining gene in mammals. Work from the Capel laboratory centers on cell fate and patterning decisions that underlie the development of the bipotential mammalian gonad into either testis or ovary. She directs the Developmental and Stem Cell Biology Program at Duke, and has served on the boards of the Society for Developmental Biology, the Society for the Study of Reproduction, the Scientific Advisors at the Jackson Laboratory, and FASEB. She is a member of AAAS, and current president of the Society for Developmental Biology.

### How the environment affects ovarian function and the oocyte

The developing oocyte resides in the ovarian follicle; a dynamic structure which responds to changes in the maternal physiological environment. Changes in the composition of the follicular milieu can affect oocyte physiology in a range of subtle ways. Adaptation of the endoplasmic reticulum and mitochondria to the ovarian environment can lead to metabolic reprogramming, and in addition, expression of key genes in the resulting embryo can be influenced directly by the ovarian environment. It has been postulated that such changes might contribute to the life-long health of the resulting offspring. This presentation, will examine evidence from a range of species that the ovarian environment has profound effects on early development.



#### Dr Roger Sturmey

*Senior Lecturer in Reproductive Medicine, Hull York Medical School*

Roger Sturmey is Senior Lecturer of Reproductive Medicine at the Hull York Medical School. He is interesting in studying metabolic function at the nanoscale of individual embryos and how this links to embryo physiology and has now applied these interests to somatic cells and stem cells. His laboratory studies oocytes and embryos of domestic species; notably bovine and equine, in addition to work on human embryos in collaboration with the Hull IVF clinic. His research has identified key metabolic adaptations of early embryos in response to nutritional and physiological challenges, informing the debate on maternal health around conception. His group has also developed a novel model of the female reproductive tract which has provided new insight into the formation of reproductive tract fluid. He is a board member of the Association Européenne de Transfert Embryonnaire, member of the ACE Scientific Advisory Committee and the Basic Science Officer for the ESHRE Embryology Special Interest Group.

### Replenishing the adult ovarian follicular population: Isolation and characterisation of germ line stem cells from adult women

For the past 60 years, management of ovarian insufficiency and failure, including infertility caused by aging or insults, has been governed by the belief that the entire germ cell (oocyte) pool is endowed at birth, after which ovaries lose capacity for oocyte renewal (oogenesis). In 2004, studies with mice challenged the idea of a fixed ovarian reserve, and the controversy of whether postnatal oogenesis occurs in mammals was re-ignited. Almost a decade later, a body of evidence has emerged which supports the idea that a rare population of germline cells with oocyte-forming potential can be isolated from ovaries of adult mice and women.

These cells, termed female germline stem cells (fGSCs) or oogonial stem cells (OSCs), are characterised by expression of primitive germ cell and stem cell markers. When combined with somatic cells these cells form what appear to be oocytes/follicles. However, the physiological relevance of these cells to adult ovarian function and fertility remains to be determined.

Whilst at present there remains controversy over the biological significance of these cells, it must be acknowledged that their identification and isolation represent a significant advance with the potential to change infertility treatments, and possibly even non-reproductive consequences of the loss of ovarian function, in the future. Whilst practical and conceptual obstacles remain before clinical application of OSC-based technologies can be fully realised, it is important to move on from scepticism towards solid testing to determine the potential utility of these cells. This presentation will focus on the isolation and characterisation of these cells from adult women. The relevance of these cells will be discussed and data will be presented to show their utility in vitro and in vivo.

## PLENARY SPEAKERS



### Prof Evelyn Telfer

*Personal Chair in Reproductive Biology, University of Edinburgh*

Prof Evelyn Telfer holds a personal chair in Reproductive Biology at the University of Edinburgh where she heads a research group in ovarian development within the Institute of Cell Biology and Centre for Integrative Physiology.

Her group has a particular interest in developing in vitro models to support oocyte development from immature stages in domestic species and human. Her group is now using these models to study the potential of female germ line stem cells isolated from adult ovaries in a range of species. She has published widely in this area and is a regular invited speaker at International meetings.

### The Anne McLaren Memorial Lecture The role of sister germ cells in oocyte differentiation

Eggs are unusual cells whose study raises some of the most important and interesting questions in animal biology and genetics. By applying the powerful genetic techniques available in *Drosophila* and mouse, we find that egg development in both species is similar in many unexpected ways. In both *Drosophila* and mice, most early germ cells act as nurse cells, transferring organelles and cytoplasm to sister cells that become oocytes before undergoing apoptosis. Germ cell chromatin is reprogrammed during this period, and we have developed a new technique that allows one to test functionally whether any specific chromatin region of interest in developing germ cells is silenced or whether genes within it can be expressed. Ovulation in *Drosophila*, like in mammals, is based on the local digestion by matrix metalloprotease of part of the granulosa cells and basement membrane. The remaining granulosa cells become a corpus luteum and express steroid hormone biosynthesis genes. Finally, we have studied how *Drosophila* eggs become quiescent and are able to survive storage in the ovary prior to fertilization. We identified several genes that are required for normal storage, including the *Drosophila* fragile X homolog *Fmr1*. Our studies argue that *FMR1* acts by controlling the translation of just a few specific targets.



### Dr Allan Spradling

*Department of Embryology, Carnegie Institution for Science/ HHMI, Baltimore, USA*

Allan Spradling received his B.A. degree from the University of Chicago and PhD. from M.I.T.

During postdoctoral studies with Tony Mahowald at Indiana University, he developed a lifelong interest in eggs. He joined the Department of Embryology at the Carnegie Institution in Baltimore in 1980, became an HHMI Investigator in 1988, and served as Director from 1994-2016. Spradling is a member of the U.S. National Academy of Sciences, the American Academy of Arts and Sciences and the American Philosophical Society. He has received the NAS Molecular Biology Prize (with Gerald Rubin), the George W. Beadle Award of the Genetics Society of America, the E. F. Conklin Medal of the Society for Developmental Biology, the M.C. Chang award in reproductive biology, and the Gruber Foundation Medal in Genetics.

### Friday 6 January

### Why is aneuploidy so common in oocytes and why does it increase with a woman's age?

Women show a remarkable decline in the quality of their eggs as they age. This is manifest in an exponential rise in aneuploidies, especially during meiosis I, which most times generate non-viable embryos. Although sometimes regarded as a problem specific to human, it is also observed in other mammals including mice, where it can be investigated in some detail.

The fact that aneuploidy rates are high in females, and rise further with maternal age, suggests oocytes have an innate susceptibility to mis-segregate their bivalents during meiosis I, which is exacerbated with age. In all cells including oocytes, cell cycle progression is coupled to faithful chromosome separation by the activity of the spindle assembly checkpoint (SAC). This checkpoint blocks anaphase until all chromosomes are properly attached to spindle microtubules. Our lab is therefore investigating how the SAC is controlled in mouse oocytes during meiosis I. We have found the checkpoint is insensitive to a small number of bivalent attachment errors, so leading to segregation errors and aneuploidy in mature eggs. Furthermore its surveillance properties also appear to deteriorate with maternal age, so allowing greater levels of mis-segregation. Therefore, although aneuploidy in oocytes is unlikely to have a single cause, it seems that the behaviour of the SAC and its loss in functionality with age, helps create a cell in which chromosome mis-segregation is permissive.



### Prof Keith Jones

*Head of Biological Sciences, Professor of Cell Biology, Principal Investigator, University of Southampton*

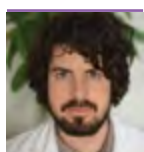
Keith Jones is Head of Biological Sciences, and Chair of Cell Biology at the University of Southampton. He has an honorary Professorship at the Chinese Academy of Sciences. Having worked as a postdoc at the MRC Experimental Embryology & Teratology Unit in London and at UCL, between 1998-2008 he went on to an academic position at the University of Newcastle-upon Tyne. In 2008, until 2012, he worked at the University of Newcastle, Australia. Currently he is a member of the Faculty of 1000, and the BBSRC's pool of experts. He has developed the use of Fluorescent Proteins to study the process of meiosis in real-time leading to developments in the understanding of how the meiotic divisions of oocytes are regulated.

### Meiosis in mammalian oocytes

Human preimplantation embryos have an exceptionally high incidence of chromosome aneuploidy. These are predominantly of maternal origin and arise through errors in chromosome segregation in the two meiotic divisions (meiosis I and II) of oogenesis. These errors increase with maternal age and contribute to the decline in a woman's fertility with advancing age as well as the associated increase in miscarriages and viable trisomic pregnancies. SNP genotyping and maternal haplotyping of all three products of female meiosis (MeioMapping), both polar bodies (PB) and the



corresponding oocyte/embryo, allows simultaneous analysis of patterns of recombination and chromosome segregation. Analysis of oocyte-PB trios confirmed that premature sister chromatid separation was the most frequent cause of segregation errors in the first meiotic division but also identified a novel reverse segregation mechanism predisposing to errors in the second meiotic division. MeioMapping can diagnose maternal aneuploidies in preimplantation embryos and is a powerful preclinical assessment tool of IVF protocols as well as as tool to establish a baseline for studies of mosaicism in primpantation embryos.



### Dr Christian Ottolini

*School of Biosciences, University of Kent*

Dr Ottolini trained as an embryologist at the renowned PIVET Medical Centre in Perth, Australia before moving to the UK in 2009. He has spent the last seven years at the Bridge Centre where he also completed a PhD in preimplantation genetics. Along with Professor Alan Handside, he led the research identifying a new mechanism resulting in abnormal chromosome copy number in human oocytes and developed MeioMapping which is a powerful tool for identifying chromosome segregation and recombination patterns in oocytes.

### Can we stop ovarian ageing?

Understanding the fundamental biology of human oogenesis is vital if we are to define oocyte developmental competence (quality) and characterise the impact of age and interfile pathologies on female reproductive function. This important issue can be addressed by combining targeted studies of human oocytes with mechanistic in vivo and in vitro models of oocyte development in animals. By integrating different non-invasive methodologies with powerful molecular genetic techniques it is now possible to link multiple measurements of oocyte energy and amino acid metabolism with the quantitation of oocyte mitochondrial activity, chromosome health and/or the transcriptome of the same cell. These functional genomic approaches will ultimately enable us to generate a high-resolution map of the key developmental milestones of human oogenesis and in so doing help to define how human oocyte biology differs between fertile and infertile women. This research strategy can also be used to investigate how the developmental competence of oocyte is influenced by the altered endocrine milieu and associated reduced ovarian reserve that accompany ovarian ageing.



### Prof Helen Picton

*Head of Division of Reproduction and Early Development, Leeds Institute of Cardiovascular and Metabolic Medicine*

Prof Helen Picton is an ovarian biologist. She held the Chair of Reproduction and Early Development in the Leeds Institute of Cardiovascular and Metabolic Medicine within the School of Medicine at the University of Leeds. She is the Scientific Director of the Leeds Centre for Reproductive Medicine within the Leeds Teaching Hospitals NHS Trust. Her research programme is focussed on developing an in depth understanding of the cell and molecular biology of oocyte, follicle and embryo development in large animals and humans. The insights provided by the study of the fundamental biology of these different cell types is then used to help explore the aetiology of female infertility, to design and

improve infertility treatments, and to preserve the fertility of young female cancer patients.

### Howard Jacobs Lecture

### Ovarian stimulation for infertility treatment: Past, present and future

Since the early 60s, clomiphene - a drug originally tested in the context of endometrial hyperplasia - is available to effectively stimulate ovarian function. Around the same time, urinary and human pituitary gonadotropins could be used to directly stimulate human ovarian function. During the first 2 decades these drugs were tested extensively in the context of infertility treatment in anovulatory women, chiefly women diagnosed with PCOS.

After the first birth following natural cycle IVF, both drugs were tested in the early 80s in the context of IVF. Complex regimens have subsequently been developed with GnRH agonist or antagonist co-treatment, prestimulation interventions, additional stimulation drugs next to FSH (like androgens, and many others), oocyte maturation trigger interventions and finally luteal phase supplementation.

The need for ovarian stimulation in the context of unexplained subfertility (with or without intra-uterine insemination) remains a topic of distinct controversy.

In my personal view, the current major challenges regarding ovarian stimulation include; 1) what is the role of ovulation induction in the current era dominated by IVF, 2) what is the optimal number of oocytes to be retrieved following ovarian stimulation for IVF, and can robust FSH individualised dosing regimens be developed to achieve this aim, 4) are empirical interventions like ovarian stimulation in unexplained infertility useful strategies in the context of spontaneous pregnancy chances, burden of treatment, cost, and complications.



### Prof Bart Fauser

*Visiting Professor and Senior Consultant in Reproductive Medicine, The Bridge Centre*

He is a gynecologist and professor of reproductive medicine, University of Utrecht,

The Netherlands, former Chair of the Department of Reproductive Medicine & Gynecology, and former Head of the Division Woman & Baby, University Medical Center, Utrecht. Professor Fauser also acts as Chief Editor of Reproductive Biomedicine Online (RBMO), as a member of the board of the Dutch Medical Research Council (ZonMW), as chair of the WHO steering committee infertility guidelines, and as consultant. He is a visiting professor at Siena (It), Adelaide (Au), and Southampton (UK), and a senior lecturer at the London Women's Clinic (UK). In 2016 he was elected as fellow ad eundum of the RCOG.

Prof Fauser previously held the following positions: Fulbright post-doctoral Scholar, University of California, San Diego, California (1987-1988); Visiting Professor, Stanford School of Medicine, Palo Alto, California (1993-1994), USA; Saal van Zwanenberg Professor, Center of Reproductive Medicine, Free University, Brussels, Belgium (1995-2008); Professor of Reproductive Endocrinology and director Center of Reproductive Medicine, Erasmus Medical Center, Rotterdam, The Netherlands (1997-2003), and Editor-in-Chief 'Human Reproduction Update' (2000-2006). His major research interest is the pathophysiology of human ovarian function. He authored



## PLENARY SPEAKERS

close to 400 PubMed publications, and is amongst the most cited authors in Reproductive Medicine. His work has been widely covered in the national and international news media. Prof. Fauser has served on many international editorial boards, has been active in many international societies, and has received multiple international awards.

**Saturday 7 January**

### Bob Edwards Memorial Lecture: What we know, what we think we know and what we don't know



#### Prof Gerald Schatten

*Professor of Cell Biology and Physiology, University of Pittsburgh, USA*

Prof Schatten is Director of the Pittsburgh Development Center, Professor of Obstetrics, Gynecology and Reproductive Sciences, Cell Biology, Bioengineering and Director of the Division of Developmental and Regenerative Medicine. Dr Schatten has directly trained >50 doctoral and postdoctoral fellows, along with several MD, MD-PhD and DVM trainees. He is extremely active in advanced research training and was one of the three founding directors of the Frontiers in Reproduction, the premier reproduction training vehicle for MD and PhDs. Along with Dr Roger Pedersen, Dr Schatten is the founding course director of Frontiers in Human Embryonic Stem Cell Research (FrHESC) – an intensive laboratory and lecture-based introduction to this emerging research field. He co-directs Frontiers in Stem Cells and Regeneration taught annually at Woods Hole and directs Frontiers in Stem Cells in Cancer at Howard University and Ponce School of Medicine, Frontiers in Aging and Regenerative Medicine at Xavier University, Morehouse School of Medicine and Meharry Medical College and Rehabilitative and Regenerative Medicine for Minority Health and Health Disparities at Howard University and Morehouse School of Medicine, all of which are supported by the NIH. He is currently President of UNESCO's International Cell Research Organization. With extensive funding from the National Institutes of Health, Dr Schatten is the recipient of an NIH MERIT, and earlier a Research Career Development Award, was honored by the Czech Academy of Sciences with their Purkinje Medal of Science, elected as a Delegate of the American Association for the Advancement of Sciences, a Mentor Awardee of the American Society for Cell Biology, Elected Australian Society for Reproductive Biology President's Lecturer, awarded the Daniel Mazia Award from Stanford University and a Doctor Honoris Causa (Honorary Doctorate) from the University of Nova Gorica, presented by the President of the Republic of Slovenia, among other honors. He assisted in the human fertilization animations in the 2016 movie, directed by Terrence Mallick entitled 'Voyage of Time' (<http://www.imdb.com/title/tt1945228/>), narrated by Brad Pitt and Cate Blanchett. His > 300 papers on stem cells, regeneration, fertilization, cell biology, development, infertility, assisted reproductive technologies, as well as strategies for rectifying past injustices in scientific careers, have appeared in premier journals including Nature and Science. Dr Schatten is also an eloquent advocate for research in reproduction, development, regeneration and stem cells.

### Debate: Is it all about the hype? Mild stimulation has better outcomes than controlled ovarian hyperstimulation

Ovarian stimulation to achieve multiple follicle development has been an integral part of IVF treatment. The conventional IVF protocols can be complex, aggressive, unphysiological, unfriendly and unnecessary for women. The treatment can last up to 4 to 5 weeks and involves pituitary downregulation followed by higher doses of daily stimulation. As a result, women experience considerable discomfort. Milder stimulation approaches fit within women's natural cycles and are associated with less burden, side effects and drop outs from treatment.

The primary aim of mild stimulation is a more physiological approach to stimulation with the collection of fewer but higher quality and mature oocytes. Studies have shown that this approach may be beneficial for oocyte/embryo quality and endometrial receptivity. The effect of high stimulation on intrafollicular physiology and potential epigenetic errors in oocytes and embryos will be discussed.

Knowing the lower biological efficiency of oocytes with conventional stimulation protocols and in the context of improved laboratory performance, the need for collecting a large number of oocytes per cycle will be questioned. With the availability of "OHSS free" antagonist protocols, the use of long downregulation protocols will be challenged. The studies performed during the last decade to develop the concept of mild stimulation will be presented. I will examine the balance between IVF success and patient discomfort, short and long-term complications and cost, and how these might improve by using simpler mild stimulation protocols.



#### Dr Jane Stewart

*Newcastle Fertility Centre & Secretary, British Fertility Society*

Jane Stewart is a consultant in Reproductive Medicine and Gynaecology with a longstanding interest in miscarriage, its management and recurrence. She is Head of Department and PR at Newcastle Fertility Centre at LIFE, Honorary Secretary of the British Fertility Society, ex-Chair of the Training Committee and Clinical Sub-Editor of Human Fertility.



#### Prof Geeta Nargund

*Medical Director, CREATE Fertility & Consultant Gynaecologist, Reproductive Medicine Services, St George's Hospital London*

Geeta Nargund is the Founder and Medical Director of CREATE Fertility. She is also the Lead Consultant for Reproductive Medicine at St George's Hospital, London.

She is the President of the International Society for Mild Approaches in Assisted Reproduction (ISMAAR). Her research and clinical interests include physiological approaches to assisted reproduction and the use of advanced ultrasound technology in reproductive medicine. She is the Founder and Chief Executive of UK charity, Create Health Foundation. This charity funds and supports fertility education in schools. She is also a director of the Walking Egg Foundation, a Belgian Charity dedicated to making fertility treatments accessible globally. Geeta was appointed as the Vice President for British Red Cross in London.

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Mild stimulation in IVF has been described as ovarian stimulation using gonadotrophins at lower doses, for a shorter duration or involving oral medication. It has been suggested as an effective, acceptable and economical alternative to conventional ovarian stimulation which provides a more patient-centred approach to IVF. It is believed to be a more "natural" process which reduces the risk of ovarian hyperstimulation syndrome and multiple pregnancy, improves oocyte and endometrial quality and decreases discomfort, emotional stress and costs associated with treatment. Many of the perceived benefits of mild stimulation are based on assumptions about how different attributes of the IVF treatment pathway are valued. This presentation will critically appraise the existing literature to explore the validity of the arguments presented in favour of mild stimulation and challenge the notion that mild stimulation results in greater clinical and cost effectiveness, satisfaction and safety for women and their offspring. In particular data on the outcomes of interest will be considered in terms of the quality of the evidence, relevance to the clinical context and precision of estimates.



### Prof Siladitya Bhattacharya

*Director, Institute of Applied Health Sciences, University of Aberdeen*

Prof Siladitya Bhattacharya is the Professor of Reproductive Medicine and Director of the Institute of Applied Health Sciences at the University of Aberdeen. Professor Bhattacharya is a subspecialist in reproductive medicine and holds honorary consultant status with NHS Grampian. His main research interests include reproductive epidemiology, health services research and evidence based care in infertility.

### An update on NHS funding

Current access to NHS funded fertility treatment is inequitable and unfair, and causes great distress to patients. Despite having a National Health Service, and national recommendations in England set by the National Institute for Health and Care Excellence, treatment by postcode is the norm. Health is a devolved issue, meaning across the UK patients can face real inequities and local challenges in accessing NHS treatment. Work by patient organisation Infertility Network UK and campaigning group Fertility Fairness has, over the years, vastly improved the situation but many challenges remain to overcome the barriers and increase access to NHS treatment for those eligible.

This overview of funding for NHS fertility treatment across the UK will compare the unfair situation across the UK, highlighting in particular the recent cuts by CCGs in England with the situation in Scotland. Here a supportive Government ensures standard access criteria apply to all, and where the current provision of two cycles will increase to three full cycles to those eligible early in 2017.



### Susan Seenan

*Chief Executive, Fertility Network UK*

Susan Seenan is Chief Executive of the patient organisation Fertility Network UK, having worked for the charity since 2005: first as communications officer and the nas deputy chief executive and since January 2014 as chief executive.

Having experienced first-hand the rollercoaster of fertility problems and treatment, she understands completely what it's like to discover that having a family is not always that straightforward.

A passionate believer that eligibility for NHS fertility treatment should not depend on postcode, she is also a strong advocate for more emotional support and counselling for everyone struggling to conceive.

Susan also acts as the voice of patients on various committees including:

- Co-Chair of Fertility Fairness (FF)
- Chair of the Association of Fertility Patient Organisations
- Patient representative on the British Fertility Society committee
- Member of the Multiple Births Stakeholder Group and One at a Time editorial board
- Member of the National Infertility Group Scotland

### Predicting the menopause through genetics

Current methods for predicting age at menopause are reliant on detecting the perimenopausal changes in oocyte number and are therefore poor long range predictors. Currently the best predictor of menopause age is mother's menopause age and this is likely to be largely due to genetic factors. Genetic predictors of menopausal age have the obvious advantage of being present from birth and while the potential of genetic factors alone may be limited at present, as new genes are discovered it may be possible to combine genetic and non-genetic risk factors into a useful model. Such a model has the potential to offer women advice about their reproductive lifespan from an early age, enabling them to make informed reproductive choices.

Recent large genetic and epidemiological studies have made significant advances in understanding the factors which influence reproductive lifespan and the associated disease outcomes. Genetic studies have found multiple loci involved in menopause timing, with both monogenic and polygenic modes of inheritance. Despite this success, the proportion of variation explained by genetic variants is less than 10% and few single gene causes of primary ovarian insufficiency have been described. Identification of novel genetic loci and understanding of their mechanisms of action has provided new insights into the biology of female reproductive ageing, which has increasing relevance as women delay childbearing and live longer. Once we have a better understanding of the risks factors involved we may be able to predict age at menopause in young women, prior to exhaustion of ovarian reserves, enabling them to make informed choices.



### Dr Anna Murray

*Associate Professor, University of Exeter Medical School*

Anna Murray is an associate professor at the University of Exeter Medical School and has worked in human genetics for over 20 years. She is interested in the genetics of female reproductive ageing, from menarche to menopause. Anna is one of the lead investigators in the ReproGen consortium. Prior to joining the Medical School in Exeter, Anna spent 11 years at the Wessex Regional Genetics

## PLENARY SPEAKERS

Lab, where she held a Wellcome Trust Career Development Fellowship. Anna did her PhD on coeliac disease and T cell lymphoma of the gut after graduating with a BSc in Biology from the University of Southampton. For a full list of Anna's publications, please go to Google scholar.

### What can we learn about the oocyte from cumulus cell gene expression?

The mammalian oocyte is known to grow in the protective and supported environment of the follicle. There is a strong interaction between the 3 cell types it comprises. The closest and most persistent contact is with the cumulus cells (CC) and this is especially interesting because CC are in close contact with the oocyte during the crucial period when the oocytes acquire their cytoplasmic and nuclear maturity/competence. In mice models the first studies using micro array analysis on CC, allowing the screening of >30,000 gene transcripts have been published quite some time ago. What can we learn from these experiments? Are there novel pathways described in CC and can they be confirmed in human CC? And last but not least could they be indicative of the oocyte quality or developmental competence?



#### Tom Adriaenssens

*Vrije Universiteit, Brussels*

Tom Adriaenssens graduated as a master in biomedical sciences at the Vrije Universiteit Brussel (VUB), Belgium. He has been working as a research associate at the UZBrussel for more than fifteen years; first in the Center of Medical Genetics (CMG) and currently in the Follicle Biology laboratory (FOBI) in close collaboration with the Center of Reproductive medicine (CRG) in the UZBrussel. He studies folliculogenesis and oogenesis in vivo and in vitro in animal models and in human. His work focusses primarily on gene expression occurring in the oocyte and cumulus cells in order to understand the crosstalk between both cell types, and the follicle. He contributed to several international clinical trials and is Associate Editor of Human Reproduction. He is currently mainly involved in the development and porting of a cumulus cell gene expression assay which is designed to improve the live birth rate in the ART clinic.

### Latest understanding in the control of GnRH secretion

It is well established that GnRH is the conductor of the reproductive orchestra. However in the last decade a wealth of information regarding how the secretion of GnRH itself is controlled has emerged, following from the demonstration of the obligate involvement of the hypothalamic neuropeptides kisspeptin and neurokinin B for normal human reproductive function. These, together with the opioid dynorphin, are direct regulators of GnRH and integrate steroid feedback as well as many other signals that impact on reproductive function. Both kisspeptin and neurokinin B have a stimulatory role on GnRH secretion while dynorphin is inhibitory, and while it appears that neurokinin B is generally 'upstream' of kisspeptin, there is clearly a complex interaction between these pathways, which also impacts on vasomotor symptoms as well. Therapeutic regulation of these pathways is an emerging

area in reproductive medicine, in IVF, PCOS and menopausal symptoms: in this talk I will give a background to this new understanding of neuroendocrinology, and how this is being translated into clinical practice.



#### Prof Richard Anderson

*Head of Section, Obstetrics and Gynaecology, University of Edinburgh*

Richard Anderson is currently Elsie Inglis Professor of Clinical Reproductive Science and the Head of Section for Obstetrics and Gynaecology at the University of Edinburgh. He is also a consultant in reproductive medicine at the Royal Infirmary of Edinburgh. Richard's undergraduate medicine degree was punctuated by a PhD in the MRC Brain Metabolism Unit in neuroendocrinology. Subsequently he trained in Obstetrics and Gynaecology in Edinburgh, and after completing Subspecialty training in Reproductive Medicine as a lecturer at the University of Edinburgh with David Baird and a year in Sam Yen's lab in San Diego he returned to the MRC Human Reproductive Sciences Unit in 1998 with a consultant post at the Royal Infirmary of Edinburgh. Richard was appointed to his current post in the University in 2005: Over subsequent years he has established a group investigating the female reproductive lifespan, and the role of novel neuropeptides as key regulators of human reproduction.





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|                                       |         |
|---------------------------------------|---------|
| Male Fertility                        | 19 June |
| Embryo Transfer & IUI                 | 21 June |
| Preserving Fertility in Cancer        | 22 June |
| Modern Families                       | 22 June |
| <b>AND NEW FOR 2017</b>               |         |
| <b>PGD PGS Study day</b>              | 20 June |
| <b>Nurses Study Day</b>               | 21 June |
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## UPDATE SESSION 1

### BFS update

#### Controversies in reproductive medicine

### Managing unexplained infertility - evidence vs expectations

Infertility is described as unexplained in couples in whom tests of ovulation, semen analyses and tubal evaluation fail to reveal any abnormalities. Prediction models can provide information about chances of pregnancy leading to live birth over the next 12 months based on female age, previous pregnancy and duration of infertility. In the absence of an identified correctable pathology, the evidence base underpinning the effectiveness and cost effectiveness of common interventions for unexplained infertility is limited. This presentation examined the evidence base for the use of treatments conventionally used in unexplained infertility including clomifene citrate, unstimulated and stimulated intrauterine insemination (IUI), in-vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). The conventional outcome of choice in infertility has always been pregnancy leading to live birth but time to pregnancy is gaining currency as an outcome in its own right. Having a baby soon is potentially valued more than giving birth one in the distant future. Additionally, access to, and experience of treatment are valued by couples as are agency and individual choice. A capability-based approach is emerging as a key concept in our attempts to measure quality of life in reproductive health but a sense of urgency needs to be balanced against the dangers of over-medicalising reproduction resulting in risks to women and their children.



### Prof Siladitya Bhattacharya

*Director, Institute of Applied Health Sciences, University of Aberdeen*

Please see page 18.

### IUI vs IVF

IUI and IVF are first line treatments in couples with unexplained or mild male subfertility. The evidence on the effectiveness and safety of IUI and IVF have been evaluated in two Cochrane reviews which both suggested that there is insufficient evidence to conclude that IUI or IVF is effective compared to sexual intercourse in couples with unexplained subfertility. Most guidelines agree that treatment in these couples should only be provided after one or more years of trying to conceive naturally. The most recent NICE fertility guideline advises not to offer IUI any longer and suggests two years of sexual intercourse continued by in vitro fertilisation (IVF). This recommendation has generated an ongoing debate, with only 4% of all gynecologists in the United Kingdom discontinuing the use of IUI.

The results of a Dutch trial comparing in vitro fertilisation (IVF) to IUI, demonstrating similar live birth rates, have been used to build a case supporting the effectiveness of IUI. Yet this conclusion might be somewhat premature, as the superiority of neither IUI nor IVF over no treatment has ever been proven.



### Dr Madelon van Wely

*Centre for Reproductive Medicine, Amsterdam, Netherlands*

Dr van Wely is a clinical epidemiologist and assistant professor specialised in human reproduction. She completed her PhD in 2004 at the University of Amsterdam on optimal treatment of women with polycystic ovary syndrome. She presently works at the Center for Reproductive Medicine and at the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynecology, both located in Amsterdam, The Netherlands. She has extensive experience in design, management, analysis and reporting of large-scale randomised trials, many of which were conducted within the Dutch Obstetrics and Gynecology Consortium ([www.studies-obsgyn.nl](http://www.studies-obsgyn.nl)). On daily basis she assists PhD students with methodological advice on their studies. She has been involved in many successful grand applications and PhD theses. Dr van Wely's interests are into trial design, meta-analyses, prognostic models, personalised medicine, economic evaluations and discrete choice experiments.

She participated in more than 100 peer-reviewed publications and is a registered reviewer for many scientific journals, is methodological editor for the Cochrane Gynaecology and Fertility Group and Deputy Editor of Human Reproduction.

### ACE update

Advancing our knowledge of embryo selection

### Embryo selection: What evidence is required, and do we even need it?

The IVF procedure has been subject to many changes ever since its beginning. In the early days of IVF oocyte retrieval was carried out in a natural cycle. This changed to a stimulated cycle, as this resulted in more oocytes, in more embryos available for transfer, and with that better pregnancy rates. However, with improving clinical and laboratory protocols over time, transfer of multiple embryos not only led to improved pregnancy rates, but also to an increased number of multiple pregnancies. Because of the risks to mother and child associated with these multiple pregnancies, the necessity of transferring only one or two embryos per transfer became clear. And with that, embryo selection became an increasingly important part of the IVF procedure. At first morphological assessment of the embryo at a single time-point before transfer was used to select embryos. Later on, morphological assessment at multiple time points became common, using an increased number of morphological characteristics. But not all morphologically high quality embryos implanted, where embryos with suboptimal morphology sometimes did. And improvement of IVF effectiveness was wished for as only one in four transfers resulted in a live birth. This led to the search for alternative embryo selection methods with the goal of increasing live birth rates after IVF. Well known examples of such alternative selection methods are preimplantation genetic screening (PGS) for aneuploidies, assays using culture medium to determine metabolic activity and viability of the embryo, time-lapse systems that allow the use of morphokinetic parameters, or microscopical techniques such as birefringence imaging to assess the meiotic spindle or the zona pellucida. Some of these methods are offered today in routine clinical practice with the actual promise of increased live birth rates. But are such claims of improved IVF effectiveness justified? This presentation will provide an overview of available evidence, rate the quality of evidence, and evaluate what recommendations can actually be made to women that opt for IVF.



#### Dr Sebastiaan Mastenbroek

*Assistant Professor & Clinical Embryologist,  
Centre for Reproductive Medicine of the  
Academic Medical Center, Amsterdam*

Dr Sebastiaan Mastenbroek is an assistant professor and one of the Clinical Embryologists of the Center for Reproductive Medicine of the Academic Medical Center – University of Amsterdam. An important focus of his research has been Preimplantation Genetic Screening (PGS). In 2007, publication of his randomized controlled trial on PGS in the New England Journal of Medicine started a fiercely debated controversy on the use of PGS as it showed that the technique lowered pregnancy rates after IVF instead of increasing the pregnancy rates. He then published research that provided technical as well as biological reasons for the inefficacy of the first generation PGS. In a broader perspective he is interested in early human development, implantation, assisted reproductive techniques and evidence based laboratory practice. He is

a board member of the SAF foundation, chair of the LSFD laboratory working group, board member of the special interest group ART of the Dutch Society of Obstetrics and Gynaecology, Associate Editor of Human Reproduction Open, editor of the Cochrane Gynaecology and Fertility Group, and member of the Science Committee of the Dutch Society for Clinical Embryology.

### The zinc spark as a novel marker of oocyte and embryo quality

Activation or fertilisation of mammalian eggs initiates a series of extracellular “zinc sparks” that are highly coordinated with intracellular calcium (Ca<sup>2+</sup>) transients and also necessary to induce the egg-to-embryo transition. Although Ca<sup>2+</sup> transients are known to correlate with embryo development, they cannot serve as clinical biomarkers as they occur intra-cellularly. In contrast, because zinc is released into the extracellular space, this element can be detected in a non-invasive manner and objectively quantified. Thus, we hypothesize that the zinc spark represents an early extracellular physiochemical marker of the developmental potential of the zygote. In this study, we for the first time showed that zinc fluxes accompany human egg activation. To demonstrate the physiological significance of this biological event, we further tested the critical functions for zinc dynamics and establish the zinc spark as an extracellular marker of early human development in mouse. Interestingly, we found that zinc spark closely correlates with oocyte quality and embryo development. Currently, we are performing studies to understand how zinc dynamics is regulated under pathological condition, such as aging. We have shown that zinc spark profile can act as a predictor of egg quality in naturally aged eggs. Altogether, our study suggests that zinc spark has a great potential to developing into an oocyte quality biomarker in the near future.



#### Dr Nan Zhang

*Postdoctoral Fellow, Woodruff Lab,  
Northwestern University, Canada*

Dr Zhang earned a PhD degree from University of Massachusetts at Amherst in the lab of Dr Rafael Fissore in 2012. His doctoral thesis focused on the regulation of calcium signaling in mammalian eggs. Dr Zhang joined Woodruff lab as a postdoctoral research fellow at 2014. He has been studying the zinc signaling during maturation and fertilization in mouse. His current work involves translating the zinc spark technology from mouse to human and investigating gametes dynamics with the goal of improving fertility outcome in human.

### Embryo biomarkers

The application of SET in clinical practice places an increasing demand on the laboratory for improved methods of reliable assessment of embryo quality. In principle, embryos can be selected by morphological appearance or by methods based on analyses of molecular components. These analyses can be performed on data obtained either invasively or non-invasively. The lecture will provide an overview of selected topics regarding non-invasive biomarkers for embryo selection, in particular the challenges of embryo selection using dynamic morphological evaluation (time-lapse imaging) and the non-invasive molecular-based approaches such as proteomic, metabolomic and miRNA analysis of the spent culture media.

## UPDATE SESSION 1



### Kirstine Kirkegaard

*Department of Clinical Medicine, Aarhus University, Denmark*

Kirstine Kirkegaard received her PhD from Aarhus University based on the dissertation "Human embryo development and viability assessed by time-lapse imaging". She is 1st author of 11 papers, co-author of five and last author of two papers published in international peer-reviewed journals. She was awarded a Sapere Aude grant from the Danish Council for Independent Research, Ministry of Higher Education 2014, the Aarhus University Research Foundation (AUFF) PhD prize 2014, and is winner of the PhD prize competition Health, Aarhus University 2013. She has been shortlisted for best abstract at ESHRE 27th, 28th, 29th and 30th annual meeting (first author). She is Associate Editor for Human Reproduction. She has been an invited speaker at several meetings, including ALPHA, ASRM and ESHRE.

### SRF update

Endometrial and embryo dialogue

## Extrinsic and intrinsic regulation of pregnancy establishment in ruminants

The failure to establish pregnancy after natural and assisted conception is due to both embryonic and maternal factors. Many of the pregnancy losses observed in natural or assisted reproductive technology (ART)-derived pregnancies can be attributed to inadequate uterine receptivity and conceptus-maternal interactions, resulting in defective conceptus development, pregnancy recognition signaling, and implantation and perhaps later pregnancy complications such as preeclampsia and fetal growth restriction. Mammalian uteri contain glands in their endometrium that synthesize or transport and secrete substances important for conceptus survival and implantation. Sheep that lack uterine glands, known as uterine gland-knockout (UGKO) ewes, are infertile and display recurrent early pregnancy loss due to defects in conceptus survival and growth. Studies with conditional forkhead box a2 (Foxa2) mutant and progesterone-induced UGKO mice found that uterine glands and, by inference, their secretions are required for blastocyst implantation and impact stromal cell decidualization and placental growth. A systems biology approach, utilizing functional genomics and discovery-based methods in combination with genetically engineered mouse models that lack uterine glands and animal models with innate differences in uterine receptivity, is useful to discover essential uterine-derived factors with biological roles in establishment of pregnancy. Those factors may serve as biomarkers for the diagnosis, prevention, and treatment of fertility and pregnancy problems.



### Prof Tom Spencer

*Professor of Reproductive and Developmental Biology, University of Missouri, USA*

Tom Spencer is a Professor and Distinguished Scholar in the Division of Animal Sciences at the University of Missouri in Columbia, Missouri USA and the Editor-in-Chief of Biology of Reproduction. His research is funded

by the NIH, USDA and Science Foundation Ireland and has been conducted in collaboration with more than 20 graduate students and postdoctoral fellows. He has presented over 100 invited talks and authored or coauthored over 300 scientific articles, reviews and book chapters. Spencer has earned many honors including the: American Society of Animal Science Physiology and Endocrinology Award in 2013; Society for the Study of Reproduction Research Award in 2013; and the Society for the Study of Reproduction Trainee Mentor Award in 2013. The long-term goal of his research program is to discover and understand key physiological and genetic mechanisms regulating development and function of the uterus and placenta in order to prevent and treat infertility, pregnancy loss and pregnancy complications in domestic animals and humans.

## Prostaglandin F2α in embryo-maternal interactions in the pig

In humans and other mammals, implantation is a critical period during which high embryonic mortality rates occur. Prostaglandins are key mediators regulating interactions between the maternal system and conceptus (embryo with extraembryonic membranes). Although the significance of prostaglandin F2α (PGF2α) as a regulator of corpus luteum regression is well established, the role of its high amounts in the uterine lumen in the most mammals, regardless of placentation type, during the implantation period remains unresolved. We hypothesized that PGF2α acting as an embryonic signal mediator contributes to pregnancy establishment. Using a porcine model, we showed that the conceptus and its signal (estradiol-17β) elevated endometrial expression of PGF2α receptor (PTGFR) in vivo and in vitro. PGF2α increased the mitogen-activated protein kinases 1/3 pathway in endometrial luminal epithelial cells that coincided with elevated gene expression and secretion of endometrial vascular endothelial growth factor (VEGFA) protein. PGF2α-PTGFR and adenylyl cyclase signaling were involved in this process. PGF2α-induced VEGFA acting through its receptors, stimulated proliferation of endometrial endothelial cells. Moreover, PGF2α elevated expression of genes potentially involved in tissue remodeling in the endometrium. Summarizing, our study indicates that PGF2α participates in pregnancy establishment by promoting angiogenesis and conceptus-maternal interactions in porcine endometrium during early pregnancy. Research supported by the National Science Centre in Poland (2012/05/E/NZ9/03493).



### Dr Agnieszka Wacławik

*Associate Professor, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland*

Dr Agnieszka Wacławik is as an associate professor in the Institute of Animal Reproduction and Food Research of the Polish Academy of Sciences in Olsztyn. Her research has been focused on understanding the maternal-embryo interactions during early pregnancy, especially the role of prostaglandin synthesis and signalling in this process. She has been working also on uterine receptivity markers in periimplantation period. This project was associated with COST-Gemini Action within the European Union programme. She has been a visiting research fellow at Gene Center, LMU Munich, the Medical Research Council, Human Reproductive Sciences Unit in Edinburgh and University of Turku in Finland.



Her research has been awarded with many national and international prizes, among them: The PhD Student Prize and New Investigator Award from the Society for Reproduction and Fertility, Burgen Scholarship Award from the Academia Europaea. She has been as a member of the Management Committee COST Action FA1201 Epigenetics and Periconception Environment and Academy of Young Scientists of the Polish Academy of Sciences.

### Predicting recurrent implantation failure in IVF

Nick Macklon is Professor of Obstetrics and Gynaecology at the University of Copenhagen and the University of Southampton, where he co-founded the Complete Fertility Centre.

After training in Edinburgh and Glasgow, he was appointed Senior Lecturer at Erasmus University Rotterdam, and then Professor of Infertility and Periconceptional Medicine in Utrecht before returning to the UK in 2009. In 2016 he was appointed to a part time Professorship at the Zeland University Hospital in Roskilde. His research interests include implantation and periconceptional medicine, areas in which he has published extensively. He is a past Chairman of the ESHRE Special Interest Group in Reproductive Medicine, a current member of the ESHRE Executive Committee and Associate Editor of Human Reproduction Update.



**Prof Nick Macklon**

*Professor of Obstetrics and Gynaecology, University of Southampton*

Nick Macklon is Professor of Obstetrics and Gynaecology at the University of Copenhagen

and the University of Southampton, where he co-founded the Complete Fertility Centre.

After training in Edinburgh and Glasgow, he was appointed Senior Lecturer at Erasmus University Rotterdam, and then Professor of Infertility and Periconceptional Medicine in Utrecht before returning to the UK in 2009. In 2016 he was appointed to a part time Professorship at the Zeland University Hospital in Roskilde. His research interests include implantation and periconceptional medicine, areas in which he has published extensively. He is a past Chairman of the ESHRE Special Interest Group in Reproductive Medicine, a current member of the ESHRE Executive Committee and Associate Editor of Human Reproduction Update.

### Nursing update

Challenges in reproductive medicine

### Dilemmas for couples considering egg donation treatment

'I had a panic attack when I heard the consultant say to move onto donor eggs. I went straight to the GP and signed myself off work for 2 weeks to get over the initial shock.'

This is a recent quote from a patient during an egg donation implications counselling session.

This presentation will provide insight into the patient journey from the hope for a child conceived naturally to the reality of the options of donor egg treatment, adoption or a decision to not have any (more) treatment. The particular different and similar issues for single women considering treatment with donor eggs and donor sperm will also be examined.

Drawing on evidence from hundreds of counselling sessions with couples considering egg donation – what are the choices and dilemmas they face? What are the issues that they present during implications counselling that often cause angst and distress and sometimes relationship difficulties as differences between the individuals emerge and how can these patients be helped to find the right solution for them and to accommodate the loss of genetic connection and the particular legal and ethical framework associated with egg donation.



**Ruth Wilde**

*Senior Fertility Counsellor, Complete Fertility Southampton*

Ruth is a board member of the HFEA, the former Chair of the British Infertility Counselling

Association (BICA) and has recently completed two three year terms as Counselling Representative on the British Fertility Society's (British Fertility Society) Executive. She has represented British Fertility Society and BICA's interests, and infertility counselling generally, at national events and meetings. Ruth lives near Salisbury in Wiltshire and has worked as the Senior Fertility Counsellor at the Complete Fertility Centre in Southampton since 2011. From there, she runs a monthly patient support group for anyone in the south of England who is experiencing fertility difficulties, as well as providing the infertility counselling service. Ruth has been a counsellor for over eighteen years specialising in infertility since 2002. She has previously worked in infertility clinics in Birmingham and London helping both NHS and private patients through their treatment journeys from initial diagnosis to the end of treatment and beyond. Prior to this, Ruth held the position of Staff Counsellor for various organisations in the public sector and particularly enjoyed her time as counsellor for all the staff working for the Historic Royal Palaces in London.

### Prediction and prevention of miscarriage



**Prof Arri Coomarasamy**

*Director of Tommy's National Centre for Miscarriage Research, University of Birmingham*

Prof Arri Coomarasamy is the Director of Tommy's National Centre for Miscarriage

Research, with specialist teams in Birmingham, Coventry and London, putting patient priorities at the heart of efforts to tackle the widespread and devastating condition of early pregnancy loss. Professor Coomarasamy received his undergraduate medical education from the University of Birmingham, and completed his subspecialist training in reproductive medicine and surgery at Guy's Hospital, London. Today Professor Coomarasamy leads a research group at the forefront of early pregnancy care, reproductive medicine and global women's health. His portfolio includes numerous national and international multicentre randomised controlled trials, including the PROMISE trial (the role of progesterone



## UPDATE SESSION 1

in women with unexplained recurrent miscarriages), the TABLET Trial (levothyroxine therapy for women with thyroid antibodies), the PRISM Trial (progesterone therapy for women with early pregnancy bleeding), the RESPONSE Trial (G-CSF treatment for recurrent miscarriage), the AIMS trial (the effects of prophylactic antibiotics before miscarriage surgery in low-income countries) and the WHO CHAMPION trial (the role of carbetocin to prevent postpartum haemorrhage). He has published over 120 medical articles in high impact journals such as NEJM and the Lancet. Professor Coomarasamy takes particular pride in mentoring junior doctors and researchers, and several of his trainees have become outstanding clinicians and researchers.

### Screening for viruses and effect of positive results on fertility storage and treatment

Undertaking viral screening of fertility couples has become a mandated part of the work up for fertility couples having treatment in the UK. Interpretation can sometimes be confusing. Referral to specialised units is required for those deemed 'viral positive'. Some clinics can perform some services but not all (e.g. freezing). Fertility advice for discordant couples has also evolved as treatment improves. This talk aims

to help de-mystify this area of our field. The British Fertility Society & ACE have been working on a guideline on this topic for some time and the information given will form the basis of the guideline which is in line with advice from SaBTO (Safety of Blood Tissue and Organs). Topics covered include: current HFEA screening requirements, interpretation and second line tests, storage, quality and safety standards.

#### Andrew Drakeley

*Consultant Gynaecologist, Hewitt Fertility Centre, Liverpool*

Andrew Drakeley MD FRCOG is the Clinical Director at the Hewitt Fertility Centre, Liverpool Women's NHS Foundation Trust. He is very clinically involved and takes a lead on viral discordancy, fertility preservation, surrogacy and egg donation, as well as undertaking a lot of the associated surgery required for fertility couples. The Hewitt Fertility Centre is the regional referral centre for the treatment of viral discordant couples.



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### BFS update

Emerging evidence and new approaches to management

### Premature ovarian insufficiency

The guideline development group (GDG) formulated 99 recommendations answering 31 key questions on the diagnosis and treatment of women with POI.

It was produced by a multidisciplinary group of experts in the field, including a patient representative, using the methodology of the Manual for ESHRE Guideline Development, involving a systematic search of the literature, quality assessment of included papers up to September 2014 and consensus within the GDG on all recommendations. The European Society for Human Reproduction and Embryology (ESHRE) members and professional organisations were asked to review the draft guideline. There are 17 recommendations on diagnosis and assessment of POI and 46 recommendations on the different sequelae of POI and their consequences for monitoring and treatment. Furthermore, 24 recommendations were formulated on hormone replacement therapy, and two on alternative and complementary treatment. A chapter on puberty induction resulted in five recommendations. The main limitation of the guideline is that, due to the lack of data, many recommendations are based on expert opinion or indirect evidence from studies on postmenopausal women or women with Turner Syndrome. Despite that, the GDG is confident that this document will be able to guide best practice for healthcare professionals managing women with POI.



**Lisa Webber**

*Consultant Gynaecologist, University College London Hospitals*

Lisa Webber is a consultant gynaecologist and subspecialist in reproductive medicine at UCLH. She graduated from Oxford University Medical School and obtained her PhD at Imperial College London, studying the development of preantral follicles in the normal and polycystic ovary. She specialises in disorders of ovarian function, PCOS and premature ovarian insufficiency (POI).

Lisa has published in The Lancet, Journal of Clinical Endocrinology & Metabolism and the Journal of Endocrinology. She is a contributing author to the Oxford Textbook of Medicine, the Oxford Textbook of Endocrinology and Diabetes and co-author of a patient information book, Infertility: The Facts. She was co-chair of the ESHRE guideline on management of POI.

### Infertility, fertility treatment and risk of cancer

Cancer is a key outcome for human health. That is why it is nationally recorded, in most countries. (The late) Professor David Barker, referred to the concept of resilience, and a measure of that resilience is incidence of cancer in any given population. A healthier population be it, children or indeed women would have a lower rate of cancer than a less healthy population. So in the presentation I will present research about cancer risk in children conceived via ART and also the

preliminary results of the the study regarding women and their risk of cancers when treated with ART cycle (s) whether they conceived or not. Both these research topics were possible due to the skilled work of members of the audience. As well as collaborations including the HFEA.



**Prof Alistair Sutcliffe**

*Professor of General Paediatrics, Institute of Child Health, London*

Prof Alastair Sutcliffe is a children's doctor working at UCLH and GOSH in London. He is an internationally known expert on the health of IVF children and has published many articles on this topic over the past 25 years. He also has a broader range of research expertise and is presently working with a team of ten researchers on a variety of topics relevant to improving the lives of child patients and their parents. He has recently opened at the Portland Hospital for Women and Children a clinic specifically for IVF conceived children and their families, possibly unique. When not doing these things he has time for his own children, growing up, and obeying his Turkish Boss (and wife!)

### Preparing for gender transition

People who change their social gender role do not have a psychiatric illness; their body simply very profoundly doesn't match their sense of themselves. Gender identity clinics assess, advise and support people with gender dysphoria through the emotional, social, legal and occupational process of changing social gender role. Usually, there is high-dose cross-sex hormone treatment, bilateral mastectomy and male chest reconstruction, hysterectomy and salpingo-oophorectomy and often also speech therapy, vulvoplasty, cliteroplasty and vaginoplasty; phalloplasty is less common. Satisfaction with clinics is very high and with careful assessment outcomes, both medium and longer term, are excellent. Most patients positively thrive in their new social gender role, repaying all the costs of treatment through increased tax revenue. Gender dysphoria medicine intersects with fertility medicine at two very distinct points. The first is before any hormone treatment, when gamete storage is still possible; the second is later, when a settled life (and often relationship) in a new gender role might be completed by parenthood, sometimes deploying previously stored gametes.



**Dr James Barrett**

*Clinical Lead and Consultant in Adult Gender Dysphoria Medicine, Charing Cross Gender Identity Clinic*

Dr Barrett trained as a liaison psychiatrist but is now the Clinical Lead and Consultant in Adult Gender Dysphoria Medicine at the Charing Cross Gender Identity Clinic. In a thirty-year career he has assessed about ten thousand people with gender dysphoria and is the author of a textbook on the subject and is President of the British Association of Gender Identity Specialists. Outside of Gender Dysphoria Medicine his only connection with fertility is being father to three children.

## UPDATE SESSION 2

### ACE update Emerging technologies

#### Is spending the first few days of life in a test tube good for your health? The EpiHealth project

Clinical Assisted Reproduction Technology (ART) is now considered routine treatment with an estimated 6 million babies born globally since 1978. However, the pace of scientific and technological advances means that ART practitioners now have access to an increasing array of new and invasive technologies. In parallel with this, wider scientific and medical advances mean that we are becoming increasingly aware of the potential impact of ART on embryonic development, gene expression, epigenetics, and the long-term health of ART children according to the Developmental Origins of Health and Disease (DOHaD). I will describe our research on the impact of ART on the transcriptome of human preimplantation embryos and cells, and on the birthweight and early growth of children arising from ART treatment. This work is funded by the UK MRC and the EU FP7 Health programme as part of the EpiHealth consortium.



#### Prof Daniel Brison

*Honorary Professor of Clinical Embryology and Stem Cell Biology; Scientific Director of the Department of Reproductive Medicine; and Co-Director NW Embryonic Stem Cell Centre (NWESCC)*

Prof Daniel Brison is a professor of clinical embryology and stem cell biology at the University of Manchester and Scientific Director of the Department of Reproductive Medicine Central Manchester University Hospitals. He is a member of the HFEA's Scientific and Clinical Advances Advisory Committee, the UK Association of Clinical Embryologists Scientific Advisory Committee, Clinical Lead for the UK National MSC in Reproductive Sciences and an examiner for the Royal College of Pathologists. His clinical and research interests include: Improving the effectiveness and safety of clinical assisted reproductive technologies (ART), the characterisation of early human development at the molecular level the regulation of pluripotency in embryos and embryonic stem cells and the derivation and use of clinical grade embryonic stem cells for the treatment of disease, and the impact of environmental factors and ART on embryonic and child health.

#### Mechanisms of lineage specification in human embryos and stem cells

During early human development totipotent zygotes diverge into pluripotent embryonic cells, which form the fetus, and extra-embryonic cells, which contribute to the placenta and yolk sac. Understanding the molecular mechanisms that regulate pluripotency in human embryos and how is it disengaged during cellular differentiation is of fundamental biological importance. Using single-cell RNA-sequencing of human and mouse embryos we have elucidated conserved transcriptional programs along with those that are human-specific. By

modulating signaling pathways we discovered a requirement for TGF- $\beta$  signaling in the maintenance pluripotency in human embryos. By uncovering the molecular basis of these early cell lineage decisions we underscore their significant clinical implications for infertility, miscarriages, developmental disorders and therapeutic applications of stem cells.



#### Kathy Niakan

*Group Leader, Francis Crick Institute*

Kathy Niakan obtained a B.Sc. in Cell and Molecular Biology and a B.A. in English from University of Washington. She obtained her PhD at University of California, Los Angeles. She undertook postdoctoral training with Kevin Eggan at Harvard University. She was a Centre for Trophoblast Research Next Generation Research Fellow at University of Cambridge. She started her lab at the Francis Crick Institute (formerly the MRC's National Institute for Medical Research) in May 2013 to understand the mechanisms of lineage specification in human embryos and stem cells.

#### What can we learn from the embryo in its first 14 days?



#### Sanna Vuoristo

*Postdoctoral Scientist, University of Cambridge*

Sanna finished her PhD thesis in 2014 at the University of Helsinki on human pluripotent stem cells and the extracellular matrix protein Laminin-511. Afterwards, she joined the group of Professor Taneli Raivio, also at the University of Helsinki, to model Kallman syndrome using human pluripotent stem cells. Sanna joined Magdalena Zernicka-Goetz's group at Cambridge in 2015 to investigate pre- to post-implantation development in different mammalian model systems.

### SRF update Infectious threats to reproduction

#### Consequences of bluetongue and schmallenberg on ruminant reproduction

In recent years we have seen the global or regional emergence of many different and important viral diseases of humans and or livestock species. Several of these viruses can cross the placenta (including Schmallenberg virus, bluetongue virus and Zika virus), which, depending on the stage of development of the foetus, can cause abortion or resorption, or may lead to teratogenic affects particularly damaging the development of the central nervous system. Many of these viruses are transmitted primarily by insect vectors (including mosquitoes and biting midges), which have responded to climate change and increased global trade and travel, by expanding their global distribution and seasonal activity, explaining the increased risk (e.g. Aedes albopictus in southern Europe). However in order to survive through the colder winters at more northerly



latitudes, when adults of vector species are absent, some of these viruses can make use of alternative 'overwintering' mechanisms. For bluetongue virus (which can infect all ruminant species) vertical transmission in cattle or sheep can provide such an overwintering mechanism, leading to annual recrudescence of the disease in northern Europe. However the virus can also be detected in semen, suggesting long term infection of an immuno-privileged in the testes, with the possibility of damage to sperm production and potentially explaining long term persistence and re-emergence of individual or multiple virus strains, as seen for BTV-8, which re-emerged during 2015 in central France after an absence of 5 years.



### Prof Peter Mertens

*Professor of Virology University of Nottingham, The School of Veterinary Medicine and Science, University of Nottingham*

Prof Peter Mertens studied Virology at Warwick and Oxford Universities, followed by a post-doctoral fellowship at the University of Guelph in Canada. In 1981 he returned to The Pirbright Institute in the UK, leading the Vector-borne Viral Diseases Programme and the Arbovirus Molecular Research Group, carrying out research on bluetongue virus and the other orbiviruses (for over 35 years). His group developed diagnostic assays used to identify and track bluetongue outbreaks in Europe (including the UK), helping to eradicate the disease from the region in 2008-2009. Prof Mertens has over 240 scientific papers and has supervised over 20 Ph.D. students. He is Visiting Professor at the University of Glasgow; the University of Minas Gerais in Brazil; and LUVAS Veterinary University in Hisar, India. Prof Mertens is a Jenner Investigator (Oxford); Fellow of the Royal Society of Biology; a Fellow of the Linnaean Society (London); OIE Bluetongue expert; and a Fellow of the Higher Education Academy. Prof Mertens is currently working on next generation diagnostics and vaccines for bluetongue, African horse sickness viruses and other orbiviruses, as Chair of Virology at the School of Veterinary Medicine and Science, University of Nottingham.

## Pathogenesis of enzootic abortion and identification of immune correlates of protection

Ovine enzootic abortion (OEA) is the most common diagnosed cause of infectious abortion in sheep flocks in the UK. The causative agent is *Chlamydia abortus*, a zoonotic, obligate intracellular Gram-negative bacterium which is transmitted oronasally and poses a serious health threat to women who are exposed during pregnancy. Characteristic features of OEA are persistent, subclinical infection in non-pregnant sheep followed by abortion in final stages of gestation associated with severe placental inflammation. Protective immunity develops after abortion, such that repeat abortions are rare. Characterisation of this immunity is the key to developing a novel vaccine that is both safe and effective. We have analysed humoral and cellular recall immune responses in sheep experimentally infected prior to pregnancy and during pregnancy. We show that antibody and interferon-gamma can both be correlates of infection and protection depending on the stage of disease and discuss how this relates to vaccine development.



### Prof Gary Entrican

*Principal Research Scientist, The Moredun Foundation and Honorary Professor, University of Edinburgh and University of Glasgow*

Gary Entrican is a principal research scientist at the Moredun Research Institute, Edinburgh and is also Honorary Professor within the College of Medicine and Veterinary Medicine at University of Edinburgh. His research interests include the characterisation of immune responses to intracellular pathogens that cause reproductive failure in ruminants, with a particular focus on chlamydial infections. This includes disease pathogenesis studies and identification of immunological correlates of protection to underpin novel vaccine design. He has extended this work to include studies on host-pathogen interactions in human chlamydial infections. He is currently Chair of the International Union of Immunological Societies (IUIS) Veterinary Immunology Committee (VIC) and is a member of the Steering Committee of the BBSRC UK Veterinary Vaccinology Network.

## Role of chlamydial infection in early pregnancy failure

Genital *Chlamydia trachomatis* infection is the commonest bacterial sexually transmitted infection worldwide. Infection prevalence peaks in young women aged between 18-25 years. Infection in women has been associated with reproductive tract pathology, infertility, and adverse pregnancy outcomes including ectopic pregnancy and miscarriage. The underlying mechanisms of these associations are not completely understood. The aim of this lecture is to present emerging data from ex-vivo, in-vitro and mouse models to explain the link between chlamydial infection and ectopic pregnancy and miscarriage.



### Prof Andrew Horne

*Professor of Gynaecology and Reproductive Sciences and Honorary Consultant Gynaecologist, University of Edinburgh*

Andrew obtained an MB ChB from Edinburgh in 1994. In 1999, he obtained an MRC Clinical Training Fellowship to complete a PhD focused on the role of the endometrium in reproduction at Imperial College London. He completed his core training in Obstetrics and Gynaecology in Edinburgh (2002-2005) and was appointed Clinical Lecturer (2005-2009). As a lecturer, he developed research interests in Fallopian tube biology and ectopic pregnancy, and secured an MRC Clinician Scientist Fellowship (2009-2012). In 2014, he became Professor of Gynaecology and Reproductive Sciences. He is also clinical lead of the Edinburgh EXPPECT Centre for Pelvic Pain and Endometriosis.

## UPDATE SESSION 2

### Nursing update Reproductive endocrinology

#### New concepts in PCOS

Polycystic ovary syndrome (PCOS) is a far reaching condition with a number of reproductive and general health implications. The diagnosis of PCOS is made when two out of three criteria are met: Namely clinical or biochemical hyperandrogenism, menstrual cycle disturbance and/or polycystic ovaries on ultrasound, after investigations to exclude other causes of menstrual disturbance and androgen excess. There is significant heterogeneity of presentation, such that signs and symptoms manifest across a spectrum and their severity may vary and amplified by insulin resistance, which is promoted by obesity. There are also ethnic variations in expression of PCOS. PCOS may also be associated with an increased risk

of developing type 2 diabetes, the metabolic syndrome and endometrial cancer. The symptoms of PCOS may have a profound impact on psychological wellbeing. Obesity has a major impact on the expression of PCOS and the efficacy of the management of all aspects of the syndrome, in particular infertility. The management of anovulatory infertility involves lifestyle modification and therapies to induce ovulation, namely clomifene citrate, gonadotrophin therapy and laparoscopic ovarian diathermy. For those who do not wish to conceive the management of menstrual problems requires prevention of endometrial hyperplasia and adenocarcinoma and consideration of the long term metabolic risks.



#### Prof Adam Balen

*Leeds Centre for Reproductive Health and Chair, British Fertility Society*

Adam Balen is a full time National Health Service consultant at the Leeds Centre for Reproductive Medicine. His special interests include all aspects of PCOS, Assisted Conception, Paediatric & Adolescent Gynaecology and Disorders of Sexual Development. Adam is Chair of the British Fertility Society, past Chair of the ESHRE Special Interest Group in Reproductive Endocrinology, a member of the WHO Global Infertility Guidelines Committee and Chair of the WHO Expert Working Group on the management of PCOS. He is the author of 12 books and over 220 peer-reviewed papers. Books include Infertility in Practice (4th edition 2014) and Current Management of Polycystic Ovary Syndrome (2010). As Chair of the British Fertility Society, Adam has overseen the creation of two new national task forces: Fertility Preservation UK, to ensure nationwide provision for those who require fertility preservation and The Fertility Education Initiative, to improve the provision of education to young people about all aspects of reproductive health, including factors that may influence their future fertility.

Please look at [www.AdamBalen.com](http://www.AdamBalen.com) to read his blog and follow him on Twitter @BalenAdam.

#### Thyroid disease and reproductive problems

The thyroid gland is considered to be integral to healthy reproductive function. Controversy exists about 'sub-clinical hypothyroidism of fertility patient', its definition and management. The talk covers evidence behind current practice and highlights gaps in our understanding.

#### Dr Ephie Yasmin

*Consultant in Reproductive Medicine and Surgery, University College London Hospitals*

#### Pitfalls of ovarian reserve assessment

Functional ovarian reserve (FOR) assessment is a modern phenomenon with great potential use within reproductive medicine, but whose deployment has been undermined by technical problems and confused debate. The latter probably driven by the former. The two principal contenders for the marker of choice are anti-Mullerian hormone (AMH) and antral follicle count (AFC). Over the last decade the measurement of AMH has been effected using numerous assay formats, and although generally measuring the same molecule, differences in calibration and sensitivity and sample storage problems have led to confusion in results and interpretation. These uncertainties have been quantifiable, but have undoubtedly undermined confidence in the test. The measurement of AFC is undermined by technical issues such as variable ultrasound machine sensitivity, considerable inter-observer errors, and also patient biological circumstance, such as obesity. Since early 2015, AMH assays have been available on 2 automated platforms, with exceptionally low variability error credentials. Both assays use the same antibody combinations, and they provide virtually identical results. This means that the new tests show a degree of reliability only seen in batch assay assessments hitherto. The future is bright for AMH assessment of FOR, while the problems with AFC remain.



#### Prof Richard Fleming

*Honorary Professor of Reproductive Medicine (Retired), University of Glasgow*

Richard Fleming has worked as a scientist in research and clinical service in reproductive medicine for more than 30 years. His principal interest is control of human ovarian function, and he has contributed to a number of developments, including the first use of ultrasound of the ovary (1979), and also the use of GnRH-agonists to control pituitary activity during controlled ovarian stimulation (1982). Recent work has included exploration of AMH as the ideal marker of ovarian reserve prior to assisted reproduction.

### BFS update

General update session

### Environmental factors and infections that affect sperm quality



#### Prof Allan Pacey MBE

*Professor of Andrology, University of Sheffield*

Allan is Professor of Andrology at the University of Sheffield School of Medicine and Biomedical Science, Department of Oncology and Metabolism. He is also the Head of Andrology for Sheffield Teaching Hospitals. His research interests include understanding aspects of male infertility and this includes laboratory projects investigating the basic biology of human sperm to large epidemiological studies. He is currently the chairman of the Steering Group for the UK National External Quality Assurance Scheme for Andrology and the Editor in Chief of the BFS journal Human Fertility. He was until January 2015 the Chairman of the British Fertility Society and also served as BFS Secretary between 2005 - 2010. In addition to Science and Clinical Work, Allan is an accomplished broadcaster and has regularly appeared on the Today programme and Woman's Hour. Recent television programmes include Britain's Secret Code Breaker (2011), Donor Unknown (2011), The Great Sperm Race (2009), The Truth About Food (2007), Make me a Baby (2007) and Lab Rats (2004). In the 2016 New Year's Honors list, he was awarded an MBE for Services to Reproductive Medicine. You can follow his general musings about science, sperm, male fertility and the life of an academic at <http://www.twitter.com/allanpacey>. His University of Sheffield webpage is at <http://www.sheffield.ac.uk/oncology-metabolism/staff/pacey>.

### Use of SPRMs in fertility and gynaecology

Progesterone plays a pivotal role in endometrial physiology and reproductive function. Progesterone action is mediated through interaction with the progesterone receptor. Selective progesterone receptor modulators (SPRMs) are now a valuable treatment option for hormone dependent conditions (for example, uterine fibroids) which have a major impact on women's quality of life. SPRM compound class members include mifepristone, asoprisnil and ulipristal acetate (UPA). SPRMs markedly reduce heavy menstrual bleeding and reduce uterine and fibroid size. There is an important need for alternatives to surgical interventions for women with gynaecological complaints who desire to preserve their fertility. The efficiency of longer-term intermittent use of SPRMs as a medical management approach for symptomatic fibroids has now been reported. Much however remains to be determined regarding mechanisms of action of SPRMs and the curious histological features in the endometrium induced by SPRMs and described as, progesterone receptor modulator associated endometrial changes (PAEC). SPRM administration alters expression of endometrial sex steroid receptors and progesterone-regulated genes. The clinical potential for SPRMs in the context of fertility management when there are coincident gynaecological pathologies such as uterine fibroids, has not been fully explored.



#### Prof Hilary Critchley

*Professor of Reproductive Medicine, University of Edinburgh*

Hilary Critchley is Professor of Reproductive Medicine (University of Edinburgh) and Consultant Gynaecologist (Edinburgh Royal Infirmary). Her research programme focuses upon local uterine mechanisms involved in menstruation, addressing common processes in this pivotal reproductive event (injury and repair, and immune-endocrine interactions). Recent studies include development of models for studying menstruation and endometrial bleeding. Data from these studies have contributed to understanding the local endometrial response to withdrawal of progesterone, both physiological and pharmacological. This has informed potential development of novel treatment strategies for problematic uterine bleeding. Her expertise in endometrial biology and reproductive medicine has been nationally and internationally recognised (Fellowship of the Academy of Medical Sciences; 2009 and Fellowship of The Royal Society of Edinburgh; 2012).

### Better information = better care

The new HFEA website and Choose a Fertility Clinic function will provide a more rounded picture of clinic performance with an emphasis on the quality of care provided rather than just statistics. At the same time, new clearer information on treatment options, including so-called 'add-ons', will put patients in a stronger position to understand what might work for them. Come along to hear how the HFEA believes that better information can drive improvements in care.



#### Peter Thompson

*Chief Executive, Human Fertilisation & Embryology Authority*

Peter joined the HFEA in January 2009 as the Director of Strategy and Information and became its Chief Executive in April 2012. Before joining the HFEA Peter worked as a civil servant for a number of Government departments, including the Ministry of Justice and the Cabinet Office. Among a variety of roles, Peter was responsible for the Government's policy on the legal recognition of transsexual people, EU justice policy and the Prime Minister's programme of constitutional renewal. As Chief Executive, Peter is responsible for the overall performance of the HFEA. Peter believes that the HFEA should focus its work around encouraging high quality care and providing patients with the information they need to make effective choices. Peter is also a school governor in an inner city secondary in east London.

### ACE update

Pre-implantation genetic

### Innovations in PGD of single gene disorders: The karyomapping revolution

SNP genotyping and karyomapping is being used increasingly worldwide for linkage-based preimplantation genetic diagnosis (PGD) of single gene defects. The ability to genotype a universal set of hundreds of informative SNPs across each chromosome in a single, low cost test has significantly reduced



## UPDATE SESSION 3

the time and effort required to develop patient and disease specific tests. The use of these markers for high resolution detection of chromosome abnormalities including aneuploidy and structural chromosome imbalance in translocation carriers is also increasing. Unlike quantitative methods of copy number analysis, including array comparative genomic hybridisation (array CGH) and next generation sequencing (NGS), karyomapping identifies the parental origin of these abnormalities. This unique combination of features is providing new insights into the origins and mechanisms behind a range of chromosomal abnormalities in the preimplantation embryo.



### Prof Alan Handyside

*Consultant in Pre-implantation Genetics, The Bridge Centre and Visiting Professor, University of Leeds*

Prof Handysides' early research focussed on preimplantation development of the mouse embryo and involvement in the first attempts to isolate embryonic stem cells directly from mouse blastocysts with Prof Matt Kaufman and Sir Martin Evans (Nobel Laureate). He developed the first transgenic mouse knockout of the HPRT gene using embryonic stem cells as a model of the human X-linked inherited disease, Lesch-Nyhan SYndrome. Subsequently joined Prof Lord Robert Winston at Hammersmith Hospital, London and in 1990 achieved the first pregnancies worklife following the vitro fertilisation (IVF) and preimplantation genetic diagnosis (PGD) of inherited disease. First chairman of the European Society for Human Reproduction and Embryology (ESHRE) Special interest group in reproductive genetics and co-founder and first chairman of the ESHRE PGD Consortium. Currently a consultant in preimplantation genetics at the BRidge Centre, London. Principal Scientist, Illumina, Cambridge. He is Visiting Professor in the Faculty of Biological Sciences, University of Leeds, Leeds and Honorary Professor at the School of Biosciences, University of Kent in Canterbury, UK.

## PGS using next-generation methodologies: A review of the clinical evidence

Aneuploidy in embryos is now acknowledged as a commonly occurring phenomenon. This talk will discuss the latest findings of embryonic aneuploidy, its prevalence and complexity. The talk will then discuss how preimplantation genetic screening (PGS) is being used to select euploid embryos and the clinical impact of euploid embryo selection, where it will focus the latest clinical evidence from PGS studies and trials.



### Dr Tony Gordon

*Laboratory Director, Genesis Genetics*

Dr Gordon is a PhD molecular cytogeneticist with over 20yrs experience in molecular diagnostics. After working at the Institute of Cancer Research in the '90's he moved to a number of companies in the diagnostics field, firstly MWG Biotech then Tecan before joining BlueGnome in 2006. In 2008 Dr Gordon started the 24sure product line within BlueGnome, aiming to bring BlueGnome's copy number microarray expertise to pre-implantation genetic screening (PGS). The vast majority of global PGS is performed using 24sure/VeriSeq PGS and in

2012 BlueGnome was sold to Illumina. After briefly working for Illumina, in 2013 Dr Gordon joined Genesis Genetics, a leading global company for PGD and PGS where he was the Managing Director for the five Genesis Genetics USA laboratories, plus Laboratory Director for Genesis Genetics two UK laboratories. In 2015 Dr Gordon started the Genesis Serenity NIPT program. In April 2016 Genesis Genetics laboratories were sold to Cooper Surgical Industries (USA). Dr Gordon is currently the laboratory director for the Genesis Genetics UK labs and is leading the Cooper Genomics global business development (outside the US). Dr Gordon is also a UK State Registered Clinical scientist and is a Fellow of the Royal Society of Biology.

## Should all IVF patients undergo preconception 'carrier' screening?

### Alexander Bisignano

*CEO, Recombine*

### SRF update

*Influence of reproduction on lifetime health*

## One carbon metabolism: Linking nutritional biochemistry to epigenetic programming of long-term development

One-carbon (1C) metabolism consists of an integrated series of metabolic pathways that include the folate cycle and methionine remethylation and trans-sulfuration pathways. Most, but not all, 1C metabolic enzymes are expressed in somatic cells of the ovary, mammalian oocytes and in preimplantation embryos with subtle differences in expression existing between species. The metabolic implications of this, with regard to the provision of methyl donors, are not fully understood but mathematical models developed in house predict consequences for intra-cellular trans-methylation. These predicted effects are currently being tested experimentally both with ovarian somatic cells and zygotes cultured in vitro. However, we demonstrated previously in sheep that physiologically relevant reductions in the dietary supply of vitamin B12, folate and methionine around the time of conception can epigenetically modify DNA in their progeny and lead to sex-biased insulin resistant and hypertensive offspring. Epigenetic alterations to DNA methylation in genes involved in key pathways associated with insulin signalling and endoplasmic reticulum stress have also been confirmed in adult offspring. Furthermore, we've observed similar sex-biased effects in offspring of rats fed folate, choline and methionine deficient diets. Focus has now turned to consider the contribution of polymorphic variances in genes encoding 1C enzymes, where initial studies have reverted back to the outbred sheep as a model species. Preliminary findings from these investigations will be presented.



### Prof Kevin Sinclair

*Professor of Developmental Biology,  
University of Nottingham*

Prof Sinclair's research interests are on the effects of assisted reproduction and parental nutrition on metabolic programming during early mammalian development, where epigenetic outcomes are determined in embryonic cells and tissues, and long-term developmental consequences assessed in offspring. First to discover that developmental anomalies following mammalian embryo culture were due to errors in genomic imprinting (Nature Genetics, 27: 153-154). Similar phenomena have since been reported in human IVF pregnancies. First to demonstrate that reductions in folate and vitamin B12 in the diets of intending mothers (rat and sheep) lead to epigenetic modifications to DNA methylation and adult offspring with increased body fat and blood pressure, altered immune function and insulin resistance (showcased to the NICHD Advisory Council in Washington DC in January 2007; PNAS, 104: 19351-19356). First to report comprehensive assessments of metabolic, cardiovascular and musculoskeletal health in aged offspring cloned by somatic-cell nuclear transfer (Nature Communications, 7: 12359-12369).

### Testosterone and health in ageing men

In male hypogonadism, the testes are unable to produce physiological levels of testosterone (T) and to maintain normal spermatogenesis. Classical male hypogonadism starts before or at puberty and is caused by an intrinsic anatomic or genetic defect of the hypothalamic-pituitary-testicular (HPT) axis. Its prevalence is about 0.2% in the general population and it is both under-diagnosed and under-treated. The other type, adult-onset, or late-onset hypogonadism (LOH), is a more contentious diagnostic entity. It entails milder functional suppression of the HPT axis without anatomical or genetic defect, and it is usually associated with ageing, co-morbidities and/or obesity. The symptoms of LOH are diffuse and T is usually marginally below the reference range. It is less common than believed (and advertised); according to the European Male Ageing Study (EMAS) about 2% in men aged 40-79 years. About 75% of men diagnosed with LOH are over-weight or obesity, the rest 25% due to aging and/or comorbidities. There is no dispute about the high benefit-risk ratio of T replacement therapy in young hypogonadal males. In contrast, T therapy of LOH is surrounded by controversy, mainly because evidence based information about its benefits and risks is still missing. Because LOH is mostly caused by modifiable conditions (obesity and chronic diseases,) it is more logical to address them first before embarking on T replacement therapy with unknown benefits. A T treatment trial can be made if there are no contraindications (e.g. erythrocytosis, prostatic or cardiovascular diseases), but the uncertain benefits and potential risks of the treatment have to be explained to the patient.



### Prof Ilpo Huhtaniemi

*Professor of Reproductive Endocrinology,  
Imperial College London*

Ilpo Huhtaniemi is Professor Emeritus of Reproductive Endocrinology at Imperial College London. He received his MD and PhD at University of Helsinki, Finland. He has clinical specialty in chemical pathology. He held 1986-2002 the post of Professor and Chairman of Physiology at University of Turku, Finland and moved in 2002

to Imperial College London. His research interests include clinical and basic reproductive endocrinology, in particular gonadotrophin action and male reproductive endocrinology. His H factor is 74, and he has authored about 700 peer-reviewed research articles and reviews.

### Prenatal steroids programme metabolic dysfunction in sheep

Understanding how prenatal environments modify postnatal health potential is an essential component of ensuring extended healthy lives - as we live (and work) longer, our 'health-span' must extend congruently with lifespan. Fetal life is sensitive to the 'orchestrated' hormonal interactions driving development, growth and maturation, and perturbations of hormonal interactions may have with lifelong consequences. Endocrine 'disruption' due to steroidal excess, whether of maternal, fetal, or chemical origins, may underpin functional changes with immediate and/or long-term health effects likely consequences.

Ovine models have an enviable history in reproductive sciences, and have emerged again as a 'go to' model in terms of investigations into the origins, and developmental trajectory, of Polycystic Ovary syndrome (PCOS). Utilising both maternal and fetal steroid overexposure models, insights into how metabolism is coloured by prenatal steroid exposure, informative in terms of both PCOS, and in terms of environmental endocrine disruption have been made. Over the last decade or so, there have been a series of findings from different groups that highlight how insulin sensitivity, and more recently, insulin secretion, may be coloured permanently by the fetal steroidal environment, and this paper will discuss these and their potential human translation.



### Dr Mick Rae

*Edinburgh Napier University*

Mick Rae attended what was then Napier College to study for his undergraduate degree, during which his interest in reproduction developed. This was further developed by a PhD in the University of Edinburgh, and post-doctoral positions in the Universities of Kent and Edinburgh, and the James Hutton Institute in Aberdeen. Examining the life-long effects of nutrition during development on the reproductive system has led to a career focus on how the fetal environment impacts upon lifelong health. He is now a Reader in Reproductive Biology, and convener of research degrees, at what is now Edinburgh Napier University.

### Nursing update

#### Female reproductive organs

### Management of ovarian cysts in fertility patients

Ovarian cysts seen in fertility patients are mostly benign. These are either functional ovarian cysts or cystic ovarian tumors. The commonest cystic ovarian tumors are benign teratomas (dermoid cysts) and endometriosis cysts (endometriomas).

With advances in ultrasound technology and improved image quality, pattern recognition is used to differentiate the types

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ovarian cysts. Where features of potential malignancy are identified, specialist advice should be sought.

Large ovarian and para-ovarian cysts have the potential to cause ovarian accidents (torsion, rupture) which may require emergency surgery and potential ovarian tissue loss. When identified in the course of infertility investigations, patients should be counselled about benefits and risks of surgical and expectant management for an informed decision. Conservative laparoscopic approach is recommended to minimize ovarian tissue loss.

Non-ovarian adnexal cysts (hydrosalpinges, fimbrial cysts) are common and could easily be confused for ovarian cysts. These cysts have negative impact on fertility and should be managed appropriately.

Pituitary downregulation prior to ovarian stimulation is responsible for most functional cysts seen in IVF / ICSI. A good understanding of the pathophysiology and endocrine features is invaluable for their management.



**David Ogutu**

*Consultant Obstetrician and Gynaecologist, North Middlesex University Hospital and Fertility Specialist, Herts and Essex Fertility Centre (HEFC)*

David is a consultant gynaecologist Person Responsible to the HFEA at Herts and Essex fertility Centre. He graduated from medical school in 1999 and received specialist training in obstetrics & gynaecology at the Royal Free Hospital and North Middlesex University Hospital, followed by advanced training in assisted conception, reproductive endocrinology and minimal access surgery at King's College Hospital, London. David worked as a consultant at North Middlesex University Hospital until August 2016. His special interests include gynaecology ultrasound, minimal access surgery and reproductive care in alternative families (surrogacy, egg donation among others).

### Ultrasound screening prior to fertility treatment

Ultrasound is used on a day-to-day basis to assess subfertile women as part of their initial work up and/or prior to their treatment. This is done both to identify problems that may impact on natural fertility and to predict the response to treatment in an attempt to individualise that treatment and provide an estimation of and its' effectiveness and the chance of success. Numerous, healthy, asymptomatic subfertile women will be shown to have benign lesions following a routine ultrasound scan. A key question is what should we do when we find a benign lesion in a subfertile woman? Is it responsible for their struggles to conceive, will it affect the chance of treatment working, could it have a negative impact on pregnancy? These are just some of the questions patients understandably ask us. We should know the answers but despite numerous descriptive studies the exact impact fibroids, ovarian cysts, uterine anomalies, polyps, adenomyosis and other benign gynaecological conditions have on conception and reproductive outcome remains far from clear. Furthermore there are very few well-designed trials looking at interventions, medical or surgical, and so much of our advice and practice is based on evidence synthesis and expert opinion.



**Prof Nick Raine-Fenning**

*Clinical Associate Professor and Reader in Reproductive Medicine and Surgery, University of Nottingham*

Nick Raine-Fenning is a reader of Reproductive Medicine and Surgery at the University of Nottingham and a Consultant Gynaecologist at Nottingham University Hospitals' NHS Trust. Nick is also co-Medical Director and Research Lead for Nurture Fertility, part of The Fertility Partnership. Nick is an internationally recognised expert in 3D ultrasound and gynaecological imaging. He has given numerous invited talks, plenary sessions and workshops and published over 130 peer-reviewed papers, review articles, opinions and editorials. Nick serves on Council of the RCOG, is a clinician representative for the British Fertility Society, and Chair of ISUOG's Clinical Standards Committee and Patient Liaison Group.

### The uterus and the window of implantation



**Prof Siobhan Quenby**

*Director, Biomedical Research Unit in Reproductive Health, Professor of Obstetrics, University of Warwick and Honorary Consultant at University Hospital Coventry and Warwickshire NHS Trust*

Prof Siobhan Quenby is Director of the locally funded Biomedical Research Unit in Reproductive Health and Tommy's@UHCW part of the National Center for Miscarriage Research.

Siobhan is clinically active as part of the obstetric team. She runs recurrent miscarriage, implantation and preterm prevention clinics dedicated to the management of and research into recurrent pregnancy loss prevention.

Siobhan has over twenty years of experience in research into implantation and recurrent miscarriage and has published over 125 original articles and 22 chapters for academic books. Siobhan is co-ordinator of the ESHRE Special Interest Group in Early Pregnancy, a member of the executive committee of the Association of Early Pregnancy Units, chair of the RCOG early pregnancy clinical study group and a member of the MHRA -Expert advisory panel member for women's health. Siobhan's research is funded by Tommy's, NIHR, UHCW and other medical charities. Her work has received considerable media interest, including from national newspapers, BBC radio and TV, ITV and Channel 4 news. She is also a media spokesperson for the RCOG.



A new recombinant human follicle-stimulating hormone to

# Help her step forward on the fertility journey

Undergoing fertility treatment requires a combination of strength, flexibility and commitment. Ovaleap® (follitropin alfa) combines efficacy and tolerability to help support your patients as they pursue their goals.<sup>1</sup>

Ovaleap® is indicated in:

- Anovulation in women unresponsive to clomifene citrate<sup>2</sup>
- Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies<sup>2</sup>



Ovaleap® is suitable for use by patients in conjunction with the reusable Ovaleap Pen®.

CE 0120

TEVA

Women's Health

UK/WHC/16/0005  
Date of Preparation: January 2016

#### References:

1. Strowitzki T et al. *Reprod Biol Endocrinol* 2016;14(1):1
2. Ovaleap® Summary of Product Characteristics. Teva UK Limited

Please refer to the Summary of Product Characteristics (SmPC) for full details of Prescribing Information

**Presentation:** Ovaleap® (follitropin alfa) 300IU/0.5ml, 450IU/0.75ml, 900IU/1.5ml solution for injection. Each ml of the solution contains 600IU (equivalent to 44micrograms) follitropin alfa. Each 300IU/0.5ml cartridge contains 300IU (equivalent to 22micrograms) follitropin alfa in 0.5mL solution for injection. Each 450IU/0.75mL cartridge contains 450IU (equivalent to 33micrograms) follitropin alfa in 0.75mL solution for injection. Each 900IU/1.5mL cartridge contains 900IU (equivalent to 66micrograms) follitropin alfa in 1.5mL solution for injection.

**Indications:** In adult women: Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomifene citrate. Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer. Ovaleap in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and follicle stimulating hormone (FSH) deficiency. In adult men: Ovaleap is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.

**Dosage and administration:** Special requirements: Treatment with follitropin alfa should be initiated under the supervision of a physician experienced in the treatment of fertility disorders. Women with anovulation (including polycystic ovarian syndrome): Follitropin alfa may be given as a course of daily injections. In menstruating women, treatment should commence within the first 7 days of the menstrual cycle. A commonly used regimen commences at 75-150IU FSH daily and is increased preferably by 37.5 or 75IU at 7 or preferably 14 day intervals if necessary, to

obtain an adequate, but not excessive, response. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and/or oestrogen secretion. The maximal daily dose is usually not higher than 225IU FSH. If a patient fails to respond adequately after 4 weeks of treatment, that cycle should be abandoned and the patient should undergo further evaluation after which she may recommence treatment at a higher starting dose than in the abandoned cycle. Women undergoing ovarian stimulation for multiple follicular development prior to in vitro fertilisation or other ART: A commonly used regimen for superovulation involves the administration of 150-225IU of follitropin alfa daily, commencing on days 2 or 3 of the cycle. Treatment is continued until adequate follicular development has been achieved (as assessed by monitoring of serum oestrogen concentrations and/or ultrasound examination), with the dose adjusted according to the patient's response, to usually not higher than 450IU daily. In general, adequate follicular development is achieved on average by the tenth day of treatment (range 5 to 20 days). A single injection of 250micrograms r-hCG or 5,000IU up to 10,000IU hCG is administered 24-48 hours after the last follitropin alfa injection to induce final follicular maturation. Women with anovulation resulting from severe LH and FSH deficiency: In LH and FSH deficient women (hypogonadotropic hypogonadism), the objective of follitropin alfa therapy in association with lutropin alfa is to develop a single mature Graafian follicle from which the oocyte will be liberated after the administration of hCG. Follitropin alfa should be given as a course of daily injections simultaneously with lutropin alfa. Since these patients are amenorrhoeic and have low endogenous oestrogen secretion, treatment can commence at any time. A recommended regimen commences at 75IU of lutropin alfa daily with 75-150IU FSH. Treatment should be tailored to the individual patient's response as assessed by measuring follicle size by ultrasound and oestrogen response. Men with hypogonadotropic hypogonadism: Follitropin alfa should be given at a dose of 150IU three times a week, concomitantly

with hCG, for a minimum of 4 months. If, after this period, the patient has not responded, the combination treatment may be continued; current clinical experience indicates that treatment for at least 18 months may be necessary to achieve spermatogenesis. Method of administration: Ovaleap is intended for subcutaneous administration. The first injection of Ovaleap should be performed under direct medical supervision. Self-administration of Ovaleap should only be performed by patients who are well motivated, adequately trained and have access to expert advice. As the Ovaleap multidose cartridge is intended for several injections, clear instructions should be provided to patients to avoid misuse of the multidose presentation. The Ovaleap cartridge is designed for use in conjunction with the Ovaleap Pen only, which is available separately. Special populations: There is no relevant use of follitropin alfa in the elderly population. Safety and effectiveness of follitropin alfa in elderly patients has not been established. There is no relevant use of follitropin alfa in the paediatric population. Safety, efficacy and pharmacokinetics of follitropin alfa in patients with renal or hepatic impairment has not been established.

**Contraindications:** Hypersensitivity to the active substance follitropin alfa, FSH or to any of the excipients; tumours of the hypothalamus or pituitary gland; ovarian enlargement or ovarian cyst not due to polycystic ovarian syndrome; gynaecological haemorrhages of unknown aetiology; ovarian, uterine or mammary carcinoma. Ovaleap must not be used when an effective response cannot be obtained, such as: primary ovarian failure; malformations of sexual organs incompatible with pregnancy; fibroid tumours of the uterus incompatible with pregnancy; primary testicular insufficiency. **Precautions and warnings:** Follitropin alfa is a potent gonadotropic substance capable of causing mild to severe adverse reactions and should only be used by physicians who are thoroughly familiar with infertility problems and their management. In women, safe and effective use of follitropin alfa calls for monitoring of ovarian response with ultrasound, alone or preferably in



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follitropin alfa

combination with measurement of serum oestradiol levels on a regular basis. There may be a degree of interpatient variability in response to FSH administration, with a poor response to FSH in some patients and exaggerated response in others. The lowest effective dose in relation to the treatment objective should be used in both men and women. **Porphyria:** Patients with porphyria or a family history of porphyria should be closely monitored during treatment with follitropin alfa. Deterioration or a first appearance of this condition may require cessation of treatment. **Treatment in women:** Before starting treatment, the couple's infertility should be assessed as appropriate, and putative contraindications for pregnancy evaluated. In particular, patients should be evaluated for hypothyroidism, adrenocortical deficiency, hyperprolactinemia and appropriate specific treatment given. Patients undergoing stimulation of follicular growth, whether as treatment for anovulatory infertility or ART procedures, may experience ovarian enlargement or develop hyperstimulation. Adherence to recommended follitropin alfa dose and regimen of administration and careful monitoring of therapy will minimise the incidence of such events. For accurate interpretation of the indices of follicle development and maturation, the physician should be experienced in the interpretation of the relevant tests. **Ovarian Hyperstimulation Syndrome (OHSS):** A certain degree of ovarian enlargement is an expected effect of controlled ovarian stimulation. It is more commonly seen in women with polycystic ovarian syndrome and usually regresses without treatment. The following symptomatology may be observed in severe cases of OHSS: abdominal pain, abdominal distension, severe ovarian enlargement, weight gain, dyspnoea, oliguria and gastrointestinal symptoms including nausea, vomiting and diarrhoea. Adherence to recommended follitropin alfa dose and regimen of administration can minimise the risk of ovarian hyperstimulation. Monitoring of stimulation cycles by ultrasound scans as well as oestradiol measurements are recommended for the early identification of risk factors. Mild or moderate OHSS

usually resolves spontaneously. If severe OHSS occurs, it is recommended that gonadotropin treatment be stopped if still ongoing, and that the patient be hospitalised and appropriate therapy started. **Multiple pregnancy:** In patients undergoing ovulation induction, the incidence of multiple pregnancy is increased compared with natural conception. To minimise the risk of multiple pregnancy, careful monitoring of ovarian response is recommended. **Pregnancy loss:** The incidence of pregnancy loss by miscarriage or abortion is higher in patients undergoing stimulation of follicular growth for ovulation induction or ART than following natural conception. **Ectopic pregnancy:** Women with a history of tubal disease are at risk of ectopic pregnancy, whether the pregnancy is obtained by spontaneous conception or with fertility treatments. **Reproductive system neoplasms:** There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women who have undergone multiple treatment regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumours in infertile women. **Congenital malformation:** The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. **Thromboembolic events:** In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, treatment with gonadotropins may further increase the risk for aggravation or occurrence of such events. In these women, the benefits of gonadotropin administration needs to be weighed against the risks. **Treatment in men:** Elevated endogenous FSH levels are indicative of primary testicular failure. Such patients are unresponsive to follitropin alfa/hCG therapy. Follitropin alfa should not be used when an effective response cannot be obtained. Semen analysis is recommended 4 to 6 months after the beginning of treatment as part of the assessment of the response. **Interactions:** Concomitant use of follitropin alfa with other medicinal

products used to stimulate ovulation may potentiate the follicular response, whereas concurrent use of a GnRH agonist or antagonist to induce pituitary desensitisation may increase the dose of follitropin alfa needed to elicit an adequate ovarian response. **Pregnancy and lactation:** **Pregnancy:** There is no indication for use of Ovaleap during pregnancy. Data on a limited number of exposed pregnancies indicate no malformative or foeto/neonatal toxicity of follitropin alfa. No teratogenic effect has been observed in animal studies. In case of exposure during pregnancy, clinical data are not sufficient to exclude a teratogenic effect of follitropin alfa. **Breast-feeding:** Ovaleap is not indicated during breast-feeding. **Effects on ability to drive and use machines:** Ovaleap has no or negligible influence on the ability to drive and use machines. **Adverse reactions:** **Serious:** Hypersensitivity, anaphylactic reaction, thromboembolism, severe OHSS. **Very Common:** Headache, ovarian cysts, local injection site reactions. **Common:** Abdominal pain, acne, gynaecomastia, varicocele, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea, mild or moderate OHSS, weight gain. **Overdose:** The effects of an overdose of follitropin alfa are unknown. There is a possibility that OHSS may occur. **Price:** 300IU/0.5mL £75.20, 450IU/0.75mL £112.80, 900IU/1.5mL £225.60. **Legal category:** POM. **Marketing Authorisation Number:** EU/1/13/871/001\_3. **Marketing Authorisation Holder:** Teva B.V., Swensweg 5, 2031 GA Haarlem, The Netherlands. **Job Code:** UK/MED/15/0092. **Date of Preparation:** December 2015.

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Teva UK Limited on 0207 540 7117 or [medinfo@teva.uk.com](mailto:medinfo@teva.uk.com)



### Thursday 5 January

A1

#### Emerging strategies in ART

### A1.1 Multilocus genetic risk scores for poor ovarian response

**Lledo Belen<sup>1</sup>; Ortiz Jose A<sup>1</sup>; Morales Ruth<sup>1</sup>; Turienzo Azahara<sup>1</sup>; Llacer Joaquin<sup>2</sup>; Bernabeu Rafael<sup>2</sup>**

<sup>1</sup>Instituto Bernabeu Biotech; <sup>2</sup>Instituto Bernabeu, Spain

**Aims/objectives:** Infertility results from a complex interplay of genetic and environmental factors. Recent developments in genomics have progressed in the discovery of susceptibility genes and add expectations about opportunities of genetic profiling for personalising medicine. Personalised medicine requires a test that fairly accurately predicts the disease risk. The aim of this work was to investigate if the genetic profile IBGENFIV (FSHR, AR, POLG and IL11) could be used to identify poor ovarian response (POR) patients.

**Content:** Observational case-control study was performed. We included 39 patients in the POR group and 76 with normal ovarian reserve in the control group. SNPs were analysed by TaqMan allelic-discrimination assays (rs6166-FSHR; rs2307449-POLG and rs11668344-IL-11) and AR by fluorescent-PCR. We used logistic regression to develop a multi-locus genetic risk score. Statistical differences were reported for each polymorphism alone. With the combination of all the predictive performance of the genetic risk score for POR calculated by the AUC was 80%. Different risk cut-offs were used to distinguish between patients with high or low POR risk. A cut-off risk of 0.6 gives the best results.

**Relevance/impact:** Advance identification of patients who will elicit a poor response to standard treatment would be of great clinical advantages for such patients. IBGENFIV® genetic profile could help us to identify these patients and adjust the stimulation drugs prior the overtaken treatment.

**Outcomes:** The main outcomes were sensitivity and specificity of the test.

**Discussion:** Various predictive markers of ovarian response outcome have been proposed. Besides these parameters, genetic variability also seems to be an important factor. Polymorphisms tend to have weak individual effects but, in combination, they have stronger predictive value suggesting that polymorphisms may act cumulatively. The ability of this genetic profile to predict POR could help us to offer the best treatment to POR patients.



**Joaquin Llácer**

*Instituto Bernabeu Biotech, Spain*

Joaquin Llácer is currently Medical Codirector of the Reproductive Medicine Department at Instituto Bernabeu. He is also the Medical

Doctor by the University of Valencia School of Medicine and PhD by University Miguel Hernández, Elche, Spain. Joaquin is a specialist in Obstetrics and Gynaecology, working in Reproductive Medicine since 1995. He is a professor of the Reproductive Medicine Master, University of Alicante,

Spain and Professor of the Human Reproduction Master Complutense University (Madrid; Spain). Joaquin is an author of numerous articles for prestigious national and international journals in the field of Reproductive Medicine. He was awarded by ASRM, SEF and BFS. Joaquin is a frequent speaker at academic events dealing with the speciality. His main current main areas of research include:

- Ovarian stimulation in women with low ovarian response
- Genetic variations in poor responders [patients]
- Genetic polymorphisms and ovarian response

### A1.2 For women undergoing double embryo transfer on day five, the addition of a poor quality embryo may have a detrimental effect on assisted reproduction outcome

**Richardson Alison<sup>1</sup>; Davey Tracey<sup>2</sup>; Zujovic Lyndsey<sup>2</sup>; Hopkisson James<sup>2</sup>; Raine-Fenning Nick<sup>2</sup>**

<sup>1</sup>University of Nottingham/Nurture Fertility; <sup>2</sup>Nurture Fertility

**Aims:** To investigate whether the transfer of additional embryos always increases clinical pregnancy (CP) and live birth (LB) rates during double embryo transfer (DET) on day five, or whether, specifically, the addition of a poor quality embryo may be detrimental.

**Methods:** We undertook a retrospective review of day five embryo transfers between 01.06.09 and 31.12.13 at Nurture Fertility. Women aged  $\geq 36$  years undergoing single embryo transfer (SET) and all women undergoing DET were included. CP, LB and multiple pregnancy (MP) rates were correlated with the number and quality of embryos transferred. The Chi-square test was undertaken to determine if the differences observed between DET and SET of the highest quality embryo available were significant. Risk ratios were computed.

**Results:** There were 206 SETs and 593 DETs. Compared to SET of the highest quality embryo, there was: no significant increase in CP (RR=1.19, 95% CI 0.90-1.57,  $p=0.23$ ) or LB (RR=1.19, 95% CI 0.96-1.48,  $p=0.11$ ) rate following DET of two good quality embryos ( $n=221$ ); a significant decrease in CP rate (RR=0.73, 95% CI 0.57-0.94,  $p=0.01$ ) and a non-significant decrease in LB rate (RR=0.86, 95% CI 0.70-1.05,  $p=0.13$ ) following DET of one good and one poor quality embryo ( $n=167$ ); a significant increase in CP (RR=1.25, 95% CI 1.06-1.47,  $p<0.01$ ) and LB (RR=1.19, 95% CI 1.03-1.37,  $p=0.02$ ) rate following DET of two poor quality embryos ( $n=205$ ); and a significant increase in MP rate in all groups ( $p<0.01$ ).

**Conclusion:** The addition of a poor quality embryo to a good quality blastocyst during DET on day five appears to have a detrimental effect on outcome. Our results are limited but further work in the form of a prospective RCT is warranted. If confirmed, clinical application of our findings could significantly reduce the number of DETs performed (and therefore also MP rates), without compromising CP rates.



## SHORT PAPER SESSIONS



**Alison Richardson**

*University of Nottingham*

Alison Richardson is a specialty trainee in Obstetrics and Gynaecology. She has just returned to clinical training (ST6) at the Royal Derby Hospital after taking time out of programme to work as a clinical research fellow at Nurture Fertility in Nottingham. She is just finishing her PhD undertaken at the University of Nottingham under the supervision of Dr Nick Raine-Fenning and Professor Bruce Campbell. Her special interests include reproductive medicine and early pregnancy development.

### A1.3 A second injection of kisspeptin-54 safely improves oocyte maturation during in vitro fertilisation therapy in women at high risk of ovarian hyperstimulation syndrome

**Abbara Ali<sup>1</sup>; Clarke Sophie<sup>1</sup>; Islam Rumana<sup>2</sup>; Prague Julia<sup>1</sup>; Comminos Alexander<sup>1</sup>; Narayanaswamy Shakunthala<sup>1</sup>; Peters Deborah<sup>1</sup>; Roberts Rachel<sup>1</sup>; Izzy-Engbeaya Chioma<sup>1</sup>; Ratnasabapathy Rishika<sup>1</sup>; Nesbitt Alexander<sup>1</sup>; Vimalasvaran Sunitha<sup>1</sup>; Salim Rehan<sup>2</sup>; Lavery Stuart<sup>2</sup>; Bloom Stephen<sup>1</sup>; Huson Les<sup>1</sup>; Trew Geoffrey<sup>2</sup>; Dhillo Waljit<sup>1</sup>**

<sup>1</sup>Imperial College London; <sup>2</sup>Hammersmith Hospital

**Aims/objectives:** IVF is an effective therapy for infertility, but can result in the potentially life-threatening complication ovarian hyperstimulation syndrome (OHSS). We have previously reported that a single injection of kisspeptin results in an LH-surge of ~12-14hrs duration, sufficient to safely trigger oocyte maturation in women at high risk of OHSS. We investigated whether increasing the duration of LH-exposure by administering a second dose of kisspeptin could further optimise oocyte maturation.

**Content:** We conducted a phase 2 single-blinded randomised placebo-controlled trial of 62 women at high risk of OHSS. Following a standard recFSH/GnRH-antagonist IVF protocol, all patients received a subcutaneous injection of kisspeptin-54(9.6nmol/kg) 36hrs prior to oocyte retrieval. Patients were then randomised 1:1 to receive either a second dose of kisspeptin 10hrs later (D;Double), or saline placebo (S;Single). IVF physicians, embryologists and participants were blinded to the randomisation. Retrieved oocytes were assessed for maturation and fertilised by ICSI. Elective single embryo transfer(eSET) was carried out in all patients with at least one high quality blastocyst.

**Outcomes:**

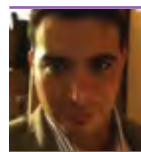
**Primary Outcome:** Proportion of patients achieving a satisfactory oocyte yield (% of mature oocytes retrieved from follicles  $\geq 14$ mm in diameter)  $\geq 60\%$ .

**Secondary Outcomes:** Implantation rate and occurrence of OHSS.

**Discussion:** A second injection of kisspeptin at 10hrs following the first induced a significant further mean fold-rise in LH-secretion at 4hrs (S:3.3, D:14.7;  $P < 0.0001$ ) and 10hrs (S:1.5, D:3.1;  $P = 0.0002$ ) thereafter when compared to pre-trigger

levels. The proportion of patients achieving a satisfactory oocyte yield was improved following two doses of kisspeptin (S:45%, D:71%; RD 25.8%, CI 2.1-49.5%). There was a trend towards a higher implantation rate following 2 doses of kisspeptin (S:23.3%; D:37.1%;  $P = 0.20$ ), but no difference in the frequency of OHSS.

**Relevance/impact:** Prolonging the duration of LH-exposure by administering a second dose of kisspeptin safely improves oocyte yield in women at high risk of developing OHSS undergoing IVF treatment.



**Ali Abbara**

*Imperial College London*

Dr Abbara is an academic clinical lecturer in Reproductive Endocrinology at Imperial College London. His research interests include the hormonal control of fertility disorders including hypothalamic amenorrhea, polycystic ovarian syndrome, and hyperprolactinaemia. In particular, his research has focused on the novel reproductive hormone kisspeptin which controls the release of GnRH from the hypothalamus and its role in IVF treatment.

### A1.4 Progesterone assay concentrations to guide whether to proceed to a fresh embryo transfer or to freeze all suitable embryos are insufficiently reliable

**Lyon Jennifer; Fairbairn Craig; Gaudoin Marco; Fleming Richard**  
*GCRM*

**Aims/objectives:** An early rise in progesterone concentration during ART stimulation is associated with asynchronicity between endometrial development and the subsequent embryo development, resulting in reduced implantation rates. It has been quoted that if the progesterone concentration is  $> 5$  nmol/L on day of trigger, it may be expedient to vitrify all suitable embryos (segmentation). This increases the risk of losing viable embryos. Furthermore, there are uncertainties about the accuracy of commercially available progesterone assays at low concentrations. We aimed to determine if commercially available progesterone assays can be used to guide a policy of fresh embryo transfer versus segmentation if the progesterone concentration is deemed to be too high.

**Content:** Objective multicentre comparative cohort study. Sixteen successive monthly distributions of 80 serum samples were sent to contributing laboratories running one of five different progesterone assay systems (Abbott Architect<sup>®</sup>, Beckman Coulter Access 2<sup>®</sup>, Roche Elecsys<sup>®</sup>, Siemens Centaur<sup>®</sup> and Siemens Immulite<sup>®</sup>) through the NEQAS quality control system. The mean and percentage coefficient of variation (%CV) of the progesterone concentrations (as published by UK NEQAS) were compared.

**Outcomes:** At a mid-luteal progesterone concentration of 40 nmol/L the mean %CV was 8%. As the progesterone concentration decreased, the %CV increased. At progesterone concentration of 7 nmol/L (i.e. peri-ovulatory levels in a normal menstrual cycle), the %CV was 14%, equating to a progesterone "result" of anything from 5 to 9 nmol/L (at  $\pm 2$ SDs).

## SHORT PAPER SESSIONS

VENUE PLAN

PROGRAMME

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INFORMATION

ABSTRACTS  
AND BIOGRAPHIES

POSTER  
PRESENTATIONS

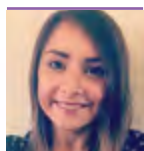
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Discussion: Commercially available progesterone assays show progressively greater inter-laboratory and inter-assay variability as progesterone concentrations decrease. This increased variability could result in inappropriate decisions when deciding to proceed with a fresh embryo transfer or to employ segmentation and should be taken in to consideration by ART clinics.



**Jennifer Lyon**

GCRM

Jennifer Lyon graduated from Glasgow Caledonian University in 2013 with a BSc (Hons) in Biomedical Science. Her undergraduate research project

included the use of colorimetric assays for assessing cell metabolic activity (MTT) and provided a background to essential molecular biology research. This experience provided the opportunity for a career within the biological field. She took on her first post at GCRM Ltd in 2015 as reproductive laboratory technologist in the biochemistry department and has been involved in various research projects within the clinic, most recently, the reliability of progesterone to guide clinical practice.

### A1.5 The clinical value of time-lapse as an efficacious embryo selection tool: A systematic literature review and meta-analysis of 45 studies involving 28876 embryos

**Yip Stephanie<sup>1</sup>; Hickman Cristina<sup>2</sup>; Lavery Stuart<sup>3</sup>**

<sup>1</sup>Imperial College; <sup>2</sup>Boston Place Clinic; <sup>3</sup>The Fertility Partnership

**Aim:** To identify, appraise and summarise available evidence regarding the efficacy of different types of morphokinetic parameters in predicting embryo implantation potential.

**Content:** PRISMA method was used to systematically identify, review and meta-analyse relevant publications reporting data applicable towards calculation of efficacy of embryo selection with regards to implantation potential. Data extracted were used to calculate diagnostic odds ratio(DOR:95% confidence interval) and categorised for meta-analysis.

**Relevance:** Armstrong et al (2015) concluded in a recent cochrane review of only four studies that there was insufficient evidence for a recommendation for a change of routine practice to be justified from conventional incubation to Time-lapse incubation. This review did not take into account a number of relevant studies towards this conclusion, or the wide variation in how the technology is used. Of the several morphokinetic embryo selection methods reported in the literature, it is unclear which are clinically relevant. Using a novel method of assessing embryo selection, this study compares the effectiveness of different reported methods in order to improve the practice of time-lapse based on efficacy.

**Outcomes:** 23 morphokinetic model and 22 single parameter studies were identified. Evidence for 5 selection methods supported their significant effectiveness at predicting implantation potential: t2(1.7:1.4-2.1), direct uneven cleavage (17.8:7.3-43.5), multinucleation (1.3:1.1-1.5), Messeguer model(1.5:1.2-1.7) and Eeva model (2.2:1.6-3.0). Evidence indicated using multiple parameters for selection was more effective than single parameters ( $p<0.001$ ). Parameters assessing late embryo development were more predictive than early development

( $p<0.001$ ). Time-lapse monitoring provided improved selection efficacy compared to morphology alone (1.5:1.4-1.7).

**Discussion:** Despite the reduced quality of evidence available in the literature, there is consistency between papers when assessing embryo selection potential using DOR. The findings from this study are in favour of clinical use of morphokinetics for embryo selection. Consistency between centres concerning the efficacy of methods demonstrated the extent of their predictive value.

**References:** Armstrong, S., Arroll, N., Cree, L.M., Jordan, V., Farquhar, C. (2015) Time-lapse systems for embryo incubation and assessment in assisted reproduction. Cochrane Database Syst Rev. 2015 Feb 27;(2)



**Stephanie Yip**

Imperial College London

Stephanie is a recent graduate from Imperial College London with a bachelor degree in Biomedical Science. Her BSc year specialised in reproductive and developmental sciences. Her work presented at the Fertility conference comprises her final year project, which she completed at Boston Place Clinic. Stephanie is now working in open access scientific publishing, as an editorial assistant with F1000Research.

### A1.6 Intralipid infusion does not result in improved live birth rates in women with recurrent implantation failure undergoing IVF treatment and is associated with an increased risk of congenital fetal malformations: A double blinded randomised controlled trial

**Gamaleldin Islam<sup>1</sup>; Awadallah Ahmed<sup>2</sup>; Akande Valentine<sup>3</sup>; Gomaa Mostafa F<sup>2</sup>**

<sup>1</sup>University of Bristol; <sup>2</sup>Ain Shams University; <sup>3</sup>Bristol Centre of Reproductive Medicine

**Aims/objectives:** To assess the effect of intralipid infusion on outcomes in women with unexplained Recurrent Implantation Failure (RIF) undergoing IVF treatment.

**Relevance:** High levels of serum natural killer (NK) cells are said to be associated with a reduction in the success of IVF treatment (1) and therefore recurrent implantation failure (2). In vitro studies suggest that intralipids are able to suppress NK cytotoxicity (3) and therefore potentially improve IVF outcomes.

**Design:** Women meeting the eligibility criteria undergoing treatment in a tertiary IVF centre between October 2012 and September 2014 were approached to enter a double blinded RCT. Women who had 3 or more failed IVF cycles with good quality embryos and who were under the age 37 years were identified as having RIF. Intralipid infusions were administered on the day of oocyte retrieval and repeated if pregnant on the day of a positive pregnancy test and a final dose 2-3 weeks later when attending for pregnancy scan.

**Outcomes:** One hundred patients with RIF were randomised to receive intralipid (n=50) or placebo (n=50). There were no

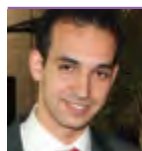
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differences in demographic or cycle characteristics in both groups, nor in clinical pregnancy rates 38 vs 26%, RR 1.46 (CI 0.81-2.64),  $P=0.207$  and live birth rates 28 vs 18%, RR 1.56 (CI 0.74-3.27),  $P=0.244$  in both groups. Two neonates (14%) in the intralipid group were found to have congenital "external ear" anomalies causing deafness and requiring corrective surgery while there were none in the control group.

**Discussion:** Our study found that intralipid infusions given to women with RIF did not improve IVF outcomes and worryingly demonstrated a serious adverse effect of potential deafness in offspring. In light of these unexpected findings, caution should be applied to its further use in women undergoing IVF treatment.

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### Islam Gamaleldin

*University of Bristol*

Islam Gamaleldin, MD, MSc, MRCOG, is an NIHR academic clinical lecturer in Bristol University. Dr Gamaleldin earned both his undergraduate degree, Masters degree and his medical degree from Ain Shams University, Cairo, Egypt. In 2009, he started his training in Obstetrics and Gynaecology at Ain Shams University Hospitals, Cairo, Egypt. He then joined Southmead Hospital, Bristol NHS Foundation Trust in 2013 to continue his training programme. His clinical interest is reproductive medicine, with particular interests in recurrent implantation failure and recurrent miscarriage.

A2

Sperm integrity and function

## A2.1 SRF/SRB Exchange paper - Cellular Samurais and Sperm: KATNAL2 is an essential regulator of microtubules in haploid male germ cells and Sertoli cells

**Dunleavy JM, O'Connor AE, Okuda H, Merriner DJ, Ahmad AAM, Jamsai D, Bergmann M, O'Bryan MK**  
*Monash University, Australia*

Spermatogenesis is characterised by several complex microtubule structures. As such, dysregulation of the microtubule-regulatory machinery is likely to be an important cause of male infertility. KATNB1 regulates the activity

of several microtubule-severing enzymes that are highly expressed in the testis. Previously, we have shown *Katnb1* loss-of-function causes male sterility, however, the target severing enzyme(s) of KATNB1 has not been identified. We sought to characterise the microtubule-severing related protein KATNAL2 in spermatogenesis and determine if it could mediate KATNB1 testis functions. Using both a *Katnal2* point-mutant and a KO mouse model we have confirmed KATNAL2 is essential for spermatogenesis. Both *Katnal2* full ablation and loss-of-function resulted in impaired spermatid remodelling and a complete retention of elongated spermatids. Our analysis showed the failure of sperm release was due to an absence of tubulobulbar complex and residual body formation. KATNAL2 loss also resulted in supernumerary centrioles in spermatids, an absence of axoneme generation, and sperm head shaping defects (teratospermia) as a result of manchette dysfunction and acrosome detachment. The subsequent generation of *Katnal2* germ cell-specific and *Katnal2* Sertoli cell-specific KO mice revealed KATNAL2 has distinct germ cell autonomous and Sertoli cell autonomous functions. Within germ cells, it is essential for spermatid remodelling, whereas tubulobulbar complex and residual body formation is driven by Sertoli cell KATNAL2. To ascertain if KATNAL2-KATNB1 microtubule-severing complexes form in the testis, proximity ligation and co-immunoprecipitation assays were performed. Consistent with phenocopying between *Katnal2* and *Katnb1* mouse models, KATNAL2-KATNB1 complexes were immunoprecipitated and localised to microtubule structures within spermatids. Collectively, this work demonstrates that KATNAL2, likely under KATNB1 regulation, has critical functions in regulating both germ cell and Sertoli cell microtubule dynamics during spermatogenesis.



### Jessica Dunleavy

*Monash University, Australia*

Jessica Dunleavy is a third year PhD student in the Male Infertility and Germ Cell Biology Laboratory at the Monash Biomedicine Discovery Institute, Monash University. She received her Bachelor of Science from the University of Otago in 2011. In 2012, she was awarded a University of Otago Scholarship in Science and completed a Post Graduate Diploma in Science with high distinction. Following this she was awarded an Australian Postgraduate Award in 2014 and relocated to Melbourne to undertake a PhD under the supervision of top sperm biologist Professor Moira O'Bryan. Her current research project utilises spermatogenesis as a model to reveal novel aspects of microtubule regulation. Her work has shown these previously overlooked processes are of critical relevance to male fertility and cognitive function. In 2016 she was awarded the Society for Reproductive Biology David Healy New Investigator Award for this research.



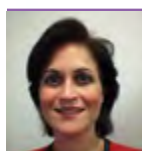
### A2.2 Does exposure to cisplatin impair survival and proliferation of spermatogonial stem cells in prepubertal mouse testis?

**Lopes Federica; Smart Ellie; Rice Siobhan; Anderson Richard; Mitchell Rod; Spears Norah**

*University of Edinburgh*

Preserving the future fertility of young boys undergoing cancer treatment requires understanding of the site and mechanism of damage on the testicular cell population of different chemotherapy drugs [1]. Cisplatin is an alkylating-like agent commonly used in the treatment of childhood cancer. Here we focused on how it affects spermatogonial germ cells, and their most important subpopulation, spermatogonial stem cells (SSCs). Testes from pnd 5 CD1 mice were fragmented and cultured in  $\alpha$ MEM+10% KSR (Day 1). On Day 2, tissues were exposed to 0.1  $\mu$ g/ml of cisplatin (in the low range of concentrations found in the serum of patients), followed by a further 2 days in drug-free medium, supplemented with BrdU on Day 4. Immunofluorescence for germ cells (MVH), spermatogonial stem cells (PLZF) and proliferation (BrdU) was performed on wax-embedded tissues. Cisplatin caused a 12-fold fall in germ cell numbers ( $p<0.001$ ). Similarly, an 11-fold reduction was observed in SSCs ( $p<0.01$ ). SSCs accounted for about 35% of the overall germ cell population in both control and treated groups thus there was no evidence for selective loss of this cell type. Cell proliferation within the seminiferous tubules decreased significantly after cisplatin exposure, with a 2-fold drop in BrdU-positive cells ( $p<0.001$ ). While around 30-40% of SSCs were actively dividing in control testis (PLZF-positive/BrdU-positive), very few proliferating SSCs were seen in cisplatin-treated testis (approx 90% fall). The future fertility of young cancer patients relies on the retention of healthy SSCs, since with their self-renewal ability, SSCs could potentially repopulate seminiferous tubules therefore restoring fertility. Results here indicate that even concentrations of cisplatin that are low relative to the clinically relevant range result in a marked loss of the important SSC population in this in vitro mouse model.

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**Federica Lopes**

*University of Edinburgh*

Dr Federica Lopes is Postdoctoral Research Fellow in reproductive physiology at the University of Edinburgh. Federica graduated in Veterinary Medicine and holds a PhD in the Physiology of Reproduction. In Professor Spears' lab, Federica investigates the effect that chemotherapeutic drugs have, both on male and female reproduction. Using mouse and human in vitro models, Federica and her colleagues have demonstrated that each class of drugs displays a drug-specific mechanism of action, with male and female gametes also showing different sensitivities to drug exposure. Understanding the type of damage produced by chemotherapy drugs on the gametes and their supportive cells is the first step towards the development of strategies for their protection.

### A2.3 Effect of electronic-cigarette flavourings on (I) human sperm motility, chromatin integrity in vitro and (II) mice testicular function in vivo

**O'Neill Helen<sup>1</sup>; Nutakor Alfred<sup>2</sup>; Magnus Emily<sup>1</sup>; Bracey Edward<sup>3</sup>; Williamson Elizabeth<sup>4</sup>; Harper Joyce<sup>1</sup>**

*<sup>1</sup>UCL; <sup>2</sup>Imperial; <sup>3</sup>Sainsbury Wellcome Centre for Neural Circuits and Behaviour – UCL; <sup>4</sup>UCLH*

A global survey showed that one out of eight smokers have attempted e-cigarettes, with most utilisation among young, non-minority individuals<sup>1</sup>. Presently, there are no regulations on the use of these products. While detailed studies have been carried out looking at the effects of conventional smoking on sperm quality, no studies to date, have looked at the effects of e-cigarettes on male fertility. In this study, multiple methods have been utilised to distinguish whether e-liquid exposure affects testes function and sperm quality. The ejaculates from 30 men were investigated post gradient centrifugation. Semen samples were split into three groups and cultured with two popular e-liquid flavourings (bubblegum and cinnamon), which have been shown to have a cytotoxic effect on certain cell types<sup>2</sup>, and propylene glycol (the base humectant found in all e-liquid solutions). Concentration, motility and progression were analysed and compared with control cultured sperm using Computer Assisted Sperm Analysis software. High concentrations of cinnamon and bubblegum were both statistically significant ( $P=<0.01$ ) for reducing motility, progression and concentration. In order to assess the effect of e-cigarette inhalation on testes morphology in vivo, adult male C57/BL/6 mice were exposed to e-liquid flavor vapour for four weeks in air controlled cages before undergoing gonadectomy ( $n=3$  for each exposure). The testes were sectioned, TUNEL stained and apoptosis measured using cell counts. Bubblegum flavouring yielded statistically significant results ( $P=<0.05$ ) as the most damaging exposure causing apoptosis in mouse testes. This study highlights the need for further studies into the harmful effects of electronic cigarettes and provides evidence for the restriction of unregulated flavourings in e-liquids as well as the need for effective regulation internationally.

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**Helen O'Neill**

*UCL*

Dr Helen O'Neill completed her BSc in Molecular Genetics at University College Cork in Ireland. She went on to do her MSc in Prenatal Genetics and Fetal Medicine at University College London. She did her PhD and postdoctoral research in the Department of Stem cell biology and developmental genetics in the laboratory of Professor Robin Lovell-Badge at the National Institute for Medical Research (now the Francis Crick Laboratories, Mill Hill). There, she researched the genes involved in sex determination, including genes crucial for the formation of

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ovaries. Helen is currently working with Professor Joyce Harper in the Embryology, IVF and Reproductive Genetics Group at the Institute for Women's Health in UCL. Here she has studies looking at the effects of different freezing parameters as well as the effects of e-cigarettes on sperm survival, DNA fragmentation and gonadal function. Helen is currently using CRISPR/Cas gene editing on sex chromosome mutations.

### A2.4 Sperm DNA quality in Hr6b (Ubiquitin-conjugating enzyme) knockout mice: DNA damage study

**Kumar Kishlay<sup>1</sup>; Lewis Sheena<sup>1</sup>; Enguita Andrea<sup>2</sup>; Mass Alex<sup>2</sup>; Baarends Willy<sup>2</sup>**

<sup>1</sup>Queen's University Belfast, United Kingdom; <sup>2</sup>Erasmus MC - Dept. of Reproduction and Development, Rotterdam, The Netherlands

**Introduction:** Male infertility in the Ube2b/Hr6b knockout mouse is associated with impaired spermatogenesis. The Hr6b gene is an ubiquitin-conjugating enzyme implicated in regulation of chromatin structure. Hence, infertility in Hr6b knockout males could be related to impaired sperm DNA compaction. In this study we compared DNA fragmentation in sperm from the caput and cauda epididymis from wild type (WT) (mHR6B+/+), heterozygous (HET) (mHR6B+/-) and knockout (KO) mice (mHR6B-/-).

**Method:** 26 mouse samples were included in the study (n=7 wild type, n=14 heterozygous, n=5 knockout). Adult males (11 weeks) were sacrificed and sperm collected from caput and cauda regions of the epididymis. A modified alkaline Comet assay was performed to analyse sperm DNA damage. ANOVA and Independent Samples Tests were used (p<0.05 was considered significant).

**Results:** DNA damage in sperm from the cauda epididymis was significantly more than in the corresponding caput epididymis of WT, HET and KO. The mean sperm DNA damage in caput region of WT, HET and KO was 6.96±2.5, 11.64±2.8 and 20.98±6.63 respectively. While the mean sperm DNA damage in cauda region of WT, HET and KO was 13.45±4.2, 15.95±4.0 and 26.91±5.3 respectively.

**Discussion/conclusion:** The marked deterioration in sperm DNA quality following transit through the epididymis was in accordance to previous reported studies in human where better DNA quality was reported in testicular sperm compared to ejaculate. This can be further explained by oxidative exposure to sperm while transition through epididymis. The increase in damage in the KO mice is consistent with previous observations that indicated aberrant chromatin structure and nuclear shape in Hr6b KO spermatids and sperm. The absence of HR6B is associated with greater sperm DNA damage possibly due to ineffective chromatin packaging.



**Sheena Lewis**

Queen's University Belfast

Professor Sheena Lewis' research has been focused on male infertility and in particular sperm DNA damage testing where her goal has been to identify causes of and treatments for male infertility by developing novel biomarkers. Professor Lewis is Chair of the British Andrology Society, national representative for UK

and past chair of the Andrology special interest group of the European Society of Human Reproduction and Embryology (ESHRE), past member of the executive committee of the British Fertility Society and a founder member and past Vice Chair of the Irish Fertility Society. She is on the ESHRE Task Force developing new guidelines for recurrent miscarriage. She also on the Editorial Boards of Reproductive BioMedicine Online, Systems Biology in Reproductive Medicine and Life in vitro (USA) and is associate editor of Basic & Clinical Andrology (BACA). She has published over 100 full papers and book chapters and numerous reviews. She is committed to raising ethical debate, particularly in issues relating to ART, within the medical and scientific communities. She also has a strong commitment to public engagement with research and regularly communicates her group's latest research findings through international TV, radio and online interviews.

### A2.5 DNA sequence analysis of the sperm HALO provides evidence for sequence-specific compartmentalisation of chromatin in the mature spermatozoon nucleus

**Binhuraihem Adel; Iles David; Miller David**  
University of Leeds

**Aims/objectives:** We recently reported evidence for nucleosome and developmental gene sequence enrichment in chromatin released by salt-extracted nuclei (1, 2). A large halo in the sperm chromatin dispersion test corresponds with low levels of DNA fragmentation and hence good sperm quality (3). We sought to link these findings by high resolution sequencing of halo DNA.

**Content:** Dispersion halos were generated by treating human sperm nuclei with NaCl solutions (4). Halos and remaining nucleoids were recovered and processed for DNA sequencing. The mapped read depth and coverage of genomic regions by sequences from halos and the 'insoluble' nucleoid core were compared. Halo and nucleoid DNAs were also fluorescently labelled for FISH on salt-extracted sperm nuclei. Protein extracts recovered during halo formation were analysed by immunoblotting.

**Relevance/impact:** Sperm DNA fragmentation is a major concern for embryo viability but nothing known about the fragmented sequences or how they may compromise the sperm.

**Outcomes:** Quantitative sequence analysis of low-salt halo fractions revealed a significant enrichment of genomic features, with CpG islands (>9x) > 5'UTRs (>4x) > CDS (>2x). Intronic sequences were depleted (x2). Enrichments were reduced in high salt halos but showed similar hierarchical arrangements. Genes enriched in the halo fraction are involved in development, cell-cell interactions and DNA replication. FISH-halo hybridisation signals localised almost exclusively to the periphery of sperm nuclei while nucleoid signals localised to both peripheral and internal regions. Histones, but not protamines, were detected in low-salt halo extracts.

**Discussion:** We propose a model where CpG islands and the 5'UTRs and exons of many developmentally important genes are located close to the nuclear envelope in sperm nuclei. Our data also suggest that at least some of this chromatin is nucleosomal. Sperm DNA fragmentation as assessed by halo

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formation could include vulnerable sequences essential for normal reproductive function.

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### Adel Binduraihem

*University of Leeds*

Adel Binduraihem is a hospital (KFSH&RC) sponsored PhD student (KFSH&RC; <http://www.kfshrc.edu.sa/en/home>) currently

completing his studies on the nucleohistone compartment in relation to sperm HALO formation, DNA damage and DNA sequence analysis under the supervision of Dr David Miller and Dr John Hunniss. As a PhD student, Adel has joined different meetings and conferences within and outside the UK to present the findings of his project.

Before coming to the University of Leeds, Adel undertook a Master's programme in prenatal diagnosis and fetal medicine at University College of London (UCL), Institute for Women's Health, London, UK, graduated in 2009. He has published his MSc project work at Reproductive BioMedicine Online 'Increased incidence of mosaicism detected by FISH in murine blastocyst cultured in vitro' (2011) 22, 621- 631.

## A2.6 As defined by sperm chromatin integrity, a complementary relationship exists between sperm affinity for hyaluronic acid and sedimentation properties in density gradients

**Torabi Forough; Binduraihem Adel; Miller David**  
*University of Leeds*

**Aims/objectives:** Hyaluronic acid (HA) binding is a promising method for selecting good quality sperm for ICSI [1, 2]. We investigated the ability of post-density gradient centrifuged (DGC) sperm to bind to solid-state HA-coated substrates in relation to the integrity of sperm chromatin and the effects of capacitation.

**Content of presentation:** Freshly ejaculated semen samples with normal parameters from volunteers were resolved into 90% (pelleted) and 45% (interface) fractions by DGC. Sperm from these fractions were assessed for HA binding. Chromatin integrity of sperm binding or not binding to a HA substrate was measured by acridine orange (DNA fragmentation) and

aniline blue staining (chromatin compaction). HA-binding was also microscopically investigated using specific (anti-CD44 monoclonal) and generic (TRITC-labelled HA) detection reagents. The effect of sperm capacitation on HA binding affinity was also assessed. All semi-quantitative data were analysed by Graphpad Prism.

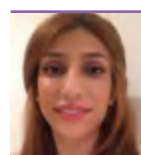
**Relevance/impact:** Most ART laboratories rely on DGC to purify sperm for IVF or ICSI. Linking this common procedure with newer methods of sperm selection would be highly relevant, particular if there are too few sperm for normal processing.

**Outcomes:** Sperm recovered from pellets had a greater affinity for HA than sperm recovered from the interfaces. Both pelleted and HA-binding sperm had lower levels of DNA fragmentation and higher levels of chromatin compaction than both 45% and non HA-binding sperm. Capacitation increased HA-binding capacities slightly. CD44 was located mainly on the acrosome and equatorial segment of pelleted sperm while HA-TRITC preferentially labelled the neck region. Observed changes in labelling patterns were related to capacitation-dependent increases in HA-binding.

**Discussion:** Sperm HA binding and centrifugation sedimentation properties correspond closely and reflects sperm chromatin integrity. Changes in HA-binding following capacitation may reflect associated changes in the expression of HA-binding proteins. These data support the argument for further research into HA-based sperm selection.

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### Forough Torabi

*University of Leeds*

Forough Torabi is a Marie-Curie Sklodowska sponsored PhD Student (Reprotrain; [http://cordis.europa.eu/result/rcn/149644\\_en.html](http://cordis.europa.eu/result/rcn/149644_en.html))

currently completing her studies on the dynamics of sperm maturation and capacitation in relation to hyaluronic acid binding under the supervision of Dr David Miller and Prof Paul Millner. As a Marie Curie research fellow: Forough has joined different meetings and congresses within and outside the UK to present the findings of her project. As well as working on her own project as a Marie Curie research fellow she did two months of training in proteomics and interpretation of proteomics data under Dr. Rafael Oliva at IDIBAPS (Barcelona, Spain, Jun-July 2015). Before coming to the University of Leeds, Forough undertook a master's programme in Biochemistry at the Islamic Azad University, Science and Research Branch, Tehran, Iran in collaboration with the Avicenna Research Institute, Tehran, Iran, graduating with distinction in 2011. She has presented aspects of her MSc project work at the Molecular Immunology and Immunogenetics Congress in April 2012, Antalya, Turkey and the seventh European Congress of Andrology (November 2012, Berlin, Germany).



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### A3 Social challenges of infertility

#### A3.1 Kisspeptin modulates sexual and emotional processing in men

**Comninou Alexander<sup>1</sup>; Wall Matthew<sup>2</sup>; Demetriou Lysia<sup>2</sup>; Shah Amar<sup>1</sup>; Clarke Sophie<sup>1</sup>; Narayanaswamy Shakunthala<sup>1</sup>; Nesbitt Alexander<sup>1</sup>; Izzi-Engbeaya Chioma<sup>1</sup>; Prague Julia<sup>1</sup>; Abbara Ali<sup>1</sup>; Ratnasabapathy Rishika<sup>1</sup>; Salem Victoria<sup>1</sup>; Nijher Gurjinder<sup>1</sup>; Jayasena Channa<sup>1</sup>; Tanner Mark<sup>2</sup>; Bassett Paul<sup>3</sup>; Mehta Amrish<sup>4</sup>; Rabiner Eugenii<sup>2</sup>; Hönigsperger Christoph<sup>5</sup>; Silva Meire<sup>6</sup>; Brandtzaeg Ole<sup>5</sup>; Lundanes Elsa<sup>5</sup>; Wilson Steven<sup>5</sup>; Bloom Stephen<sup>1</sup>; Dhillon Waljit<sup>1</sup>**

<sup>1</sup>Imperial College London; <sup>2</sup>Imanova Centre for Imaging Sciences; <sup>3</sup>Statsconsultancy Ltd; <sup>4</sup>Imperial College Healthcare NHS Trust; <sup>5</sup>University of Oslo; <sup>6</sup>University of Oslo, University of Sao Paulo

Kisspeptin is a crucial for reproduction, playing a critical role in the hypothalamus to activate GnRH neurons and downstream reproductive hormones. However, kisspeptin and its receptor are also expressed in other brain areas, yet little is known about their function here. The limbic system plays a key role in reproductive behaviours and has a high expression of kisspeptin receptors. We therefore hypothesised that kisspeptin administration may modulate limbic brain activity in humans. We mapped brain activity using fMRI in 29 heterosexual men (age 25.0±0.9y) using a randomised blinded two-way placebo-controlled protocol. We used validated sexual/couple-bonding/negative/neutral-themed images to stimulate limbic brain activity and determined if kisspeptin administration altered this response. Reproductive hormone and psychometric assessments were performed throughout. Kisspeptin administration increased circulating kisspeptin and LH, but not testosterone for the duration of the scans, as expected. fMRI analysis revealed that kisspeptin (vs. vehicle) markedly enhanced activation in key limbic structures on viewing sexual images including the amygdala and cingulate. Viewing non-sexual couple-bonding images resulted in increased activity in similar structures with the addition of the thalamus and globus pallidus, important reward regions. These modulations of limbic activity by kisspeptin correlated with psychometric measures including sexual aversion, mood, and reward. Kisspeptin did not affect limbic activity on viewing negative images, but did enhance activity in the medial frontal gyrus. Consistent with this, psychometric analysis demonstrated that kisspeptin reduced negative mood ( $p=0.031$ ). Collectively, these data provide the first evidence that kisspeptin modulates limbic brain activity in response to sexual and emotional stimuli, and influences mood in healthy men. This is the first report of a novel role for kisspeptin in the integration of sexual and emotional processing in humans. Therefore, these data have important implications for our understanding of reproductive biology, as well as the development of kisspeptin as a potential reproductive therapeutic.



**Waljit Dhillon**

*Imperial College London*

Waljit Dhillon is professor in endocrinology & metabolism and consultant endocrinologist at Imperial College London. He completed his medical training at St Bartholomew's Hospital Medical School, University of London which included an Intercalated BSc in Biochemistry (awarded First Class Honours). He completed

a PhD as a Wellcome Trust Clinical Training Fellow at Imperial College with Professor Sir Steve Bloom. He has published 145 papers, which have been cited 5331 times. He has recently been awarded a prestigious National Institute for Health Research (NIHR) Research Professorship.

#### A3.2 Addressing the needs of orthodox Jewish couples seeking fertility treatment

**Best Katie; Jewitt Sophie; McIntosh Rachel; Wass Catherine; Keenan Kirsten**

*Gateshead Fertility Unit*

**Objectives:** To report on our engagement with the large local community of Ultra-Orthodox Jews, in relation to providing infertility assessments and treatment, in line with their idiosyncratic religious needs. Our aim has been to better understand this, often isolated, community with a view to improving local access to fertility services, as well as communicating more appropriately and empathetically with the Jewish couples.

**Content:** Since 2015 our centre has liaised with the local Jewish community through their rabbis to better provide fertility investigations and treatments in line with Halachah Jewish law. Pertinent Halachah laws forbid extra-vaginal ejaculation and intercourse during and after menstruation ("Niddah"). This can be problematic when organising sperm samples and an emphasis on modesty can result in a sexual naivety in couples leading to further reproductive difficulties. The laws regarding Niddah can create Halachah-induced infertility for women with short ovulatory cycles. There is a cultural preference of some couples for additional "Rabbi- approved" witnessing for certain laboratory procedures, including insemination and cryopreservation.

**Relevance:** The local Orthodox Jewish community have historically not presented for fertility investigations at our hospital, choosing instead to travel a great distance to access services in London or Manchester. There have been barriers to communication and a lack understanding of the idiosyncratic requirements of their faith.

**Outcome:** The NHS has clear values about reducing inequalities in healthcare with respect to The Equality Act 2010. It is important for providers to work towards eliminating indirect discrimination that may disadvantage people with a shared characteristic, such as race or religious beliefs. By engaging with community leaders and adapting our protocols within our fertility unit, we were able to better serve our local community, including the large population of Halachah Jews.

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### Katie Best

*Gateshead Fertility Unit*

Katie is the Nurse Manager/Quality Manager at Gateshead Fertility Unit. She worked as a junior sister on a gynaecology ward before helping to establish an Early Pregnancy Assessment Unit. In 1997 Katie moved into the field of Assisted Reproduction and was part of the team that established Gateshead Fertility Unit. After a short break from Assisted Reproduction she returned back to the area in 2002. She feels very privileged to work within this specialised area. Katie is an active member of the Senior Infertility Nurses Group and has been the treasurer of the group since 2013. She feels it is very important to encourage nurses to develop through education and experience. Although she has chaired at a BFS meeting in January 2016 she has never presented at the meeting.

### A3.3 Does egg sharing, in which women donate half of their eggs reduce the chances of success compared to women having self-funded IVF/ICSI cycles?

**Bora Shabana; Abdalla Hossam; Parikh Jaya; Thum Meen Yau**

*Lister Fertility Clinic*

**Objectives:** To evaluate whether assisted conception treatment success rates are lower in egg-sharers (ES), due to halving the number of available eggs for treatment, compared to women having self-funded (SF) IVF/ICSI.

**Content of presentation:** Egg-sharing offers free standard IVF to women willing to share half of their eggs in order to assist a recipient woman, giving both women an opportunity to achieve pregnancy. This was a prospective study on women undergoing consecutive IVF/ICSI cycles through SF and ES at an IVF unit between January 2008 and January 2016. Criteria included women  $\geq 21$  and  $\leq 35$  years of age. ES were required to produce  $\geq 8$  eggs, of which half were donated. Outcomes were recorded and compared using cross tabulation t-test and ANOVA.

**Outcomes:** 4979 SF and 636 ES cycles were performed. There was no difference in the mean age (SF,32.3, ES,31.2). Average number of eggs collected in SF and ES cycles was 12.0 and 15.8 respectively ( $P>0.05$ ), of which half of ES eggs were retained for self-use. There was no significant difference in fertilisation-rate (SF,69.6%; ES,71.5%) or number of embryos transferred (SF,1.5; ES,1.6). SF cycles had a greater number of available embryos for transfer compared to ES cycle (6.6 and 4.6 respectively) but pregnancy rate (SF,58.6%; ES,63.1%), live birth rate (SF,44.4%; ES,49.8%) and miscarriage rates (SF,23.7%; ES,27.2%) were similar in both groups ( $P>0.05$ ). Women having SF cycles were more likely to have embryos available for cryopreservation compared to ES cycles (SF,30.8; ES,19.4%,  $P<0.05$ ). ES offers women needing assisted reproductive treatment an opportunity to achieve a pregnancy without it compromising their rate of success.

**Discussion:** We demonstrate that in appropriately selected ES, despite a lower number of eggs available, IVF/ICSI success rates are comparable to women having SF cycles. Women having SF cycles may have more embryos available for cryopreservation.



### Shabana Bora

*Lister Fertility Clinic*

Dr Bora is a consultant gynaecologist and fertility specialist and completed her postgraduate training specialising in obstetrics and gynaecology in North West London. She has experience in complex problems of early pregnancy has written several peer reviewed articles for medical journals and book chapters. She joined the Lister Fertility Clinic in 2012 initially as a research fellow, investigating women with recurrent miscarriage and problems related to reproductive immunology. She has a special interest in all aspects of assisted conception, endometriosis, general gynaecology and early pregnancy complications.

### A3.4 Fertility preservation for young persons undertaking gender reassignment; management considerations for the clinical embryologist

**Taylor, Charlotte<sup>1</sup>; Shaikly Valarie<sup>1</sup>; Blayney Martyn<sup>2</sup>**

*<sup>1</sup>Bourn Hall Clinic Colchester; <sup>2</sup>Bourn Hall Clinic Cambridge*

**Aims/objectives:** Young adults undergoing gender reassignment prior to hormonal or surgical treatment require multidisciplinary management including considerations regarding fertility preservation. The care pathway for such patients can be complex; in this study we review our experience to improve our service for this group of patients.

**Methodologies:** Transgender patient enquiries, gamete procurement and storage and treatment were evaluated retrospectively for the last 18 months. The findings were collated for review and inclusion in a specific patient pathway.

**Relevance/impact:** With an increase in this patient group the clinic has found the patient pathway challenging with a clear requirement for further information and education in order to meet the needs of transgender persons. The greatest challenge was identifying the correct terminology to use during communication including identifying the correct name or pronoun to use. Furthermore our patient information and worksheets frequently use pronouns which may lead to confusion or distress for these individuals during treatment.

**Discussion:** This patient group requires careful management and specific adaptations to our current cryopreservation pathway including: sensitive patient communication, appropriate consent forms and patient information. In addition, training is required for embryologists to equip them with knowledge and confidence required to provide the best patient care.

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**Charlotte Taylor**

*Bourn Hall Clinic*

Following a degree in Biological Sciences with Honours in Reproductive Biology at the University of Edinburgh, Charlotte developed a keen interest in human reproduction and infertility. Charlotte began her Embryology Training at Brentwood Fertility Clinic. In 2011 she moved to Bourn Hall Clinic and completed her ACE Certificate. She is currently working towards state registration.

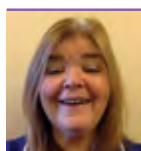
### A3.5 The role of a clinical nurse specialist in managing a successful donor sperm programme

**Kerslake Denise; Meaney Caitriona; Clarke Helen; Dark Suzanne; Cutting Rachel**

*Jessop Fertility, Sheffield Teaching Hospitals NHS Foundation Trust*

After the change of law in anonymity (2005), it became increasingly difficult to source UK sperm donors. Commercially driven overseas companies quickly marketed their services and it became an easy option to purchase and import sperm. Our centre felt this had ethical issues even if donors could be traced, for example how would a child feel knowing a donor was from overseas and how could we really ensure UK regulations are followed? The aim of this paper is to share good practice in how to set up and manage a programme for both sperm donors and recipients.

The decision to set up a donor programme was made in 2006. The programme was designed solely for in-house use with no aspirations for external sales. A CNS and embryologist were assigned for responsibility to ensure effective communication, fluidity and to ensure best patient care for both donors and recipients. Working closely together meant patients could be advised and kept informed on availability of in house donors. The pathways for both donation and treatment were agreed and linked closely with the counselling service. The embryologist took responsibility for progressing donation enquiries and the CNS responsibility for treatment. Having dedicated staff has meant that issues such as the legal parenthood forms were successfully managed. 28 donors have been successfully recruited and are currently available to our patients. In 2014 and 2015 the centre has seen a twofold rise in donor insemination; 160 patients were treated with a clinical pregnancy rate of 21.9% per IUI insemination. The cumulative pregnancy rate was 44.8% with the average number of cycles to achieve pregnancy being 1.9% + 0.99. Whilst establishing the programme some patients chose to purchase overseas sperm, we are pleased with the progress of our programme and are now able to offer the majority of our patients.



**Denise Kerslake**

*Jessop Fertility, Sheffield Teaching Hospitals NHS Foundation Trust*

Denise has worked at Jessop Fertility, as a nurse, since it opened in 2001. She obtained her certificate in infertility ultrasound in 2009, and has recently

undertaken her embryo transfer training. After the change in anonymity and the decision for Jessop Fertility to set up its own sperm bank Denise took the lead to provide the essential ongoing support for patients needing donor sperm. Denise has been instrumental in continuing to develop the service. Her role now involves helping patients access treatment with donor sperm, including finding the most suitable donor to meet their requirements. She provides information, support, counselling and advice throughout the patients treatment journey and ensures all regulatory requirements are met.

### A3.6 Surrogacy - why, where and how? A study of cycles conducted between 2012 and 2015

**Richardson Lucy; Templeman Sarah; Evans Debbie; Ogutu David; Ah-Moye Michael**

*Herts and Essex Fertility Centre*

The use of a surrogate within assisted conception affords the opportunity for parenthood for couples where this would otherwise not be possible. In some arrangements, intended parents (IPs) will use their own gametes whereas in others, an oocyte donor will also be required, adding a further level of complexity to this advanced form of assisted conception. Here, we present data from 53 surrogacy cycles, comparing and contrasting different methodologies employed within their management. We examined the demographics of IPs undertaking assisted conception using a surrogate and found an equal proportion of heterosexual and same sex male couples (52.8% compared to 47.2%). Of the heterosexual couples, the most common reason for seeking surrogacy was Mayer Rokitansky Küster Hauser syndrome (MRKH, 26%), followed by multiple failed attempts with own embryo transfer (17%). Only 36% of IPs and 32% of surrogates resided in the clinic's local patient catchment area, demonstrating that both intended parents and surrogates will travel for this specialist service. Surrogacy cycles can either be performed with an egg collection in conjunction with fresh embryo transfer or an egg collection and 'freeze-all' cycle. We compared both these strategies and found no difference in clinical pregnancy rates (CPR) (46.6% with fresh ET compared to 42.8% with transfer following freeze all at the 2PN stage), demonstrating that clinical pregnancy rates are not compromised if all embryos are frozen and replaced on a subsequent cycle. Furthermore, similar rates of successful cycles were achieved using own oocytes (40% CPR) and donated oocytes (44.7% CPR). These data support that a successful surrogacy cycle is achievable in different ways. It is therefore important that both IPs and clinics are flexible in their approach to surrogacy in order to achieve the desired outcome.



**Lucy Richardson**

*Herts and Essex Fertility Centre*

Dr Lucy Richardson is a senior clinical embryologist with over fourteen years' experience in both research and clinical embryology. She graduated with a First Class Honours degree in Anatomy and Developmental Biology from University College London before undertaking her PhD in Embryology at The University of Cambridge under the guidance of Dr Magdalena Zernicka-Goetz, where her research into embryonic axis formation identified a novel signalling centre responsible for



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anterior-posterior patterning in the mammalian embryo. Lucy is a highly skilled embryologist who prides herself on delivering the highest level of individualised patient care. She has held her current position at Herts and Essex Fertility Centre for over three years and has been integral to the development of new clinical and laboratory services, quality and laboratory, management. Lucy is Surrogacy Coordinator for the laboratory, working closely with the Surrogacy Nurse Manager to plan and oversee all surrogacy treatments cycles performed at the Unit.

### A4

#### Predicting embryo growth and development

#### A4.1 Blastocyst contraction pattern as a potential predictor of embryo chromosomal content

**Vinals Xavier; Doshi Alpesh; Loutradi Kalliopi; Cawood Suzanne; Mania Anastasia; Wigley Victoria; Gaunt Matthew; Heath Carleen; Gotts Sarah; Odia Rabi; Sowry Blair; Seshadri Srividya; Serhal Paul**  
*The Centre for Reproductive & Genetic Health*

**Aim:** Time-Lapse Monitoring (TLM) together with next-generation sequencing (NGS) have been consolidated as robust techniques for selecting the embryos with the potential to result in a healthy pregnancy. Nowadays, many selection parameters for embryonic competence based on TLM have emerged to refine this selection process. This study is aimed at investigating embryo contraction behaviour and its predictive value on embryo chromosomal content.

**Content of presentation:** 84 good quality blastocysts generated after ICSI or IMSI, derived from 35 patients (mean age 38.6 (SD 3.2) years), were included in the study. Two different outcomes were considered after NGS testing (Normal and Abnormal) in this retrospective study of TLM embryos after day 5/6 blastocyst biopsy. Different morphokinetic parameters were assessed together with some contraction pattern variables in the different groups.

**Relevance:** An understanding of blastocyst contraction pattern and its predictive value of chromosomal content.

**Outcomes:** A total of 65/84 (77.4%) blastocysts were proven to be chromosomally abnormal (not mosaic) while 19/84 were chromosomally normal embryos (22.6%). Presence of contractions was significantly greater in normal (90%) compared to those with an abnormal (35%) genetic outcome ( $p < 0.001$ ). Univariable logistic regression analyses showed significance in time of first contraction (Tc1), surface loss in first contraction (loss1), time blastocyst formation (tB) and total contractions (TC) at the 5% level between both groups. Followed by a multivariable logistic regression analysis only tc1 and loss1 showed significance at the 5% level. TC was not found to be significant related to genetic outcome and was confounded by tB.

**Discussion:** Our data suggests that a unit increase of time of Tc1 and loss1 reduces the odds of a Normal genetic result by about 8% and 9%, respectively. Therefore we suggest that contraction pattern has a predictive value, but more data is needed.

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#### Xavier Vinals

*The Centre for Reproductive & Genetic Health*

Xavier Vinals joined The Centre for Reproductive and Genetic Health as an embryologist in October 2015. His background is in Biomedical Sciences followed by an MSc in Reproductive Biology and Cytogenetics at the Autonomous University of Barcelona. His masters degree dissertation 'Clinical application of morphokinetic parameters to select embryos with better implantation possibilities' triggered his interest in embryo development and preimplantation genetic techniques. Together with his laboratory based embryology, he works in different areas of research with the aim of providing a better understanding of IVF techniques.

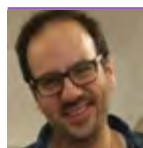
#### A4.2 The developmental potential of mosaic embryos

**Ifarawati Samer<sup>1</sup>; Kubikova Nada<sup>1</sup>; Simpkins Megan<sup>1</sup>; Spath Katharina<sup>2</sup>; Wells Dagan<sup>2</sup>; Fragouli Elpida<sup>1</sup>**  
*<sup>1</sup>Reprogenetics UK; <sup>2</sup>University of Oxford*

The fate of mosaic embryos is unclear and there is uncertainty about how to deal with such embryos clinically. NGS is increasingly being used for the purposes of (PGS). In addition to lowering PGS cost, NGS is both more powerful and more sensitive compared to other comprehensive chromosome screening methods. The aim of this study is to assess different types of chromosome errors as well as the rate of mosaicism in blastocysts examined for PGS and determine the developmental potential of such embryos. NGS was used to examine 848 blastocysts generated by 138 couples (average female age of 38.7 years). These couples were referred by 7 IVF clinics. A retrospective review was done of several hundred microarray-CGH results from blastocysts transferred to the uterus following PGS, and identified 44 with possible mosaicism. Biopsy samples from these embryos were re-assessed via NGS. Chromosome abnormalities were observed in 73% of the TE samples. The total mosaicism rate was 49%, and was similar in blastocysts generated by younger and older women (48% vs. 45% respectively). Of all examined blastocysts, 20% consisted of mosaic errors only, while 28% had abnormalities affecting the entire TE sample (possible meiotic origin), and 29% had a combination of mosaic and meiotic anomalies. We did not see any influence of the PGS indication, or the biopsy day (day-5 vs day-6) on the mosaicism rate. We did, however, observe that some IVF clinics tended to generate more mosaic embryos, compared to others. NGS has the ability to detect mosaic

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abnormalities which difficult or impossible to identify using other comprehensive chromosome screening methods such as aCGH or real-time PCR. The total mosaicism rate was determined to be 49% and was independent of female age, PGS indication, or biopsy day. We observed, however, an effect of the referring IVF clinic.



### **Samer Alfarawati**

*Reprogenetics UK*

After obtaining his BSc in Pharmacy from Damascus University, Syria in 2005 and his Master's degree in Prenatal Genetics and Fetal Medicine at University College London, London in 2007, Samer Alfarawati completed his DPhil degree from the University of Oxford in 2013. Dr Samer Alfarawati works at Reprogenetics UK, a Cooper Surgical company, as a laboratory manager and senior cytogeneticist where he works on preimplantation genetic testing in all its aspects. Samer has special interest in studying the origin of chromosome abnormalities in human preimplantation embryos.

### **A4.3 Comparing euploidy rates of blastocysts cultured in the embryoScope to conventional incubators**

**Gupta Reena; Theodorou Efstathios; Page Alex; Campbell Alison; Smith Rob**

*CARE Fertility*

**Study objective:** To identify whether there is any difference in euploidy rate between blastocysts cultured in conventional incubators or the EmbryoScope time-lapse incubator.

**Study design/method:** Retrospective multicentre analysis of euploidy rates comparing incubator type between January and December 2015. Culture media used and laboratory practice was, otherwise the same. 836 blastocysts from 442 patients were included in the analysis following PGS using array-comparative genome hybridisation (aCGH) or next generation sequencing (NGS). Blastocyst euploidy rates were compared between EmbryoScope and conventional incubators. Statistical analysis was conducted by Fishers Exact Test, considering  $p < 0.05$  significant.

**Results:** In the standard incubator group, 386 blastocysts were biopsied and analysed. Overall euploidy rate was 27.98% ( $n = 108$ ), aneuploidy rate was 70.98% ( $n = 274$ ), no result rate was 1.04% ( $n = 4$ ). In the EmbryoScope group, 450 blastocysts were biopsied and analysed. Euploidy rate was 21.78% ( $n = 98$ ) aneuploidy rate was 70.22% ( $n = 316$ ), no result rate was 8.22% ( $n = 37$ ). The euploidy rate was further analysed across five age groups and the results demonstrated no significant difference between the incubator types. The  $p$  values for each of the groups were as follows: ( $< 35$ :  $p = 0.501$ ,  $35-37$ :  $p = 0.352$ ,  $38-39$ :  $p = 0.061$ ,  $40-42$ :  $p = 0.543$  and  $> 43$ :  $p = 0.633$ ).

**Conclusion:** This was a multicentre study where incubator choice was dependant on local clinic practice which may influence results. In this study, incubation type, interrupted (standard) or continuous (EmbryoScope), was not associated with euploidy rate, which is more likely dependent on patient age, genetics or other intrinsic factors within the embryo, and not the culture environment.



### **Reena Gupta**

*CARE Fertility*

Upon finishing her Masters in Clinical Embryology from the University of Leeds, Reena began her career in embryology at CRM London as a trainee in 2010. Here, she gained all the essential laboratory skills and personal qualities needed to qualify as an Embryologist through the ACE Certificate training programme. Since completing her training in 2012, she has further developed her technical skills in vitrification and ICSI. She has been involved in many changes in laboratory protocols under the new ownership of CARE Fertility from 2013 onwards. Reena has recently registered with the Health and Care Professions Council and continues to gain further experience in a variety of laboratory procedures including embryo biopsy for preimplantation genetic screening.

### **A4.4 Impact of double cryopreservation and biopsy on PGD cycle outcome**

**Dajani Yaser; Semple Maxine; Khalaf Yacoub; Bolton Virginia**

*Assisted Conception Unit, Guy's Hospital*

**Objective:** To assess PGD treatment outcome after double-cryopreservation.

**Content:** Retrospective analysis of PGD cycles (2012-2014) in which embryos were frozen on day 1 (D1; 2PN), then thawed and biopsied (D3 or D5/6) for batched genetic testing to increase service efficiency. D3 biopsies were followed by fresh D5 embryo transfer and vitrification of supernumerary unaffected blastocysts; D5/6 biopsies were followed by vitrification of all biopsied blastocysts whilst awaiting results of genetic tests, and subsequent frozen embryo transfer. **Materials and Methods:** Slow freezing and thawing of 2PN embryos used SAGE reagents (Origio, UK); the zona pellucida was breached using acid Tyrode's solution or laser on D3; blastomere or trophectoderm biopsy was carried out on D3 or D5/6 respectively, and for the latter, laser was used to excise trophectoderm cells; blastocyst vitrification and warming used Cryotop/Kitazato reagents.

**Outcomes:** A total of 218 2PN embryos were frozen and thawed in 19 treatment cycles (19 patients); 175 (80%) survived thawing, 137 (62%) were biopsied (125 on D3; 12 on D5/6). Blastocysts were vitrified (total 38 (17%); 26 after D3 biopsy, and 12 after D5/6 biopsy). Following D3 biopsy, 20 "fresh" (once-cryopreserved) embryos were transferred in 16 cycles, resulting in 8 live births (40% per embryo). Of the twice-cryopreserved embryos, 14 have been warmed (11 from D3, and 3 from D5/6 biopsy); all survived and were transferred in 11 frozen embryo transfer cycles, leading to 8 live births (57% per embryo). Statistical analysis, using Fisher's exact test shows no significant difference between live birth rate for the once- and twice-cryopreserved embryos ( $p < 0.05$ ).

**Discussion:** This is the first report of PGD cycle outcomes following slow freezing on D1, thawing, biopsy (D3 or D5/6), and vitrification/warming/transfer of biopsied blastocysts. The findings support others showing that double-cryopreservation of embryos +/- biopsy does not appear to compromise embryo implantation potential.



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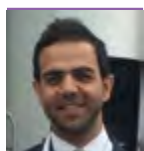
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### Yaser Dajani

*Assisted Conception Unit Guy's Hospital*

Yaser has worked as a clinical embryologist for more than 10 years. He started his career in Jordan at Farah Hospital in 2004, and then moved to the UK in 2008 to complete his MSc in stem cells and regenerative medicine at Sheffield University. Since 2012, he has been registered as a clinical scientist with the HCPC, and is currently working at Guy's Hospital as a senior clinical embryologist; where he has been actively involved in establishing the successful Trophectoderm biopsy and vitrification programme for PGD. Yaser is now the co-ordinator for the microTESE programme, and also he aids in teaching and training overseas students in assisted reproductive techniques.

## A4.5 First clinical application of a novel ultra-rapid comprehensive chromosome screening technique

**Spath Katharina<sup>1</sup>; Kubikova Nada<sup>1</sup>; Alfarawati Samer<sup>2</sup>; Whitney Emma<sup>3</sup>; Vaid Mita<sup>3</sup>; Rozis George<sup>3</sup>; Couchman Victoria<sup>3</sup>; Glynn Kathryn<sup>3</sup>; Batha Safira<sup>3</sup>; Wells Dagan<sup>1</sup>**

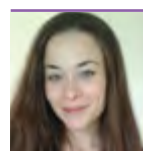
<sup>1</sup>Reprogenetics UK, University of Oxford; <sup>2</sup>Reprogenetics UK; <sup>3</sup>Lister Fertility Clinic, UK

Comprehensive chromosome screening (CCS) enhances selection of viable embryos, improving implantation rates and reducing the risk of miscarriage. However, existing techniques, such as array comparative genomic hybridisation (aCGH) or next-generation sequencing (NGS) are laborious, relatively expensive and require 24h (aCGH) or several days (NGS). Given that some blastocysts can only be biopsied late on day-5 or even day-6, current techniques may often be incompatible with fresh embryo transfer, necessitating cryopreservation. Here we report the clinical application of a novel ultra-rapid, cost-effective CCS method based on quantitative polymerase chain reaction (qPCR).

Prior to clinical application, the technique was extensively validated and demonstrated 100% accuracy in aneuploidy detection when applied to abnormal cell lines/embryos. The method was applied to 33 patients (age: 38.7) referred from a single UK clinic due to either previous miscarriage(s), IVF failure(s) or advanced maternal age. 112 blastocyst-stage embryos were assessed. Results were obtained from 109 samples (97.3%). Total aneuploidy rate was 62.4% (68/112). 21 patients (63.6%) received a euploid embryo transfer in the morning of day-6. At

the time of writing, outcomes were available for 14 transfers, which resulted in 10 pregnancies, giving a pregnancy rate per transfer of 71.0% at an average age of 38.0 years.

Here we report the first clinical application of a novel CCS approach utilising a nano-scale fully-automated array-based qPCR technology, enabling accurate diagnosis within 5h following embryo biopsy, permitting same day or early day-6 transfer. CCS can be achieved at relatively low cost and substantially reduced turn-around times compared to existing methods, potentially improving the logistics of utilisation in the IVF clinic. The fact that cryopreservation is not essential further simplifies the procedure and reduces costs for patients relative to other CCS methods. Furthermore, the technique has the capacity to quantify mtDNA and detect common microdeletions, providing extra information on embryo viability.



### Katharina Spath

*Reprogenetics UK*

Katharina Spath graduated in Biology from the University of Bayreuth, Germany, in 2009. She then moved to the UK to focus her studies on reproductive genetics, obtaining an MSc in Reproductive Biology from the University of Edinburgh. In 2011 she joined Reprogenetics UK because of her interest in PGD and PGS. Since 2012 Katharina is a DPhil student, under the supervision of Dr Dagan Wells, at the Nuffield Department of Obstetrics and Gynaecology, University of Oxford. Her studies are focused on understanding the genesis of aneuploidy in human gametes and embryos, and the development of new methodologies for their detection.

## A4.6 Haploid parthenotes and normally fertilised embryos have differential response to ammonia exposure in vitro

**Kalthur Guruprasad<sup>1</sup>; Nair Ramya<sup>1</sup>; Adiga Satish<sup>1</sup>; Mutalik Srinivas<sup>2</sup>; Dasappa Jagadeesh Prasad<sup>3</sup>**

<sup>1</sup>Kasturba Medical College, Manipal; <sup>2</sup>Manipal College of Pharmaceutical Sciences, Manipal University; <sup>3</sup>Mangalore University, Mangalore

The present study was conducted to understand the differential response of parthenogenic and normally fertilised embryos to stress induced by ammonia. Parthenogenesis was induced in MII stage oocytes were incubated with 10 mM SrCl<sub>2</sub> in calcium and magnesium free M16 medium. Normally fertilised and parthenogenetically derived embryos at 2 cell stage were exposed to different concentrations of ammonia (0, 25, 50, 200, 300 and 500 µM) and cultured till blastocyst stage. Exposure of ammonia to normally fertilised embryos resulted in significant decrease in the developmental potential ( $p < 0.0001$ ) and blastocyst quality ( $p < 0.001$ ). Whereas, in parthenotes, lower concentration of ammonia did not affect the blastocyst rate while at 200 µM concentration the blastocyst rate was two times higher than control. In addition, parthenotes exposed to ammonia had significantly higher percentage of apoptotic cells in blastocysts ( $p < 0.001$ ). At 4h after exposure to ammonia the parthenotes at 2 cell stage had perinuclear distribution of mitochondria. Expression of Oct4, Nanog and Na<sup>+</sup>/K<sup>+</sup> ion exchange channel was up regulated in parthenotes after ammonium exposure, while the cytochrome



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C expression was down regulated. This indicates that haploidy and/or absence of paternal factors in the embryo results in differential tolerance to in vitro stress induced by ammonia.



### Guruprasad Kalthur

*Kasturba Medical College, Manipal*

Guruprasad Kalthur is a professor and clinical embryologist at Kasturba Medical College, Manipal University, Manipal, India where he has been working since 2005. He was the visiting associate professor at National University of Singapore, Singapore in 2012. He received his PhD degree from Manipal University in 2004. Currently, he is the academic coordinator for the MSc in Clinical embryology course. He has more than 50 publications in reputed journals and is the recipient of several national and international awards. His main research areas are cryopreservation, reproductive toxicology, parthenogenesis and natural compounds.



### Sofia Granados Aparici

*The University of Sheffield*

Sofia Granados Aparici is a final year PhD student at the University of Sheffield. In 2012 she obtained a BSc and MSc degree in Biotechnology from Universitat Politècnica de València (Spain). In 2010, she started her MSc in the Competence Centre on Health Technologies, CCHT (Tartu, Estonia) with Prof Andres Salumets, looking at molecular factors involved in embryo-endometrium interactions. In 2013, she was awarded a PhD scholarship by the University of Sheffield to work in the Academic Unit of Reproductive and Developmental Medicine (AURDM) with Dr Mark Fenwick. Her project is focused on investigating the molecular mechanisms implicated in the maintenance and activation of primordial ovarian follicles. She has recently been involved in a collaborative project with a Sheffield artist, Kate Sully, to perform public engagement events with the aim of communicating to the general public the science of reproductive biology.

## A5

### Hormones in female reproduction

#### A5.1 Evidence for TGF $\beta$ regulation of cell cycle genes in granulosa cells of primordial follicles

**Granados-Aparici Sofia; Fenwick Mark**

*The University of Sheffield*

Primordial follicles are relatively quiescent structures that form the basis of the ovarian reserve. Each follicle, consisting of an oocyte and a layer of granulosa cells, are held in a relative state of quiescence; yet, little is known about the mechanisms that operate to maintain this phenotype. TGF $\beta$  superfamily members are known for their roles in controlling growth arrest in epithelial cells. We have previously shown the TGF $\beta$  mediator and transcription factor Smad3 is detectable in the nuclei of granulosa cells in small single-layered follicles. Smad3 can act as transcriptional regulator of genes involved in cell cycle, such as CyclinD2, p27 and Myc. Therefore we aimed to investigate whether Smad3 binds to the promoters and regulates the expression of these candidates in granulosa cells of primordial follicles. ChIP-qPCR was used to compare Smad3 binding in immature mouse ovary samples containing different proportions of primordial and growing follicles. Quantitative PCR was used to determine the level of transcriptional regulation in relation to Smad3 binding. Results showed Smad3 bound to CyclinD2 and Myc but not to p27 gene promoters with relatively more binding to CyclinD2 and Myc genes in samples enriched in primordial follicles. Increased Smad3 binding in primordial follicles was also associated with increased CyclinD2 mRNA expression, while Myc was repressed. Using immuno-fluorescence, CyclinD2 and p27 proteins co-localised in the nuclei of primordial granulosa cells and this association was confirmed using co-IP. Interestingly, follicle initiation was associated with an abrupt loss of p27 expression suggesting p27 degradation from this complex is necessary for growth. This study provided new evidence that the TGF $\beta$  mediator, Smad3, directly regulates cell cycle genes in primordial follicles, supporting a role for this signaling pathway in maintenance of the quiescent state.

#### A5.2 Effect of bone morphogenetic protein-15 (BMP15) on gonadotropin-stimulated synthesis of hyaluronan and progesterone in porcine ovarian follicle

**Nagyova Eva<sup>1</sup>; Nemcova Lucie<sup>1</sup>; Bujnakova-Mlynarcikova Alzbeta<sup>2</sup>; Blaha Milan<sup>1</sup>; Scsukova Sona<sup>2</sup>**

*<sup>1</sup>Institute of Animal Physiology and Genetics, Academy of Sciences of the Czech Republic; <sup>2</sup>Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia*

It has been suggested that BMP15 is the growth factor that can coordinate granulosa cells (GC) proliferation and differentiation. In rat, BMP15 is a potent stimulator of GC proliferation and this mitogenic effect is FSH-independent. BMP15 alone had no effect on GC steroidogenesis; however, it produced a marked decrease in FSH-induced progesterone (P4) production. We investigated the effect of BMP15 on FSH/LH-stimulated synthesis of hyaluronan (HA) and P4 by porcine oocyte cumulus complexes (OCC) and GC. Both OCC and GC were cultured either in serum-supplemented or serum-free medium. In addition, the effect of BMP15 supplementation on transcript levels (AREG, CD44, CYP11A1, HAS2, PTGS2, STAR, and TNFAIP6) at 4h, 8h, 16h, 22h, and 24h of OCC cultivation was also evaluated using real-time RT-PCR. While FSH/LH-stimulated total HA synthesis by OCC was not affected in the presence of BMP15 in serum-supplemented medium, its retention within the complex was significantly increased after BMP15 action in comparison to FSH/LH alone (69 % vs. 45%, respectively). In contrast, only 20 % of HA was incorporated within the complex in serum-free medium. To elucidate the mechanism of BMP15 regulation of FSH/LH signaling, we measured P4 production by OCC and GC in the presence/absence of serum. In the presence of serum, BMP15 markedly increased (about 69%) FSH/LH-stimulated P4 secretion by OCC compared to FSH/LH alone. In agreement with the rat, BMP15 induced a significant decrease (about 35%) of FSH/LH-induced P4 release by GC compared to FSH/LH alone. In the absence of serum, BMP15 did not significantly change P4 production by OCC. To our knowledge, this is the first

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study that demonstrates the relationship between BMP15 and formation of the HA-rich cumulus-oophorus extracellular matrix.



**Eva Nagyova**

*Institute of Animal Physiology and Genetics, Academy of Sciences of the Czech Republic*

D.V.M. Eva Nagyova, PhD, DSc; She completed her PhD (1990) from Academy of Sciences of the Czech Republic, Institute of Animal Physiology and Genetics in Prague and postdoctoral training in Norwegian College of Veterinary Medicine, Oslo (1992) and INSERM, Clamart, (1994). After receiving OECD Fellowship Awards, she worked in Cancer Research Center, Ottawa (1997) and Faculty of Medicine, University of Rome (2002, 2013). In 2002-2007, her research was supported by "Program of Scientific Co-operation between Italian and Czech Republic" and in 2012-2014 "Priority Research Collaboration between Slovak and Czech Academy of Sciences". Specifically, her research is aimed at investigating molecular events associated with the oocyte maturation and organization of the cumulus oophorus extracellular matrix. In 2016, she completed her DSc/Research Professor from Academy of Sciences of the Czech Republic.

### A5.3 British Fertility Society/AFS Exchange paper:

#### Personalised first-line ovulation induction for women with polycystic ovary syndrome - an individual participant data meta-analysis

**Wang R<sup>1</sup>; Kim B.V<sup>1</sup>; Zhang H<sup>2</sup>; van Wely M<sup>3</sup>; Homburg R<sup>4</sup>; Lambalk C.B<sup>5</sup>; Weiss N.S<sup>6</sup>; Moll E<sup>7</sup>; Johnson N.P<sup>1,7</sup>; Kar S<sup>8</sup>; Palomba S<sup>9</sup>; Falbo A<sup>9</sup>; Vegetti W<sup>10</sup>; Leanza V<sup>11</sup>; Özmen Ü<sup>12</sup>; Şahin Y<sup>13</sup>; Norman R.J<sup>1</sup>; Bhattacharya S<sup>14</sup>; Legro R.S<sup>15</sup>; Mol B.W.J<sup>1</sup> on behalf of the International Ovulation Induction Collaboration**

<sup>1</sup>The University of Adelaide, Australia; <sup>2</sup>Yale University, New Haven, USA; <sup>3</sup>University of Amsterdam, Amsterdam; <sup>4</sup>Homerton University Hospital; <sup>5</sup>VU University Medical Center, Amsterdam; <sup>6</sup>Free Medical University, Amsterdam; <sup>7</sup>University of Auckland, Auckland; <sup>8</sup>Kar Clinic and Hospital Pvt. Ltd, Orissa, India; <sup>9</sup>ASMN-IRCCS of Reggio Emilia, Reggio Emilia, Italy; <sup>10</sup>Ospedale Maggiore Policlinico, Milan, Italy; <sup>11</sup>Catania University, Italy; <sup>12</sup>Bülent Ecevit University, Zonguldak, Turkey; <sup>13</sup>Erciyes University Medical School, Kayseri, Turkey; <sup>14</sup>University of Aberdeen; <sup>15</sup>Pennsylvania State University, USA.

Clomiphene has been considered as the first-line ovulation induction in women with anovulatory PCOS for decades. However, there is a lack of high quality evidence to support personalized ovulation induction according to an individual's characteristics. We aimed to evaluate the comparative effectiveness of different pharmacological ovulation induction interventions in different subgroups of women with PCOS. We searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases without language restrictions and conducted an individual participant data (IPD) network meta-analysis. We included randomised controlled trials (RCTs) comparing the following interventions in women with PCOS: clomiphene, metformin, combined clomiphene-metformin,

letrozole, tamoxifen, gonadotropins and placebo. Studies were excluded if they studied women with clomiphene resistant PCOS. The primary outcome was clinical pregnancy. We performed pairwise meta-analyses as well as network meta-analysis using IPD. The original investigators shared IPD of 11 RCTs including 2,477 women with PCOS. Overall, letrozole (OR 1.9, 95%CI 0.7-4.8) and combined clomiphene-metformin (OR 1.8, 95%CI 0.9-3.8) showed trends with higher pregnancy rates compared to clomiphene alone. In subgroup analyses, letrozole resulted in higher pregnancy rates in women with BMI > 34.5 (OR 2.6, 95%CI 1.6-4.3), ovarian volume > 12ml (OR 2.5, 95%CI 1.5-4.1), Ferriman-Gallwey score >15 (OR 2.1, 95%CI 1.4-3.3), and free androgen index > 7.6 (OR 3.3, 95%CI 1.4-7.5), compared to clomiphene. In conclusion, in women with high BMI, large ovarian volume or severe hyperandrogenaemia/hyperandrogenism, letrozole led to higher pregnancy rates than clomiphene.



**Rui Wang**

*The University of Adelaide, Australia*

Dr Rui Wang is a PhD candidate from The University of Adelaide, Australia. He received his doctor of medicine degree in 2012 and completed his residency in obstetrics and gynaecology at Huazhong University of Science and Technology in China. He was the prize winner of "Best clinical paper - BFS exchange award" in Fertility Society of Australia 2016 annual meeting. His research interests are treatments of infertility and the use of evidence synthesis methods is fertility care.

### A5.4 Prostaglandin effects to myometrial and leiomyoma cells in vitro through microRNA profiling

**Oh So Ra; Park Jung Woo; Bae Jong Woon; Cho Yeon Jean; Han Myoungseok**

*Dong-A University, Department of Obstetrics and Gynecology*

Uterine leiomyomas (ULs) are benign uterine tumors considered to arise from transformation of myometrial cells, which develop during the reproductive years. It is clear that ovarian steroids, estradiol (E2) and progesterone (P), and many autocrine/paracrine mediators are essential for leiomyoma growth. Prostaglandin (PG) E2 and F2α known to be main inflammatory mediators are produced in a large amount during menstruation. However, their cellular effects on leiomyoma growth have been rarely studied so far. To identify whether prostaglandins have a potential role in the proliferation of leiomyoma as much as ovarian steroids, we evaluated the expression levels of 8 microRNAs (miRNAs) by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) by treating E2, P4, PGE2, PGF2α and each antagonist or cyclooxygenase-2 (COX-2) inhibitor to the cultured leiomyoma and myometrial cells. Among the eight miRNAs, let 7a, miR-21, miR-26a, and miR-200a were considered to inhibit the cell apoptosis and miR-29b, miR-93, miR-106b, and miR-100b were presumed to block the cell inflammation. While PGE2 induced more expressions of anti-apoptotic miRNAs in leiomyoma cells than E2, PGF2α did not show those effects as much as PGE2. In conclusion, this pilot study shows that PGE2 secreted during menstruation would have the possible role in the growing of ULs. Therefore, the controlling of PG

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secretion from uterus during menstruation would be an alternative therapy to inhibit the growth of ULs.

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### Myoungseok Han

*Dong-A University, Department of Obstetrics and Gynecology*

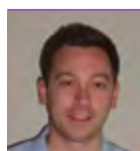
Professor Myoungseok Han (MD, PhD) graduated from Dong-A University, College of Medicine in Busan, Korea on 1992. He has been working as a professor and physician at the department. of Ob/ Gyn of Dong-A University Hospital since 2001. He is in charge of Medical Science Research Center in Dong-A University since March 2015. His research interest is the molecular mechanisms on reproductive disease, especially on endometriosis and leiomyoma, and endocrine disruptor effects on gynecologic diseases. His PhD thesis title is 'Effects of letrozole on apoptosis in cultured leiomyoma cells treated with prostaglandin E2'.

## A5.5 The impact of DHEA on endometrial receptivity

**Gibson Douglas; Simitsidellis Ioannis; Kelepouri Olympia; Critchley Hilary; Saunders Philippa**  
*The University of Edinburgh*

The establishment of pregnancy requires dynamic remodelling of the endometrium. Decidualization, a key part of this process, is characterised by differentiation of endometrial stromal fibroblasts (ESF) which secrete factors that regulate implantation and placental development. We recently discovered that ESF synthesise androgens during decidualization which modulate the expression of endometrial receptivity and decidualization markers. The adrenal androgen precursor dehydroepiandrosterone (DHEA) is abundant in the circulation, but whether changes in the bioavailability of DHEA can affect endometrial function is not known. Circulating concentrations of DHEA decline precipitously with age which may contribute to reduced fertility in older women. Given the recently elucidated role for androgens in regulating endometrial function, we hypothesised that modulating the bioavailability of DHEA could alter local tissue androgen concentrations and impact on decidualization and endometrial receptivity. Primary human ESF were isolated from endometrial biopsies collected

from women during the proliferative phase of the cycle (n=18). As previously reported, ESF expressed the enzyme required for conversion of DHEA to active androgens (3 $\beta$ -hydroxysteroid dehydrogenase; 3 $\beta$ HSD). Decidualization was induced in vitro (Progesterone + cAMP); some cells were co-treated with DHEA or with the 3 $\beta$ HSD inhibitor trilostane. DHEA increased androgen biosynthesis and was associated with increased expression of decidualization markers. Inhibition of 3 $\beta$ HSD with trilostane significantly reduced biosynthesis of testosterone and expression of the decidualization markers IGFBP1 (p<0.001) and prolactin (p<0.001). Trilostane treatment also decreased expression of the receptivity markers osteopontin (SPP1; p<0.01) and endothelin receptor type B (EDNRB; p<0.001). These data demonstrate that changes in the bioavailability of DHEA can affect endometrial expression of decidualization and endometrial receptivity markers. These findings suggest a previously unrecognised role for tissue androgen bioavailability in the regulation of the endometrium which may impact on the establishment of pregnancy in women.



### Douglas Gibson

*University of Edinburgh*

Dr Douglas Gibson is a postdoctoral research fellow in the MRC Centre for Inflammation Research at the University of Edinburgh. His research is focused on determining the impact of local steroid signalling in endometrial function, demonstrating novel roles for intracrine estrogen and androgen signalling in fertility. These studies offer insights into the regulation of stromal differentiation (decidualization), immune cell function and vascular remodelling. He is the recipient of the Society for Reproduction and Fertility Postdoctoral Scientist Award and is Chair of the Queen's Medical Research Institute Postdoctoral Society.

## A5.6 Dynamic changes in gene expression and signalling during early placental development in the horse

**Read Jordan; Cabrera-Sharp Victoria; Offord Victoria; Mirczuk Samantha; Fowkes Rob; de Mestre Amanda**  
*The Royal Veterinary College*

Placental development requires a highly regulated series of cellular processes that transform a single layer of trophoblast into a complex membrane. Although the anatomical structure of mammalian placentae is highly variable between species, many of the cellular processes that lead to its formation, namely trophoblast proliferation, differentiation, migration, remain remarkably similar. The aim of this work was to understand the molecular events that regulate trophoblast development. The objective of this study was to identify genes and signalling pathways that are activated or repressed in vivo during trophoblast development in the horse. An Agilent equine 44K microarray was performed using RNA extracted from Chorionic Girdle trophoblast and Chorion (control) from equine pregnancy days 27, 30, 31 and 34 (n=5 at each timepoint), corresponding to the period of initiation of chorionic girdle trophoblast proliferation, differentiation and migration. Data was analysed using Genespring, Ingenuity Pathway Analysis, SigPro and DAVID software and verified using qRT-PCR and western blotting. Microarray analysis showed gene expression was rapidly induced in the chorionic girdle between days 27 and 34 (compared to day 27 (p<0.05) day 30=253, day



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31=609, day 34=1508 genes). In contrast, only 19 genes were differentially expressed in the adjacent chorion. Pathway analysis identified 36 signalling pathways either activated or repressed during chorionic girdle development. These included pathways previously described in mammalian trophoblast (e.g. Rho Family GTPase, integrin, Aryl hydrocarbon receptor, MAPK and TGFB signalling) as well as pathways not previously described in trophoblast (e.g. IL-9, CD28 and ceramide signalling). Activity of MAPK pathways in the chorionic girdle was confirmed using western blotting. In summary, the purity and accessibility of equine chorionic girdle trophoblast has proven to be a powerful resource to identify candidate pathways involved in early equine placental development some of which have not previously been described in detail in any mammalian species.



### Amanda de Mestre

*The Royal Veterinary College, London*

Mandi de Mestre is a senior lecturer in Reproductive Immunology in the Department of Comparative Biomedical Science, The Royal Veterinary College, London. Mandi completed her clinical veterinary training at the University of Sydney, after which she worked as a clinician in the field of equine reproductive and neonatal medicine. She received a Ph.D. in Biomedical Sciences in 2006 from the John Curtin School of Medical Research, Australian National University, which was followed by postdoctoral training in immunobiology of pregnancy at Cornell University, USA. Dr de Mestre's laboratory dissects the molecular mechanisms that regulate equine placental development and function in normal and failing pregnancies with a broader goal of improving our diagnosis and management of pregnancy failure.

## Friday 6 January

B1

### Maturing a good egg

## B1.1 Sub-populations of oogonial stem cells can be isolated from the adult human ovary

**Clarkson Yvonne; McLaughlin Marie; Waterfall Martin; Skehel Paul; Anderson Richard; Telfer Evelyn**

*The University of Edinburgh*

**Aims/objectives:** Controversy surrounds the reported existence of oogonial stem cells in the adult human ovary (1, 2). Our aims were (1) to investigate use of an antibody-based fluorescent activated cell-sorting (FACS) technique to isolate a population of cells positive for the germline marker DEAD-box helicase 4 (DDX4) from adult human ovary and (2) characterise DDX4-positive sorted cells.

**Content of presentation:** Detailed data-plots were generated from 7 FACS experiments utilising tissue obtained, with ethical permission, from 33 women at the time of caesarean section (22-43 years). RT-PCR was performed on populations of sorted cells.

**Relevance/impact:** There is no consensus of scientific opinion regarding isolation and characterisation of germline stem cells derived from the adult human ovary. Molecular characterisation of these cells could address the current debate regarding their identity.

**Outcomes:** 3 sub-populations of DDX4-positive cells varying in size and fluorescent intensity were isolated. Different isoforms of DDX4 mRNA were found within the sorted populations. An isoform containing a 5' sequence, situated at the start of DDX4 mRNA, occurred in all sorted populations whereas an isoform containing a 3' sequence, located at the end of the DDX4 mRNA, was found in only two. The smallest and most fluorescent cells did not contain the 3'-containing isoform. Both populations of DDX4-positive cells containing the 3' isoform expressed mRNA of the pluripotency-associated markers NANOG, LIN28 and POU5F1 alongside germline markers CKIT, PRDM1, DPPA3 and IFITM3. The germline marker DAZL was expressed in the sub-population containing 5' only.

**Discussion:** Isolating sub-populations of DDX4-positive cells could clarify the debate surrounding germline cells derived from adult human ovary. Whilst the physiological relevance of these cells is currently unknown, differing DDX4 isoform expression and cell size/fluorescent intensity may be important determinants of the potential of these cells and consequently their ability to form functional oocytes.

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**Yvonne Clarkson**

*The University of Edinburgh*

Dr Yvonne Clarkson graduated from the University of Edinburgh with an Honours degree in Pharmacology with industrial experience where she worked with the pharmaceutical company Organon. She subsequently gained a PhD from the University of Edinburgh in Neuroscience working on neuro-degenerative diseases. Since 2014 Dr Clarkson has been a post-doctoral scientist in Professor Evelyn Telfer's lab where she works on identification and characterisation of oogonial stem cells from adult woman. Currently she is developing in vitro systems to test the utility and function of these cells. Today Dr Clarkson will give an overview of the isolation method used to identify sub-populations of oogonial stem cells and how the molecular signature of these different populations could be the key to their developmental potential.

### B1.2 Characterisation of P-body formation during bovine oogenesis

**Lu Jianping<sup>1</sup>; Jin Ping<sup>1</sup>; Hemmings Karen<sup>1</sup>; Cotterill Matthew<sup>1</sup>; Huntriss John<sup>1</sup>; Campbell Bruce<sup>2</sup>; Picton Helen<sup>1</sup>**

<sup>1</sup>University of Leeds; <sup>2</sup>University of Nottingham

Processing bodies (P-bodies) are RNA associated cytoplasmic foci found in all eukaryotic cells, which accommodate proteins involved in mRNA surveillance and decay, RNA-mediated silencing and translational control. The chromatin body, which is a P-body counterpart in spermatocytes, has been demonstrated to be a germ-cell-specific RNA-processing centre. During oogenesis, the formation of P-body like foci have been reported in fully grown murine GV and MII oocytes either by quantification of ectopic expression or by immune-detection of specific proteins. P-body foci formation has yet to be reported during oogenesis in other mammalian species. This study used antibodies of P-body collated proteins MVH, DICER1, AGO2, GTSF1 and DCP1a to characterise P-body formation and expression across bovine oogenesis from primordial follicles to MII oocytes. During the GV to MII transition oocytes rely on translational control to regulate their gene expression. Exposure to the translation inhibitors puromycin (dose range 0.1-500mg/ml) and cycloheximide (dose range 0.01-50mg/ml), over 24 hours of in vitro maturation (n=241 oocytes) was used to manipulate the mRNA pool in the ooplasm relative to unexposed controls in order to modulate de novo P-body like foci formation. Results demonstrate that P-body spatiotemporal expression patterns change dynamically during bovine oogenesis. P-body like foci were observed in the fully-grown GV and MII oocytes but their formation was highly variable. Most of the MVH and DCP1a detected foci were independent of each other. Protein expression was also detected in a limited number of stromal cells [HP1]. Both cycloheximide and puromycin treatment significantly altered oocyte P-body foci formation ( $p < 0.01$ ). The greatest transcriptional inhibition occurred with 10-50mg/ml cycloheximide ( $p < 0.001$ ), whereas 0.1mg/ml puromycin enhanced P-body like foci formation ( $P < 0.05$ ). These data suggest that P-body like foci formation in bovine oocytes is related to mRNA availability. The relationship between RNA storage and processing and P-body like foci formation requires further investigation.



**Jianping Lu**

*University of Leeds*

Jianping Lu is currently a research fellow of the Division of Reproduction and Early Development of Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds since 2008. His research interest is molecular mechanisms of oocyte development. He is currently focused on the transcriptomes of developing oocytes in human and sheep. Jianping Lu completed a Bsc in Shanxi Agricultural University in 1983 and completed a PhD in 1996 in the University of East Anglia.

### B1.3 Functional analysis of the oocyte specific imprinting regulator KHDC3L in bovine oocytes and embryos

**Berenyi Erika; Huntriss John D; Roxburgh Emily; Picton Helen M**  
*University of Leeds*

Familial biparental hydatidiform mole (FBHM) is a maternal-effect recessive inherited disorder. The FBHM pregnancy phenotype results from the genome-wide failure of establishment or maintenance of methylation of maternally imprinted genes in the oocyte and developing embryo. Mutation of the maternal effect gene KHDC3L (6q13) contributes to this pregnancy pathology. Together with other genes (NLRP5, OOEP, TLE6), KHDC3L forms the Subcortical Maternal Complex (SCMC). It is unknown how mutation of KHDC3L affects DNA methylation or how the intracytoplasmic KHDC3L protein regulates epigenetic modifications of DNA. This study investigated the function of KHDC3L in bovine oocytes and preimplantation embryos. PolyA mRNA was isolated from individual oocytes and embryos at different developmental stages. After SMART cDNA synthesis, the expression of the KHDC3L, NLRP2, NLRP5, OOEP and FIGLA genes were quantified against housekeeping genes H2A, and YWHAZ using SYBR-Green QPCR techniques. To study the role of KHDC3L in oocyte and embryo development dsRNA was used to knock-down gene-expression in GV oocytes. The dsRNA were delivered into cumulus intact oocytes using an Eppendorf FemtoJet<sup>®</sup> Microinjector system. After 24 hours of IVF, oocyte meiotic progression was assessed, oocyte viability confirmed by neutral-red staining and gene expression levels were quantified. Results indicated that all members of the SCMC showed high levels of expression in GV and MII oocytes, and in 2, 4, and 6-cell embryos. In contrast, expression decreased sharply in morulae and blastocysts following genome activation. Targeted dsRNA injection caused a greater than 60% knockdown of oocyte KHDC3L expression compared to controls. 80% of the injected oocytes were viable and matured to MII. These pilot data demonstrate how the expression of maternal-effect genes in the SCMC change dynamically thorough bovine oocyte maturation and preimplantation development. Further research is needed to confirm the role of KHDC3L and the SCMC members during the symmetric division of the developing embryo.



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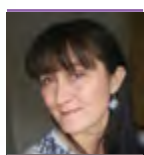
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### Erika Berenyi

*University of Leeds*

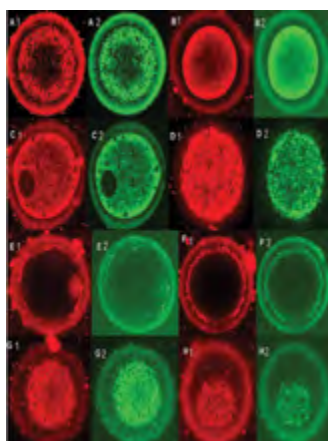
Erika Berenyi is a PhD student in Clinical Embryology at the University of Leeds. She gained a Bachelor degree in Biomedical Science and a Master degree in Molecular Biology at the University of Debrecen, Hungary. Erika has several years of experience in Molecular Biology and Microbiology. She was a research assistant and practice instructor in Biochemistry, Molecular Biology and Microbiology at the Biochemistry and Molecular Biology Department of the University of Debrecen. She published her result from Cancer Research and was the Principal Investigator in one of the papers.

## B1.4 Mitochondrial indices of ovine oocyte maturation in vitro

**Gnanaprabha Keerthi; Topipat Chutima; Lu Jianping; McKeegan Paul; Picton Helen**

*University of Leeds*

Mitochondria are the major energy providers in oocytes and so they play a crucial role in meiotic maturation, fertilisation and early embryonic development. A pilot study was conducted to investigate the relationship between mitochondrial activity and mtDNA copy number in sheep oocytes. Ovine oocytes (both post and pre-pubertal ovaries) (n=114) were harvested and either immediately denuded for analysis or matured to MII over 24hrs in-vitro. Oocytes at the GV and MII stage were assessed for mitochondrial polarisation ratio (mtPR) by staining with 5,5',6,6'-tetrachloro-1,1,3,3'-tetraethylbenzimidazolyl-carbocyanine iodide (JC1) using Zeiss 510 confocal microscope. The same individual oocytes were then analysed for mitochondrial DNA (mtDNA) copy number by qPCR. The mtPR and MtDNA measurements were conducted on 58 GV oocytes and 56 in-vitro matured (IVM) MII oocytes. Results showed that mtPR was significantly higher in MII than GV oocytes (0.72 vs 0.47,  $p < 0.0001$ ). Similarly, mtDNA copy number was significantly higher in MII than GV oocytes ( $1,103,000 \pm 95,206$  vs  $875,881 \pm 110,593$ ;  $p < 0.0002$ ). This difference in mtDNA copy number between MII and GV oocytes, was especially marked in a sub group of MII oocytes that underwent cumulus denudation prior to IVM. GV oocytes displayed a positive correlation ( $R^2=0.3517$ ) between mtPR and mtDNA copy number. Two different correlation patterns emerged when MII oocytes were analysed. MII oocytes which were matured in intact cumulus oocyte complexes showed a negative correlation ( $R^2=-0.47566$ ) between mtPR and mtDNA copy number whereas oocytes matured to MII following denudation showed a positive correlation ( $R^2=0.3740$ ). These observations suggest that mtPR and mtDNA copy number increase in parallel as oocytes progress through meiotic maturation. Furthermore, the act of precocious denudation during IVM deprives the oocyte of cumulus-derived energy substrates so altering mitochondrial metabolism. Further research is needed to confirm these findings.



### Keerthi Gnanaprabha

*University of Leeds*

Keerthi Gnanaprabha completed her under graduation in medicine (MBBS) at the PSG Institute of Medical Science and Research in Tamil Nadu, India in 2014 and subsequently pursued her Masters in Clinical Embryology and Assisted Reproductive Techniques at the University of Leeds. Her MSc research project involved assessment of oocyte metabolism before and after in-vitro maturation. She then joined the research team in the division of reproduction and early development at the University of Leeds to work on an MRC funded project to investigate the life cycle and legacy of human oocytes in health, age and infertility. She has now started her MD to fulfil her career goal of becoming a clinician scientist.

## B1.5 Mitochondrial markers associated with maternal age during ovine oocyte maturation in vitro

**Topipat Chutima; Lu Jianping; Collado-Fernandez Esther; McKeegan Paul; Huntriss John D; Picton Helen M**

*Reproduction and Early Development, University of Leeds*

Declining oocyte quality is a major contributor to reproductive ageing. As mitochondria play a fundamental role in energy provision within oocytes, key indices of mitochondrial biology such as mitochondrial DNA (mtDNA) copy number and ATP production, are hallmarks of oocyte competence leading to successful embryo development. Here, we explore the relationship between age, mtDNA copy number and carbohydrate metabolism in oocytes recovered from prepubertal and adult sheep. Abattoir-derived cumulus enclosed oocytes from both ages were either denuded at harvest (GV oocytes: n=44/age group) or after 24hrs of IVM (MII oocytes: n=45 prepubertal vs. n=44 adult). Glucose, Pyruvate and Lactate (GPL) metabolism by individual, denuded GV oocytes was measured following a 6hr incubation in defined media at 38°C and 5%CO<sub>2</sub> (n=42 prepubertal vs. n=44 adult). Oocyte mtDNA copy number was quantified by qPCR. Results indicate that regardless of oocyte age, mtDNA replication occurs during meiotic maturation. MtDNA copy number in MII oocytes (median 416,170; range 2,245-9,851,727) exceeded that of GV oocytes (median 85,090; range 454-5,657,723;  $P < 0.0001$ ). Furthermore, although there was considerable variation between oocytes, mtDNA copy number was significantly lower in adult (median 290,871, range 4,085-3,754,000) than prepubertal MII oocytes (median 674,779; range 2,245-9,852,000;  $P < 0.001$ ). Both adult and prepubertal GV oocytes consumed more pyruvate than glucose, confirming pyruvate as the predominant energy substrate in sheep oocytes. Prepubertal oocytes consumed significantly less pyruvate ( $5.64 \pm 0.32$  pmol/oocyte/h) than adult oocytes ( $7.59 \pm 0.37$  pmol/oocyte/h;  $P < 0.001$ ). There was a weak, but significant, positive correlation between mtDNA copy number and pyruvate consumption in prepubertal oocytes ( $r^2=0.134$ ;  $P < 0.05$ ) but no correlation in adult oocytes. Finally, the efficiency of utilisation of all 3 metabolites was inversely linked to oocyte mtDNA copy number in both age groups. Oocyte mtDNA copy number, carbohydrate metabolism and hence the efficiency of oxidative phosphorylation are linked to maternal age in sheep oocytes.



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### Chutima Topipat

*Reproduction and Early Development,  
University of Leeds*

Chutima Topipat is a clinician scientist. She started OBG practice in an infertility clinic before joining in academia at Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. As a lectureship role in Reproductive Endocrinology and Infertility, she involved in both clinical and training programs for medical students, OBG residents and fellowship in Reproductive Medicine. Research interest directed her to extend the career path to become a scientist. To enhance knowledge, she studied MMedSci (ART) at Nottingham in 2012 before continuing PhD study with Professor Helen Picton at University of Leeds. Her ongoing project is related to oocyte ageing and quality.

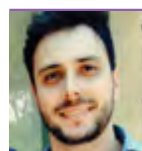
### B1.6 RNA-Seq profiling of bovine cumulus-oocyte transcript abundance after treatment with cAMP modulators

**Machado Mariana F<sup>1</sup>; Thompson Jeremy G<sup>2</sup>; Gilchrist Rob B<sup>3</sup>; Sutton-McDowall Melanie L<sup>4</sup>; Razza Eduardo M<sup>1</sup>; Pioltine Elisa M<sup>1</sup>; Botigelli Ramon C<sup>1</sup>; Fontes Patricia K<sup>1</sup>; Coutinho Luis L<sup>5</sup>; Nogueira Marcelo F G<sup>6</sup>**

<sup>1</sup>Institute of Biosciences, University of São Paulo State (UNESP); <sup>2</sup>School of Medicine, Robinson Research Institute, University of Adelaide; <sup>3</sup>School of Women's and Children's Health, University of New South Wales; <sup>4</sup>Robinson Research Institute & School of Medicine, The University of Adelaide; <sup>5</sup>University of São Paulo/ESALQ; <sup>6</sup>University of São Paulo State (UNESP)

Cyclic adenosine monophosphate modulators have been used for artificial blocking of meiotic resumption. We aimed to identify differentially expressed genes in cumulus cells and oocytes after cumulus-oocyte complexes (COCs) pre-culture with forskolin (FSK) and IBMX and after IVM. Groups of 100 COCs were cultured according to the treatment; pre-IVM: COCs were pretreated for 2h in TCM199 with FSK (100 µM) and IBMX (500 µM), followed by IVM in TCM199 supplemented with rhFSH for 24h; Control: COCs were matured for 24h in TCM199 supplemented with rhFSH (0.1 IU/mL). After 2h culture and after IVM, oocytes were separated from cumulus cells and RNA was extracted (RNeasy Micro Kit, Qiagen) and evaluated (Agilent 2100 Bioanalyzer). Sequencing was performed on HISEQ2500 Illumina platform and filtered reads were mapped to the Bos taurus reference genome UCSC bTau8. Gene expression was estimated with the R/BioConductor package edgeR version 3.12.0 and expression was tested with a quasi-likelihood F-test. KEGG and GO enrichment tests were performed with Kolmogorov-Smirnov test. We did not detect differentially expressed genes in oocytes after 2 h of culture or after IVM. In cumulus cells after 2h of culture, 722 genes were differentially expressed, 333 upregulated and 389 downregulated in pre-IVM group. GO enrichment test indicated 80 significant categories of biological processes, 22 for cellular compartment and 25 for molecular function. Also 7 KEGG pathways were found significant: 3 increased and 4 decreased in the pre-IVM group. In cumulus cells after IVM we identified 288 differentially expressed genes, 182 upregulated and 106 downregulated in pre-IVM group. GO

enrichment resulted in 164 categories of BP, 36 of CC and 43 of MF. KEGG identified 186 significant pathways: 78 increased and 108 decreased in pre-IVM group. FAPESP funding 12/50533-2, 13/05083-1, 12/10737-8 and 12/23409-9.



### Eduardo Razza

*Institute of Biosciences, University of São Paulo State (UNESP)*

Eduardo's background spans the fields of oocyte development, embryo manipulation and molecular analysis. As a member of the bilateral Danish-Brazilian consortium: Genomic Improvement of fertilisation Traits, a.k.a. GIFT, he has developed his PhD research in the University of Copenhagen, Denmark, and at the University of São Paulo State, Brazil. Eduardo develops and collaborates on many different reproductive researches using the bovine in vitro model to better understand the molecular aspects of oocyte maturation and pre-implantation embryo development.

### B2

#### The ART of sperm

### B2.1 Novel prognostic factors for sperm retrieval in patients with non-obstructive azoospermia undergoing microdissection testicular extraction (mTESE)

**Luo Seraphina R<sup>1</sup>; Jayasena Channa<sup>1</sup>; Jarvis Sheba<sup>1</sup>; Schoonejans Josca M<sup>1</sup>; Mannion Ethna<sup>2</sup>; Balendra Shiana<sup>3</sup>; Dhillon Waljit S<sup>1</sup>; Ramsay Jonathan WA<sup>3</sup>**

<sup>1</sup>Hammersmith Hospital, Imperial College London; <sup>2</sup>Charing Cross Hospital, London; <sup>3</sup>Hammersmith Hospital, London

**Background:** Non-obstructive azoospermia (NOA) accounts for approximately 9% of male infertility. A histological diagnosis of Sertoli-cell only syndrome (SCO) is particularly devastating due to its association with low sperm retrieval rates (Schulze et al., 1999, Su et al., 1999). SCO histology can occur concurrently with other major histological patterns (complete spermatogenesis, CS; hypo-spermatogenesis, HS; maturation arrest, MA). However, no previous study has measured to what extent the prognosis of sperm retrieval in patients with SCO histology is modified by concurrent histological patterns.

**Objectives:** (1) Determine the frequency and subtypes of mixed pattern histology observed following microsurgical testicular sperm extraction (mTESE) in patients with NOA. (2) Investigate how subtypes of mixed pattern histology modify the probability of sperm retrieval following mTESE.

**Methods:** Data of men with NOA undergoing mTESE at a single centre by a single surgeon (2002-2015) was reviewed.

**Results:** (1) Mixed pattern histology was observed in 67/163 (41.1%) patients. (2) Mixed pattern histology significantly modified sperm retrieval rates for SCO. When compared with pure SCO, the probability of sperm retrieval was 9-fold higher when SCO occurred in combination with CS (OR 9.1 [1.4-57.6], P<0.05), 6-fold higher when combined with HS (OR 6.2

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[2.1-17.9],  $P < 0.001$ ) and 4-fold higher when combined with MA (OR 3.6 [1.4-9.8],  $P < 0.01$ ). Mixed CS, HS and MA did not have distinct probabilities of sperm retrieval when compared with pure CS, HS and MA, respectively.

**Conclusions:** Our data suggest that mixed pattern histology is a common phenomenon in azoospermic patients with SCO. Furthermore, SCO and concurrent CS, HS or MA have 9-, 6- and 4-fold higher sperm retrieval rates following mTESE when compared with pure SCO histology. These data have important clinical implications for patients with NOA.

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### Seraphina Rong Luo

*Hammersmith Hospital*

Seraphina Rong Luo is currently an undergraduate medical student at Imperial College London. She was awarded a summer studentship under the supervision of Mr Jonathan Ramsay (Consultant Andrologist) and Dr Channa Jayasena (Consultant in Reproductive Endocrinology) to study the relationship between histology and sperm retrieval outcomes in men with non-obstructive azoospermia.

theoretical concern exists over their use.

**Outcomes:** A variety of novel sperm pathologies were detected in the low fertilisation/TFF group, including reduced kremer penetration, abnormal calcium response and abnormal electrophysiology indicating putative CatSper / K-channel abnormalities, most of which can be overcome by ICSI. 37.8% (14/37; IVF 38.1%  $n=8$ ; ICSI 37.5%  $n=6$ ) were identified to have significantly lower expression of PLCz protein. After appropriate counselling, nine of these couples have subsequently undergone ICSI and AOA (GM508 Cult Active; Gynemed - containing calcium ionophore A23187), with average M2 oocyte fertilisation rate 68.0%. To date, there have been 3 term liveborn infants, 2 ongoing pregnancies, 2 pregnancy outcomes awaited, as well as further embryos cryostored for future use.

**Discussion:** Unexpected low/TFF is an uncommon yet devastating problem. We suggest an algorithm to query potential underlying causes and provide some evidence that sperm dysfunction represents a significant element of apparently unexplained cases. There is an unmet need for enhanced sperm assessment, including PLCz quantification, to identify those who would benefit from AOA.



### Sarah Martins da Silva

*Reproductive and Developmental Biology, School of Medicine*

Sarah Martins da Silva is a consultant gynaecologist and honorary senior lecturer based at Ninewells Assisted Conception Unit and University of Dundee. She runs a translational research programme focused around male infertility, sperm biology and drug discovery, funded by CSO, MRC and TENOVUS Scotland. Her previous research as a MRC Clinical Fellow examined the processes of folliculogenesis and in vitro oocyte maturation. In-depth understanding of both eggs and sperm thus places her strongly to research gamete interaction and events at fertilisation. Her clinical activities include general and tertiary infertility clinics, ultrasound scanning, fertility and gynaecology surgery, including surgical sperm retrieval. She also runs a sperm studies research clinic for couples affected by unexplained total failed (or low <25%) fertilisation, which accepts national referrals.

## B2.2 Improving art outcome following unexplained total failed fertilisation

**Martins da Silva Sarah<sup>1</sup>; Milne P<sup>2</sup>; Williams H<sup>3</sup>; Brown S<sup>4</sup>; Adamani SN<sup>5</sup>; Jones C<sup>5</sup>; Mounce G<sup>5</sup>; Coward K<sup>5</sup>; Barratt C<sup>1</sup>**

<sup>1</sup>Reproductive and Developmental Biology, School of Medicine; <sup>2</sup>Assisted Conception Unit, Ninewells Hospital; <sup>3</sup>Reproductive and Developmental Biology and Assisted Conception Unit, Ninewells Hospital; <sup>4</sup>School of Science, Engineering and Technology, Abertay University; <sup>5</sup>Institute of Reproductive Sciences

**Aims/objectives:** Total failed fertilisation (TFF) is estimated to affect 4-7% IVF and 3-5% ICSI cycles. Improvement of the next treatment cycle is challenging due to the inherent difficulties correcting a poorly understood process.

**Content of presentation:** According to our locally developed guideline, problems with ovarian stimulation, egg maturity/maternal age and laboratory procedures were excluded before a conclusion of unexplained low fertilisation/TFF. Affected couples were recruited to attend a sperm studies research clinic (IVF  $n=21$ ; ICSI  $n=16$ ). Sperm samples were subjected to enhanced analysis, including computer-assisted sperm analysis (CASA), Kremer penetration testing, functional calcium response (FLUOstar), phospholipase C zeta (PLCz) immunocytochemistry and single-cell patch clamp electrophysiology studies.

**Relevance/impact:** Unexplained low fertilisation/TFF following ART is a devastating event, however not all patients affected benefit from use of artificial oocyte activators (AOA), and

## B2.3 The clinical value in assessing sperm total aneuploidy rate in couples undergoing failed intracytoplasmic sperm injection (ICSI) and its correlation with semen parameters

**Bracewell-Milnes Timothy<sup>1</sup>; Saso Srdjan<sup>1</sup>; Bora Shabana<sup>2</sup>; Thum Meen-Yau<sup>2</sup>**

<sup>1</sup>Imperial College London; <sup>2</sup>Lister Fertility Clinic

**Introduction:** A potential cause of male factor infertility is high levels of sperm nuclear DNA damage, or DNA fragmentation. Several studies have compared infertile men to fertile controls and found a higher rate of DNA damage<sup>1,2</sup>. DNA fragmentation has also been associated with a poorer IVF outcome with an increased rate of failure to obtain blastocysts<sup>3</sup>, reduced implantation rates<sup>3</sup>, and increased incidence of miscarriage<sup>4</sup>. DNA integrity has therefore emerged in recent years as a novel parameter of semen quality and a potential fertility predictor,



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but despite this knowledge, there is a distinct lack of clinical guidelines on DNA integrity assessment.

**Methods:** 116 couples that failed at least one ICSI cycles underwent sperm DNA fragmentation index (SDFI) (n=116). For the SDFI, a threshold of 30% was used to discriminate between samples with normal and elevated levels of DNA-damaged spermatozoa. Comparison was made with seminal fluid analysis (SFA) using WHO 2010 criteria<sup>5</sup>.

**Results:** 116 patients underwent sperm aneuploidy assessment. Karyotyping was performed in 48.3% (n=56) of male patients and was normal in all of them. There was no association found between DNA fragmentation semen quality parameters studied (sperm concentration, Pearson correlation, R=0.268, p=0.09; sperm motility, Pearson correlation, R=0.135, p=0.22) and this was consistent when the samples were divided into groups according to World Health Organisation criteria (WHO, 2010). Of the patients studies 28.87% of their sperm had a raised DFDI.

The associations between total aneuploidy rate (TAR) and sperm integrity parameters are revealed a positive and statistically significant 2.5 fold increase in sperm displaying DNA fragmentation with a raised TAR (Pearson correlation, R=0.184, p<0.05; One-way ANOVA, p<0.05).

**Discussion:** There was no association between a raised DFDI and abnormal sperm parameters. However, a strong association was demonstrated between raised TAR and DFDI. Normal appearing sperm could be selected in this failed ICSI group with a raised DFDI, which should impact.

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### Timothy Bracewell-Milnes

*Imperial College London*

Timothy Bracewell-Milnes graduated from Imperial College School of Medicine in 2007. In 2009 he was accepted into South London

specialty training in obstetrics and gynaecology and became a member of the Royal College of Obstetrics and Gynaecology in 2014. He is currently undertaking a PhD at Imperial College London entitled 'The immunology and metabolomics of endometrial receptivity to improve screening and prediction of Recurrent Failed In Vitro Fertilisation and Recurrent Spontaneous Miscarriage'. He is also involved in research on

the psychological aspects of egg donation and has worked with the 'Womb Transplant UK' group for the last 3 years.

## B2.4 Profiling the intracellular calcium dynamics in single spermatozoa and their association with IVF fertilisation success

**Kelly Mark<sup>1</sup>; Brown Sean<sup>2</sup>; Ramalingam Mythili<sup>3</sup>; Martins da Silva Sarah<sup>1</sup>; Publicover Stephen<sup>4</sup>; Barratt Christopher<sup>1</sup>**

<sup>1</sup>University of Dundee; <sup>2</sup>University of Abertay; <sup>3</sup>NHS Tayside; <sup>4</sup>University of Birmingham

Calcium entry and regulation is an essential component of normal sperm that enables multiple functions including the acrosome reaction, motility and fertilisation (1). Dysregulation of calcium pathways in populations of human sperm has previously been shown to directly affect fertilisation outcomes (2, 3). However to date, no information is available at the single cell level. As such, we do not know if all cells in a population have equal calcium regulatory capacity. Using single cell fluorescence imaging, we examined the following hypothesis: a) Spermatozoa from patients undergoing IVF have different calcium regulatory profiles in comparison to healthy donors, b) These different profiles are related to fertilisation capacity. The majority of spermatozoa from IVF patients who successfully fertilised (2 pronuclei and polar bodies observed) displayed a typical biphasic calcium increase in response to progesterone (3.6uM) with a peak increase in fluo4 fluorescence of  $171.8 \pm 11.3\%$  (n= 53 patients). Similarly, in response to progesterone, ICSI patient's cells also displayed a biphasic increase of calcium however the peak was significantly reduced at  $92.4 \pm 13\%$  (p<0.01, n=21). Intriguingly, spermatozoa from patients that failed to fertilise or previously failed in an IVF cycle displayed a limited biphasic response and significantly reduced peak at  $37.9 \pm 10.8\%$  (p<0.001, n=11). Interestingly, the occurrence of progesterone-induced calcium oscillations varied greatly among patients who successfully fertilised at IVF. Patient 1 displayed 0 % of calcium oscillations but had an 83.3 % fertilisation rate, n=6 eggs, 45 cells. In contrast, Patient 2 displayed 81 % of calcium oscillating cells with a fertilisation rate of 78 %, n=9 eggs, 41 cells. Uniquely, we have described a complex yet simple potential indication for successful fertilisation based upon single cell calcium dynamics when challenged with progesterone. Work supported by MRC, ethical approval (13/ES/0091).

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### Mark Kelly

*University of Dundee*

Mark is a postdoctoral research assistant in the lab of Professor Christopher Barratt at the University of Dundee which in collaboration with



the Assisted Conception Unit, Ninewells Hospital, primarily focuses on understanding the function of the human gamete (sperm and egg) and identify the key factors in the normal process of the union if the gametes (in vivo and in vitro) and subsequent development of the human embryos. The research uses cutting edge technology, combined with donor and patients samples, allows the lab to have a very strong translational focus. Mark currently works on understanding the regulation of calcium signalling in human sperm and how the dynamics of calcium regulation may affect the outcome of IVF success.

of Alicante (Spain) and then, she specialised in human embryology with the Master's Degree in Experimental and Clinical Biology about Human Assisted Reproduction at Hospital Universitari i Politècnic La Fe (Valencia, Spain).

### B2.5 Sperm preparation and egg activation for bovine intracytoplasmic sperm injection (ICSI)

**Gomez-Martinez Judith<sup>1</sup>; Alberio Ramiro<sup>1</sup>; Woodward Bryan<sup>1</sup>; Kershaw Claire<sup>2</sup>; Sinclair Kevin<sup>1</sup>**

<sup>1</sup>University of Nottingham; <sup>2</sup>Harper Adams University College

Bovine ICSI can overcome deficiencies associated with poor sperm viability and motility (e.g. with frozen-thawed sexed semen), but its efficiency is poor. This may be due to suboptimal sperm capacitation, leading to impaired acrosome reaction (AR). Existing bovine ICSI protocols also involve assisted egg activation, which we seek to refine in order to improve ICSI success. Working initially with Percoll-gradient separated semen from a single sire, in three replicated experiments we found that Lyshophosphatidylcholine (LPC) treatment (100 µg/ml, 15 min) increased ( $P=0.007$ ) the proportion of AR sperm (determined by lectin immunofluorescence) compared to non-treated controls ( $0.74\pm0.019$  vs  $0.37\pm0.021$ ). We then assessed dose (10, 40, 80 and 100 µg/ml) and duration of exposure (0, 15, 60 and 120 min) of heparin during sperm preparation followed by LPC treatment. In four replicated experiments,  $\geq 40$  µg/ml heparin for a minimum of 15 min led to the highest ( $P<0.001$ ) proportion of ( $\sim 0.80$ ) of AR sperm. Next we determined optimal protocols for parthenogenetic activation. In four replicate experiments ethanol (7% for 5 min) plus 5 h cyclohexamide (CHX; 10 µg/ml) and cytochalasin B (CB; 7.5 µg/ml (to produce diploid zygotes)) was similar to calcium ionophore A23187 (Cal; 5 µg/ml for 5 min) plus CHX/CB (cleaved of activated,  $0.79\pm0.036$  vs  $0.87\pm0.029$ ; and blastocysts of cleaved,  $0.31\pm0.10$  vs  $0.11\pm0.07$ ). In five additional replicated experiments, activation with SrCl<sub>2</sub> (20mM) for 6 h plus CB and Cal, increased the proportion cleaved of activated ( $0.59\pm0.042$  vs  $0.26\pm0.040$ ;  $P=0.013$ ) and blastocysts of cleaved ( $0.36\pm0.08$  vs  $0.12\pm0.07$ ;  $P=0.031$ ), and increased blastocyst cell number (126 vs 68) relative to SrCl<sub>2</sub>/CB alone. Consequently, ongoing experiments are comparing standard in vitro fertilisation with ICSI where sperm are exposed to 40 µg/ml heparin for 15 min followed by LPC treatment prior to ICSI, and eggs are activated with Cal+SrCl<sub>2</sub> (but without CB) following ICSI.



**Judith Gomez-Martinez**

*University of Nottingham*

Judith is currently a PhD student, whose work is focused in the optimisation of certain artificial reproductive techniques for genetic improvement in cattle at University of Nottingham (UK). Judith studied her Bachelor's Degree in Biology at University

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### B3 Fertility preservation

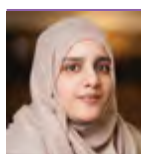
#### B3.1 Investigating the role of somatic cells in follicle dysregulation observed in a mouse model of Premature Ovarian Insufficiency using the reaggregated ovary technique

**Sheikh Sairah; Williams Suzannah**  
*University of Oxford*

**Introduction:** Premature Ovarian Insufficiency (POI) is a condition that affects 1-3% of women and is idiopathic in the majority of cases. In a mouse model of POI, the Double Mutant (DM), females show an age dependent decrease in fertility with females being subfertile at 6-weeks and infertile at 9-weeks of age. By 3 months, DM females exhibit POI with ovaries containing fewer developing follicles but more primary 3a follicles. Previously, using the reaggregated ovary (RO) technique we demonstrated germ cells from infertile DM females retained the potential to develop follicles when combined with wildtype somatic cells suggesting a defect in somatic cell function. Here we assess somatic cell function by reaggregating DM somatic cells with wildtype newborn germ cells.

**Methods:** This study was approved by the Local Ethical Review Panel (University of Oxford). Production of a reaggregated ovary involves the separation and isolation of germ and somatic cells by differential plate adhesion, and then the two cell types are combined to form a pellet. ROs were generated using somatic cells from Control (Mgat1FFC1galt1FF) or DM (Mgat1FFC1galt1FF:ZP3Cre) mice at 9-weeks of age and germ cells from newborn wildtype mice. ROs were transplanted for 21 days beneath the kidney capsule of an ovariectomised immunocompromised mouse.

**Results and discussion:** ROs generated using Control somatic cells and wildtype germ cells (n=3) contained follicles at all stages of development including late antral. Although DM somatic cell ROs (n=3) contained some follicles at later stages of development, the previous accumulation of primary follicles still exists. In the DM mouse model, gene deletion occurs specifically in the oocyte whilst all other cells are unaffected; this indicates that the oocyte-specific deletion carried by the DM mouse is affecting somatic cell physiology, imprinting the 'POI phenotype' and therefore the ability of ovarian somatic cells to sustain follicle development.



**Sairah Sheikh**  
*University of Oxford*

Sairah is a DPhil student at the University of Oxford with Dr Suzannah Williams. Her thesis has focused on investigating the mechanism of Premature Ovarian Insufficiency in a mouse model. Prior to this, she completed a BSc (Hons) in Biomedical Sciences at Queen Mary University of London and MSc Infection and Immunity at University College of London. Her work is supported by the EPA Cephalosporin Scholarship (Linacre College) and the Leverhulme Postgraduate Bursary.

#### B3.2 Ethanol extract of Moringa oleifera leaves attenuate cyclophosphamide-induced testicular toxicity by improving endocrine functions

**Nayak Guruprasad<sup>1</sup>; Khandige Nalini<sup>1</sup>; Mutalik Srinivas<sup>2</sup>; Kalthur Guruprasad<sup>1</sup>; Adiga Satish Kumar<sup>1</sup>**  
*<sup>1</sup>Kasturba Medical College, Manipal University; <sup>2</sup>Manipal College of Pharmaceutical Science, Manipal University*

Prevention of testicular toxicity during chemotherapy using natural compounds is gaining importance in the field of reproductive medicine and cancer biology, due to their low toxicity. Our previous studies have shown that ethanol extract of Moringa oleifera leaves (MOE) mitigates cyclophosphamide (CP)-induced testicular toxicity and improves sperm function. The present study is aimed at understanding whether the chemoprotective action of MOE is mediated through improving the endocrine functions of the testis. Adult mice were injected with MOE (100 mg/kg body weight, 5 days a week, 4 weeks) and CP (100 mg/kg body weight, once a week, 3 weeks) alone or in combination. 35 day after first CP injection, testosterone, follicle stimulating hormone (FSH) and inhibin B levels were assessed in blood and testis. Further, expressions of genes pertaining to specific cell types in testis were analysed by quantitative reverse transcriptase PCR (qRT-PCR). A non-significant decrease in testosterone (testis and serum) and unaltered expression of 17 $\beta$ -hydroxysteroid dehydrogenase (17 $\beta$ -Hsd) was observed in CP treated mice. FSH was found to be significantly elevated in serum and testis (p<0.001) while, inhibin B level was decreased significantly in serum (p<0.05) and non-significantly in testis. In addition, CP treatment down-regulated the expression of spermatogonial cell specific genes Oct4 and Vasa (p<0.001). Sertoli cell specific genes like androgen binding protein (Abp) (p<0.001) was down-regulated while Transferrin and FSH receptor (Fshr, p<0.001) was up-regulated. In MOE+CP group decreased FSH and increased inhibin B levels were observed in serum and testis. In addition, significant up-regulation of Oct4, Vasa and Abp and down-regulation of Transferrin and Fshr was observed. These results demonstrate that MOE ameliorated CP-induced testicular damage by improving endocrine functions and modulating the expression of Oct4, Vasa, Abp, Transferrin and Fshr genes.



**Guruprasad Nayak**  
*Kasturba Medical College, Manipal University*

Guruprasad Nayak obtained his master (MSc) degree in Medical Biochemistry from Kasturba Medical College, Manipal University, Manipal, India. He worked as research assistant in this institute for three years in ICMR funded project. He has publications in reputed journals such as Andrologia, Journal of Ethnopharmacology and Environmental Toxicology and Applied Pharmacology. Currently he is pursuing PhD at Manipal University under the guidance of Dr Guruprasad Kalthur on male fertility preservation using natural compounds. His areas of interest are reproductive toxicology, proteomics and metabolomics.

### B3.3 Human fetal testis xenografting as a model for developing fertility preservation strategies for prepubertal boys

**Hutka Marsida<sup>1</sup>; Mitchell Rod<sup>2</sup>**

<sup>1</sup>University of Edinburgh/MRC Centre for Reproductive Health

**Background/aim:** Prepubertal boys undergoing gonadotoxic therapies are unable to produce spermatozoa and therefore have no options for fertility preservation<sup>1</sup>. Given the limited availability of human prepubertal testis tissue for research, we utilised human fetal testis (HFT) xenografts as a model for immature human testis development in order to investigate factors required for ex-vivo testis development<sup>2</sup>.

**Method:** HFT tissue was xenografted subcutaneously into castrated adult nude mice. Host mice received subcutaneous injections of gonadotrophins (hCG and/or FSH), according to several short- (3-4 months) or long-term (9-12 months) regimens. Immunohistochemistry for expression of germ (MAGE-A4, spermatogonial marker; gH2AX, meiotic marker), Sertoli (Androgen Receptor (AR), 'mature' or anti-Müllerian hormone (AMH), 'immature' Sertoli cells) and steroidogenic Leydig cell (CYP11A1) markers were compared in xenografts from the different treatment groups.

**Results:** In short-term xenografts hCG treatment supported the maintenance of steroidogenesis and survival of spermatogonia, whilst the addition of FSH did not increase germ cell development or Sertoli cell maturation. In long-term xenografts, hCG treatment maintained steroidogenesis and led to 'partial' Sertoli cell maturation (AMH+/AR+) as opposed to xenografts in which hCG was withdrawn for the final 5 months. Interestingly, spermatogonial survival was increased and gH2AX was expressed in long-term hCG exposed xenografts.

**Conclusions:** The present study demonstrates that exogenous hCG stimulation of xenografted HFT supports initiation and maintenance of steroidogenesis, Sertoli cell maturation and germ cell survival/development. This may be important for developing strategies of ex-vivo testis development for fertility preservation in humans.

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**Marsida Hutka**

*The University of Edinburgh*

Marsida Hutka is a third year PhD student at the University of Edinburgh under the supervision of Dr Rod Mitchell in the Centre for Reproductive Health (<http://www.crh.ed.ac.uk/>). She is currently working on a project aimed at generating sperm using human fetal testis xenografts. Her project funded by Marie Curie ITN EU-FP7 is part of the GROWSPERM (<http://growspem.eu/>), a network that joins different EU partners to investigate in vitro and in vivo strategies for sperm development. Marsida completed her MSc in Medical Biotechnology and Molecular Medicine at the

University of Milan. After obtaining her MSc she immediately started working at the Institute of Genetic Medicine (Newcastle University) and at the Northern Institute for Cancer Research (Newcastle University).

### B3.4 Can tyrosine kinase signalling protect the ovary from cisplatin-induced damage?

**Stefansdottir Agnes; Lopes Federica; Anderson Richard; Spears Norah**

*University of Edinburgh*

**Background:** The number of patients surviving cancer has doubled in the past 40 years, but cancer treatments can result in gonadal failure and infertility. Cisplatin is a widely used chemotherapy agent in the treatment of various common childhood cancers. Cisplatin, however, also has an off-target effect on ovarian germ cells where it activates a parallel cell death pathway mediated by the tyrosine kinase (TK) c-Abl: c-Abl, in turn, upregulates p63, the ovarian homologue of p53 [1]. Activation of this pathway in the oocyte results in cell death, giving the potential for TK inhibitors to protect the ovaries. Here, we examine the protective capacity of a set of specific TK inhibitors against cisplatin-induced damage.

**Methods:** Postnatal day 4-5 mouse ovaries were collected from wild-type mice, cut into eight fragments and cultured for 6 days in a 24-well plate, during which time they attach and form a monolayer. Fragments were exposed to cisplatin +/- a TK inhibitor from a library supplied by GlaxoSmithKline, for the final 24hrs of culture. Health of growing follicles was examined following staining with a vital-dye (Trypan Blue), taken up only by unhealthy cells.

**Results & Conclusion:** Ovary fragments cultured with 10 µM cisplatin alone only had 30% of healthy follicles remaining, compared with 100% in control cultures. Fragments cultured with both cisplatin and a TK inhibitor against the p38-MAPK pathway showed a 108% increase in the proportion of healthy follicles compared with fragments cultured with cisplatin alone ( $p < 0.05$ ). In contrast, inhibition of VEGF2 kinase during cisplatin treatment resulted in a 59% reduction in follicle health compared with cisplatin treatment alone ( $p < 0.05$ ).

In conclusion, our data suggest that individual TK pathways affect the cisplatin-exposed ovary differently, with the p38-MAPK pathway able to ameliorate the damaging effect of cisplatin on follicle health, while the VEGF2 pathway exacerbates it.

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**Agnes Stefansdottir**

*The University of Edinburgh*

Agnes Stefansdottir is a postdoctoral research fellow at the University of Edinburgh in the laboratory of Norah Spears. She completed a Bachelor of Science (Honours) degree at the University of Aberdeen in 2010, graduating with First Class Honours. Agnes received her PhD from the University of Edinburgh in 2014. Her



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PhD project focused on establishing a novel embryonic mouse ovary culture system, to examine the effects of pharmaceutical and environmental compounds on the developing ovary in vitro. Since completing her PhD she has worked as a postdoctoral research fellow with Norah Spears, investigating the ability of a range of tyrosine kinase inhibitors to protect the ovary against chemotherapy-induced damage. In 2016 she received the Society for Reproduction and Fertility Postdoctoral Prize for her talk at the annual SRF conference in Winchester.

### B3.5 Development of a survey to assess interest in fertility preservation among children and adolescents with cancer: The cancer and reproductive health (CAREh) in kids and teens survey

**Panagiotopoulou Nikoletta<sup>1</sup>; van Delft Frederik W<sup>2</sup>; Hale Juliet<sup>3</sup>; Stewart Jane<sup>4</sup>**

<sup>1</sup>Aberdeen Maternity Hospital; <sup>2</sup>Northern Institute for Cancer Research, Newcastle University; <sup>3</sup>The Great North Children's Hospital, Newcastle Upon Tyne Hospitals Trust; <sup>4</sup>Newcastle Fertility Centre, Newcastle-upon-Tyne Hospitals NHS Foundation Trust

**Aims/objectives:** To develop a survey to accurately assess fertility preservation interest among children by proxy and adolescents with cancer.

**Content of presentation:** Although fertility preservation treatment options have increased, a limited number of children and adolescents with cancer undergo fertility preservation counselling or treatment albeit with subsequent regret. A valid method for assessing interest in fertility preservation at the time of cancer diagnosis is therefore needed to proceed with future interventions to support young cancer patients' decision-making and advance technologies aiming at reducing future infertility risk.

An iterative process was used to develop the survey. First, we conducted a meta-synthesis on barriers towards fertility preservation. We also reviewed previous fertility preservation surveys to draft initial survey items. Focus groups of laymen as well as fertility and oncology physicians generated additional themes. Two paediatric and adolescent oncology experts subsequently reviewed the items and items with low significance in assessing fertility preservation interest were dropped. The revised survey was pretested with 71 respondents.

**Relevance/impact:** Our developed survey tool could be used to evaluate fertility preservation interest and subsequently support patients' decision-making and care-plans formulation.

**Outcomes:** The initial survey contained 15 items in four content domains: (1) Fertility preservation awareness; (2) Attitudes about fertility preservation care; (3) Risk/benefit balance perceptions; and (4) Attitudes towards experimental fertility preservation treatment options. Focus groups data yielded one additional survey item. Expert review of the survey resulted in the deletion of two of 16 items and revision to four of the remaining 14 items. Participant pretesting confirmed face validity, usability, item understandability and scale reliability. The final survey contains 14 items in the original four content domains.

Discussion: The cancer and reproductive health in kids and teens survey was constructed using qualitative methodology to identify fertility-preservation-keen young cancer survivors and has content and face validity.



#### Nikoletta Panagiotopoulou

*Aberdeen Maternity Hospital*

Nikoletta Panagiotopoulou, who is currently a sub-specialty trainee in reproductive medicine and surgery, has been working on a set of linked projects that aim to assist in the development of safe and effective fertility preservation programmes for children and young people with cancer. She has secured scholarships from Wellbeing of Women and the National Institute for Health and Care Excellence (NICE) to support her work.

### B3.6 A nationwide UK survey on female fertility preservation prior to cancer treatment

**Abdallah Yazan<sup>1</sup>; Briggs Jonathan<sup>2</sup>; Jones Joshua<sup>3</sup>; Horne Gregory<sup>1</sup>; Fitzgerald Cheryl<sup>1</sup>**

<sup>1</sup>Manchester IVF; <sup>2</sup>Medical Student; <sup>3</sup>Homerton Hospital

**Aim:** The aim of this national survey was to examine the provision of fertility preservation for female oncology patients prior to cancer treatments, given their well-established gonadotoxic effects. The National Institute for Health and Care Excellence (NICE) recommends that all such women are seen by a fertility specialist prior to treatment and proceed to NHS-funded oocyte or embryo storage, without being subjected to restrictive In vitro fertilisation (IVF) eligibility criteria.

**Methods:** Questionnaires were sent to all UK registered IVF centres enquiring about the provision of egg or embryo cryopreservation as well as about funding for female oncology patients. Data were also obtained from the Human Fertilisation and Embryology Authority (HFEA) on the number of cryopreservation cycles in 2013 and 2014.

**Results:** Of 60 responding centres, 53 (88%) offered fertility preservation. Only 6 (11%) centres performed more than 25 oocyte or embryo cryopreservation cycles per year, with 33 centres (62%) treating fewer than 10 women per year. 44 (90%) reported some NHS funding but only 12 (23%) centres having automatic funding and only 26 (49%) centres able to offer NHS treatment to patients who did not fulfil local IVF eligibility criteria. The HFEA data reported approximately 150 NHS funded oocyte cryopreservation cycles in 2014.

**Conclusion:** The provision of fertility preservation is lacking and improvements can be made in the number of referrals from oncology, the number the cryopreservation treatments and the provision of NHS funding. Oocyte cryopreservation is preferred to embryo preservation as it offers women autonomy of their own fertility whilst being as successful. Developing a national fertility preservation network and close liaison with oncology and clinical commissioning groups (CCGs) are recommended.

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### Yazan Abdallah

#### Manchester IVF

Yazan Abdallah (MD, MRCOG, PhD) is a subspecialty training in Reproductive Medicine and Surgery at Saint Mary's Hospital in

Manchester, training in full range of fertility treatments, including fertility preservation practice in male and female cancer patients. His previous research led to safer new practice in the diagnosis of miscarriage in UK in internationally in 2011. He also researched 3D USS and uterine blood flow in studying uterine receptivity. He also contributed to the work on immune suppression in uterine transplantation. Yazan also collaborated with the IOTA group focusing on the use of ultrasound in the diagnosis of ovarian cancer.

### B4

## Predicting embryo growth and development 2

### B4.1 A method to a fully automated evaluation of bovine blastocyst images based on artificial intelligence

**Rocha José Celso<sup>1</sup>; Passalia Felipe<sup>1</sup>; Matos Felipe Delestro<sup>2</sup>; Basso Andrea C.<sup>3</sup>; Gouveia Nogueira Marcelo F<sup>1</sup>**

<sup>1</sup>Sao Paulo State University (UNESP) FCL/Assis; <sup>2</sup>Institut de Biologie de l'École Normale Supérieure de Paris, Paris, France; <sup>3</sup>In Vitro Brasil SA - Mogi Mirim, Brazil

There are discrepancies when different embryologists evaluate images of embryos. Although subjective this way to classify the embryo morphology is well established. Our work attempted to mimic what the embryologist tries to evaluate on the blastocyst images and to do an artificial neural network (ANN) to learn this. In this way genetic algorithms associated with ANN were used to grade bovine blastocysts on grade 1 (excellent or good), 2 (fair) and 3 (poor; according IETS standard). After to obtain a digital image of IVF blastocyst by an inverted optic microscope (from early to expanded stages; n=482) the images were processed to standardise them and to retrieve 24 numerical variables that could define the image (e.g., Hough transform, Watershed transform, Grey scale, etc.). They were used to the input of ANN to produce a predictable output (blastocyst grading). There was a phase of training (70% of the images), validation (15%) and blind test (15%) of the ANN. The best obtained network was 76.4% effective to predict the grades (1, 2 and 3) on the blind test. The learning of the ANN was based on the classification of the images done by three different and expert embryologists. Interestingly, when the same embryologists where required to perform a second evaluation of a sample (10%) of the same images previously evaluated there were only 54% of agreement (intra-evaluator error). However, when the ANN performed the second evaluation there was 87.5% of agreement. This show that an algorithm could be more effective - in terms of robustness, objectivity and repeatability - than the embryologist itself. This concept is cover by national (INPI) and international (WIPO) patent and under a commercial evaluation of its feasibility.

FAPESP funding 12/50533-2, 13/05083-1, 06/06491-2 and 12/20110-2.



### Marcelo Nogueira

#### São Paulo State University

Marcelo Fábio Gouveia Nogueira had his under graduation at Veterinary Medicine from São Paulo State University (UNESP) in 1988, his master degree on animal reproduction at UNESP (2001) and his PhD on animal reproduction at UNESP (2005). He has experience in veterinary medicine, acting on the following subjects: Superovulation, embryo transfer, zebu cattle (*Bos indicus*), LH receptor, chimeric embryos and in vitro maturation and embryo production. Currently he is teaching as professor assistant doctor in the Department of Biological Sciences, School of Sciences and Languages, UNESP, Campus of Assis, São Paulo, Brazil. Among others his research lines include automatised evaluation of embryo images by artificial

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intelligence and alternative approaches to enhance in vitro maturation for bovine oocytes.

### B4.2 Olina Strings: Useful marker of embryo viability

**Derrick Ranya<sup>1</sup>; Hickman Cristina<sup>2</sup>; Olina Oriol<sup>2</sup>; Wilkinson Thomas<sup>2</sup>; Gwinnett Danielle<sup>2</sup>; Rattos Annabel<sup>2</sup>; Christiansen Sandy<sup>2</sup>; Abramov Benjamin<sup>2</sup>; Carby Anna<sup>2</sup>; Lavery Stuart<sup>3</sup>**

<sup>1</sup>Imperial College; <sup>2</sup>Boston Place Clinic; <sup>3</sup>The Fertility Partnership

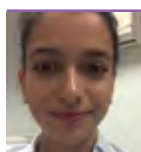
**Aims/objectives:** Olina Strings (OS) are defined as thin filaments that extend from the zona pellucida and interact with the oolemma, blastomere membrane, morula or blastocyst. We aimed to assess whether presence of OS could be used as a marker of embryo viability.

**Content of presentation:** Time-lapse imagery from 525 blastocysts were reviewed for the presence of OS, the cell stage when the OS were first observed, whether they were associated with fragmentation, ploidy (as assessed using Next Generation Sequencing) or implantation potential (foetal heart observed).

**Relevance/impact:** OS at the cellular stage have not been previously discussed in the literature, and therefore, the clinical value is unknown.

**Outcomes:** OS were observed in the majority (77%, 404/525) of embryos capable of blastulating. There was no difference in incidence of OS in embryos that were euploid (78%, 61/78) versus aneuploid (83%, 91/109;  $p > 0.05$ ); or those that implanted (73%, 64/88) versus those that did not (75%, 195/261;  $p > 0.05$ ). In the embryos where OS were observed, 97% appeared at the two-cell stage, and seemed to play a direct role in fragmentation in 95% of embryos. However, fragmentation occurred in 67% (81/121) of embryos where OS were not observed. Fragmentation occurred significantly more frequently in embryos where OS were observed compared to when OS were not observed ( $p < 0.001$ ).

**Discussion:** It is hypothesised that OS originate from the corona radiata cells interacting with the membrane of embryonic cells. This preliminary data suggests that OS may be a cause of cellular fragmentation, although the high incidence of fragmentation in string-free embryos suggests OS are not essential for fragmentation to occur. Despite increased fragmentation being associated with a reduction in embryo viability, there were no significant effects of OS on embryo ploidy or implantation. Further work is required to clarify whether the extent of OS has clinical implications.



**Ranya Derrick**

Imperial College London

Ranya is currently a fourth year medical student at Brighton and Sussex Medical School.

As part of her intercalated reproductive and developmental science BSc degree at Imperial College London, she conducted a research project at Boston Place Clinic (part of The Fertility Partnership) under the supervision of Mr Stuart Lavery and Dr Cristina Hickman. Her research involved understanding the clinical relevance of extruded embryonic fragments and how to differentiate them from cells. She identified unique embryo features not reported before, and developed and improved a novel annotation technique. She would like to express her gratitude to SRF for funding this experience.

### B4.3 Healthy baby born after preimplantation genetic diagnosis of mitochondrial DNA disease utilising next-generation sequencing

**Spath Katharina<sup>1</sup>; Babariya Dhruvi<sup>1</sup>; Konstantinidis Michalis<sup>2</sup>; Griffiths Tracey<sup>3</sup>; Spencer Jenny<sup>3</sup>; Turner Karen<sup>3</sup>; McCaffrey Caroline<sup>4</sup>; Gangrade Bhushan<sup>5</sup>; Child Tim<sup>3</sup>; Grifo James<sup>4</sup>; Patel Sejal<sup>5</sup>; Poulton Joanna<sup>6</sup>; Munne Santiago<sup>2</sup>; Wells Dagan<sup>1</sup>**

<sup>1</sup>Reprogenetics UK, University of Oxford; <sup>2</sup>Reprogenetics US; <sup>3</sup>Oxford Fertility, UK; <sup>4</sup>NYU Fertility Centre, US; <sup>5</sup>Center for Reproductive Medicine Orlando, US; <sup>6</sup>University of Oxford, UK

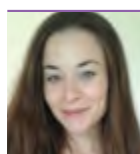
**Background:** Maternally inherited mitochondrial DNA (mtDNA) mutations lead to incurable, severe metabolic diseases. At-risk couples have limited reproductive choices. They may undergo therapeutic abortion after prenatal testing or alternatively, preimplantation genetic diagnosis (PGD). PGD minimises the risk of disease transmission by selecting mutation-free embryos or low mutation load carriers, unlikely to develop a disease.

**Objective:** Current PGD techniques for mtDNA disease do not allow incorporation of chromosome screening. To avoid the transfer of embryos affected by mtDNA mutations or aneuploidy, we developed a novel protocol based on next-generation sequencing (NGS).

**Patients:** The protocol was clinically applied to patients, referred for PGD of Leigh Syndrome (Patients 1 and 2: m.8993T>G; Patient 3: m.10191T>C). The mutation was undetectable in somatic cells of Patients 1 and 3, however children of both presented high levels of heteroplasmy (95% and 78%). Patient 2, who lost a child homoplasmic for the mutation, carried 56% of heteroplasmy.

**Results:** None of the 14 blastocysts generated by Patient 1 carried the mutation, however four were aneuploid. A single embryo transfer resulted in the birth of a healthy, mutation-free boy. Patient 2 generated one blastocyst, unaffected by the mutation, but aneuploid. One unfertilised oocyte and two arrested embryos carried 91%, 89% and 0% mutation load. Patient 3 produced four embryos. None carried the mutation, but two were aneuploid. After two failed single embryo transfers the patient conceived naturally and prenatal testing revealed a mutation-free fetus.

**Discussion:** This is the first study utilising a highly accurate NGS protocol for simultaneous detection of mtDNA mutations and aneuploidy in embryos. It is the second study reporting the birth of a mutation-free baby born after trophectoderm biopsy, supporting the testing of mtDNA disease at the blastocyst-stage. The study further provided evidence of low recurrence risk of mtDNA disease in patients with undetectable somatic mutations.



**Katharina Spath**

Reprogenetics UK, University of Oxford

Please see page 48.



### B4.4 Prostaglandin F2 $\alpha$ regulates adhesion of HTR8/SVneo trophoblast cell line

**Baryla Monika; Kaczynski Piotr; Wacławik Agnieszka**  
*Institute of Animal Reproduction and Food Research of Polish Academy of Science, Olsztyn, Poland*

Adhesion trophoblast to the endometrium is one of the most important processes prior to implantation. During this period, the uterine prostaglandin PGF2 $\alpha$  (PGF2 $\alpha$ ) content increases. On the other hand, because of PGF2 $\alpha$  luteolytic activity it is considered as a factor interrupting pregnancy. We hypothesised that PGF2 $\alpha$  may have effect on the adhesion mechanism. We have used human trophoblast HTR8/SVneo cell line. To determine effect of PGF2 $\alpha$  on human trophoblast cell line adhesion, we performed adhesion assay (Millipore ECM101 kit). HTR8/SV-neo was incubated with vehicle or PGF2 $\alpha$  (100 nM; 1  $\mu$ M) in the presence/absence of 50  $\mu$ M PTGFR antagonist (AL8810). To further confirm involvement of PGF2 $\alpha$  in adhesion we examined degree of focal adhesion kinase (FAK) phosphorylation and mitogen-activated protein kinase 1/3 (MAPK 1/3) phosphorylation in HTR8/SV-neo with the same treatments. Cells were seeded onto 6-wells plates and cultured for 48 h at 37°C in humidified atmosphere containing 5% CO<sub>2</sub>. At 90% confluence cells were pretreated for 30' (37°C/ 5% CO<sub>2</sub>) with AL8810 and after this time treated with 100 nM and 1  $\mu$ M of PGF2 $\alpha$  for 10' (37°C/ 5% CO<sub>2</sub>). Subsequently cells were harvested into Ripa buffer containing protease and phosphatase inhibitors and stored at - 35°C until western blot analysis. PGF2 $\alpha$  (1  $\mu$ M) increased (p<0.05) adhesion of HTR8/SV-neo to ECM proteins. The same dose of PGF2 $\alpha$  induced (p<0.05) FAK phosphorylation. MAPK 1/3 phosphorylation was enhanced in cells treated with 100 nM (p<0.05) and 1  $\mu$ M (p<0.001) PGF2 $\alpha$ . AL8810 was diminished all effects of PGF2 $\alpha$ . Our results indicated PGF2 $\alpha$  affects capacity of human trophoblast HTR8/SVneo cells to adhere to ECM. Moreover, PGF2 $\alpha$  regulated the activity of kinase signaling pathways that mediate trophoblast focal adhesion. Supported by the basic grant of the Institute of Animal Reproduction and Food Research of the PAS.



**Monika Baryla**

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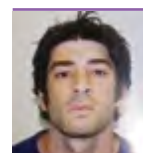
Monika is currently a PhD student in Institute of Animal Reproduction and Food Research, Polish Academy of Science, Olsztyn, Poland. Her scientific interests focuses on endocrine mechanisms between uterus and conceptus during early pregnancy, especially at the time of pre- and implantation. Main model organism uses in her studies is a pig. Monika is a member of the Society for Reproduction and Fertility (SRF) and also the Society for Biology of Reproduction (TBR).

### B4.5 Hyaluronic acid: An anti-angiogenic shield for the post-implantation embryo

**Hadas Ron<sup>1</sup>; Gershon Eran<sup>2</sup>; Cohen Aviad<sup>1</sup>; Atrakchi Ofir<sup>1</sup>; Lazar Shlomi<sup>3</sup>; Elbaz Michal<sup>2</sup>; Cohen Gadi<sup>1</sup>; Eilam-Altstadter Raya<sup>4</sup>; Dekel Nava<sup>1</sup>; Neeman Michal<sup>1</sup>**

*<sup>1</sup>The Weizmann Institute of Science; <sup>2</sup>Agricultural Research Organization, Volcani Center, Israel; <sup>3</sup>Biological Research Institute Nes Ziona, Israel; <sup>4</sup>Department of Veterinary Resources, Weizmann Institute, Israel*

The implanting embryo is embedded in the uterine stroma and maintained in a hypoxic niche, devoid of maternal blood vessels. Embryo implantation, a critical step in the establishment of pregnancy, is immediately followed by a significant increase in the permeability of the uterine blood vessels, which marks the onset of pregnancy-associated uterine neo-vascularization. Hyaluronic acid (HA) has been reported to participate in the regulation of vascular development in a number of physiological processes. Specifically, high molecular weight HA has been shown to inhibit angiogenesis, whereas its enzymatic degradation products are pro-angiogenic. On the basis of this information, we hypothesised that HA is involved in timely regulation of vascular modifications associated with implantation. To challenge this hypothesis we used several mouse models subjected to genetic manipulations. Our experiments revealed that HA deposition and degradation correlates with vascular remodeling in the implantation site during early pregnancy. Moreover, extensive changes in the distribution of HA synthesis and degrading enzymes were observed during implantation. Functional MRI inspection of pregnant mice, carrying embryos, the trophoblast cells of which over-express HA degrading enzyme, showed defective implantation. Specifically, an increased permeability of blood vessels surrounding the embryo accompanied by infiltration of endothelial cells ultimately resulted in multiple embryo resorptions. Interestingly, over-expression of HA synthesising enzyme, in trophoblast cells, resulted in the termination of pregnancy associated with reduced permeability of blood vessels in the embryonic niche and a decrease in fractional blood volume. We suggest that HA safeguards the developing embryo, prior to placenta formation, alongside with its pivotal role in vascular remodeling. Our study sheds light on the participation of the extracellular matrix in the complex chain of vascular events vital for successful pregnancy.



**Ron Hadas**

*The Weizmann Institute of Science, Olsztyn, Poland*

Ron Hadas is a PhD student in the department of Biological Regulation at the Weizmann institute of science. Ron has completed his MSc, studying 'The angiogenic role of hyaluronic acid during embryo implantation', in the labs of his two advisors: Professor Michal Neeman and Professor Nava Dekel, with whom he continued to his graduate studies. Ron has been mainly investigating the process of embryo implantation during early pregnancy, focusing on specific molecular events dictating its success or, unfortunately, responsible for its repeated failure as often seen in fertility treatments worldwide. Using live imaging modalities Ron aims at studying the crosstalk between embryo and its mother using in vitro as well as in vivo mouse models, subjected to genetic manipulations, to reveal the necessity of specific proteins, for successful embryo implantation.

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### B4.6 Does the additional transfer of a poor quality blastocyst affect clinical outcome?

**Tailor S; Vourliotis M; Francis G; Papoff F; Flouri C; Sotirchou G; Almeida P**

*Chelsea and Westminster Hospital*

**Introduction:** Emerging evidence has demonstrated that the decidualising endometrial stromal cells act as a biosensor of embryo quality, and can actively recognise and select embryos for implantation based on their developmental competence. Signals from developmentally competent embryos trigger an endometrial response which supports implantation and further development however signals from developmentally impaired embryos will elicit a stress response causing elimination of the abnormal embryo. The aim of this investigation is to determine whether the transfer of a poor quality with a good quality blastocyst negatively affects the clinical outcome.

**Materials and methods:** In a retrospective analysis, 151 fresh IVF/ICSI cycles were evaluated based on blastocyst quality. 94 cycles had one good quality blastocyst transferred (Control group) and 57 cycles had both one good and one poor quality transferred (Test group). Good blastocyst quality was defined by inner cell mass and trophectoderm grades of AA, AB, BA, BB respectively. Poor blastocyst quality was defined as BC, CB, CC grades. The main outcome measures were implantation (IR), clinical pregnancy (CPR), live birth (LBR), multiple birth (MBR) and miscarriage rates (MISCAR). Statistical analysis was performed using Fisher's exact test and t-test.

**Results:** Mean maternal age was similar between the control ( $33.5 \pm 0.36$ ) and test groups ( $34.5 \pm 0.48$ ). IR was higher in control (57.5%) compared to test groups (34.2%;  $p < 0.05$ ). However, CPR and LBR were no different between the control (CPR: 57.5%; LBR: 53.2%) and test groups (CPR: 54.4%; LBR: 54.4%). Similarly, MISCAR was comparable (Control: 5.6%; Test: 0%). Finally, MBR was significantly higher in the test than control groups (29.0% vs. 0%;  $p < 0.0001$ ).

**Conclusion:** Adding a poor quality embryo to a good quality one confers neither better nor worse clinical outcome. It is possible that the endometrium has a selective rather than a homogenous approach to permitting implantation.



**Shreena Tailor**

*Chelsea and Westminster Hospital*

Shreena Tailor is currently working as a pre-registrant embryologist at the Chelsea and Westminster Assisted Conception Unit in

London. She graduated from the University of Birmingham with a BSc (Hons) in Biological Sciences in 2007. Subsequently, she went on to obtain a Master's degree from the University of Nottingham in Assisted Reproduction Technology. Her embryology career began in 2009 where she became a trainee embryologist at Chelsea and Westminster Assisted Conception Unit. She has since been awarded The Association of Clinical Embryologists Certificate and is now working towards becoming state registered with the Health and Care Professions Council.

### B5

### Optimising health outcomes

### B5.1 An ectopic pregnancy cannot be excluded...Or can it?

**Richardson Alison<sup>1</sup>; Prior Matthew<sup>2</sup>; Hopkisson James<sup>1</sup>; Campbell Bruce<sup>3</sup>; Raine-Fenning Nick<sup>1</sup>**

*<sup>1</sup>University of Nottingham/Nurture Fertility; <sup>2</sup>University of Nottingham/Nottinghamshire Hospitals NHS Trust; <sup>3</sup>University of Nottingham*

**Introduction:** The double decidual sac sign (DDSS) was proposed in the 1980s to help differentiate a gestation sac from a pseudosac. However, several studies (of largely poorly quality) report variable diagnostic accuracy(1). Furthermore ultrasound technology has advanced considerably over the last 30 years.

**Objectives:** To determine (1) the diagnostic accuracy of the DDSS for predicting an intrauterine pregnancy (IUP) prior to visualisation of embryonic contents using modern transvaginal ultrasound (TVS) and (2) the inter- and intra-observer reliability associated with the DDSS.

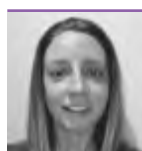
**Methods:** The diagnostic accuracy study was conducted following STARD guidelines. Ethical approval was obtained. Participants were recruited prospectively between 01.01.15 and 31.10.15 following IVF/ICSI treatment. Women underwent a TVS at 32-34 days gestation to look for an intrauterine fluid collection (IUFC). If observed, the presence or absence of the DDSS was recorded. Participants then underwent a TVS at 7 weeks gestation to confirm pregnancy location. To assess reliability, images from 25 cases were distributed to eighteen observers to interpret. Six observers subsequently underwent training and then assessed the images again.

**Results:** 67 IUFCs were included, of which 61 exhibited the DDSS and 65 were subsequently proven to be IUPs. There were two ectopic pregnancies, neither of which demonstrated the DDSS. The DDSS was therefore found to have a sensitivity 93.9% (95%CI 85.0%-98.3%), specificity 100% (95%CI 15.8%-100%) and overall diagnostic accuracy 94.0% (95%CI 88.3%-99.7%) for predicting an IUP. Inter-observer reliability was initially only 'fair' ( $K=0.2503$ ) but increased significantly after training ( $K=0.700$ ). Intra-observer reliability ranged from 'substantial' ( $K=0.6528$ ) to 'almost perfect' ( $K=0.9200$ ).

**Conclusion:** Using modern TVS, the DDSS is not only accurate in its ability to confirm an IUP prior to visualization of embryonic contents, but also both reliable and precise rendering it very useful in clinical practice as it differentiates a gestation sac from a pseudosac.

#### References:

(1) Richardson, A., Gallos, I., Dobson, S., Campbell, B.K., Coomarasamy, A., and Raine-Fenning, N. Accuracy of first-trimester ultrasound in diagnosis of intrauterine pregnancy prior to visualisation of the yolk sac: A systematic review and meta-analysis. *Ultrasound Obstet Gynecol.* 2015;46(2):142-9.



**Alison Richardson**

*University of Nottingham*

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## SHORT PAPER SESSIONS

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### B5.2 Live birth rates following the transfer of atypically fertilised embryos in an IVF/ICSI setting

**Berry Victoria<sup>1</sup>; Gibbons Corrina<sup>2</sup>; Wilson Paul<sup>2</sup>; Gordon Uma<sup>2</sup>**

<sup>1</sup>University Of Bristol; <sup>2</sup>Bristol Centre For Reproductive Medicine

**Aim:** To determine the live birth rates from transfer of atypically fertilised embryos during IVF/ICSI treatment cycles.

**Background:** Normal fertilisation check is undertaken between 16 and 20 hours post insemination/injection. Atypical fertilisations are seen as either having 1 pronucleus (1PN) (2-27% of oocytes) or no pronuclei (0PN) (20-30% of oocytes) present (1). These oocytes can go on to show signs of normal development as if normal fertilisation has occurred. Florescent In Situ Hybridisation (FISH) analysis of 0PN and 1PN embryos shows that a proportion of these are normally fertilised (2, 3).

**Methods:** Retrospective analysis of data from January 2008 to December 2015. Patients undertook long agonist protocol for controlled ovarian hyperstimulation, followed by egg collection and insemination through conventional IVF or ICSI. Fertilisation check was performed in our centre between 17-20 hours. There was no exclusion criteria for this analysis and patient age ranged from 27 to 46.

**Results:** From a total of 7512 cycles, 68 patients had embryos transferred which were solely atypically fertilised (0.9%). 7 of these patients achieved a pregnancy (10.3%), with 6 resulting in a live birth (8.8%).

**Discussion and conclusion:** Where solely atypically fertilised embryos are available for transfer an 8.8% live birth rate gives value in transferring these embryos where no normally fertilised embryos are available. Without genetic analysis knowing the true genetic makeup of the embryos is an uncertainty and patients should be counselled regarding low success rates and potential risks of transferring an abnormally fertilised embryo.

**Relevance:** The study adds to the limited data available on the transfer of atypically fertilised embryos. When no normally fertilised embryos are available for transfer atypically fertilised embryos can be used to achieve live births where otherwise no transfer would have occurred.

**References:**

1. Feenan, K. and Herbert, M. (2006) 'Can 'abnormally' fertilised zygotes give rise to viable embryos?', *Human Fertility*, 9(3), 157-169.
2. ItskovitzEldor, J. Kol, S. Manor, D. Lewit, N. Lightman, A. Pillar, H. and Stein, D. (1996) 'Undocumented embryos: Do not trash them, FISH them', *Human Reproduction*, 11(11), 2502-2506.
3. Adler, A. Fino, M. E. Grifo, J. Krey, L. McCaffrey, C. and Noyes, N. (2008) 'Embryo biopsy: the fate of abnormal pronuclear embryos', *Reproductive Biomedicine Online*, 17(6), 782-788.



**Victoria Berry**

*University of Bristol*

Victoria graduated from Bristol University in 2012 and started working at the Bristol Centre for Reproductive Medicine the same year as a medical laboratory assistant and progressed to her current role as an Associate IVF Technologist. Victoria hopes to train as a clinical embryologist in the future. To further develop her career,

whilst working full-time at the BCRM, Victoria has undertaken a part-time MSc in Reproduction and Development at the University of Bristol, completing this in 2016.

### B5.3 Can the transfer of a genetically affected embryo after PGD ever be justified? Questions of autonomy and welfare of the child in a case report of the transfer of an embryo affected by osteogenesis imperfecta

**Christopoulos Georgios; Stradiotto Lisa; Lavery Stuart**  
*IVF Unit, Hammersmith Hospital*

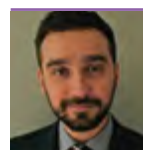
**Aims/objectives:** This is the first report to explore the ethical dilemmas surrounding the transfer of a genetically affected embryo following PGD, the couple's perspective and the Clinical Ethics Committee (CEC) recommendations. It considers the ethical position where autonomy and welfare of the child may be in conflict.

**Content:** We present the case of a patient with Crouzon syndrome and her partner with osteogenesis imperfect (OI) type 1A. After four IVF attempts with PGD for both conditions and two failed transfers of healthy embryos, the couple felt that the physical and mental strain could not allow them to proceed with further treatment. They requested to proceed with the transfer of an available embryo affected by OI. Advice was sought from the local CEC.

**Relevance/impact:** According to the HFEA Code of Practice the selection of an embryo is prohibited if it has a gene leading to serious disability. This applies only if a healthy embryo(s) is available. If not then the use of an affected embryo should be subject to consideration of the welfare of the child and receive CEC approval.

**Outcomes:** The CEC concluded that the couple were well informed through their own life experiences. A personal statement from the couple was instrumental in convincing the CEC to support treatment. The couple subsequently proceeded with the transfer of an OI-affected embryo and the pregnancy outcome is pending.

**Discussion:** Our duty to assess the welfare of children after IVF/PGD should encompass the physical, social and emotional components of their quality of life. The couple's perspective should be considered carefully and their autonomy respected. PGD was not used specifically to create an affected embryo. As the couple would normally be supported in a natural conception, we argue that they should not be denied the chance of parenthood because of the use of IVF.



**Georgios Christopoulos**

*IVF Unit, Hammersmith Hospital*

Dr Christopoulos is a subspecialty registrar in Reproductive Medicine and Surgery at Imperial College Healthcare NHS Trust. His research has focused on the safety profile of assisted conception and the use of kisspeptin as a novel oocyte maturation trigger. He recently completed his MD at Imperial College and his MSc in Advanced Gynaecological Endoscopy at the University of Surrey.



## SHORT PAPER SESSIONS

### B5.4 Slow release insemination versus conventional IUI: Initial results from a multi-centre trial

**Woodward Bryan<sup>1</sup>; Franz Maximilian<sup>2</sup>; Marschalek Julian<sup>2</sup>; Obruca Andreas<sup>3</sup>; Schenk Michael<sup>4</sup>**

<sup>1</sup>IVF Consultancy Services; <sup>2</sup>AKH Wien; <sup>3</sup>Kinderwunschzentrum Wien; <sup>4</sup>Das Kinderwunsch Institut Schenk GmbH

**Introduction:** Intra-uterine insemination (IUI) is a low technology treatment for people with unexplained infertility and mild male factor. The use of IUI as a first-line treatment for unexplained infertility has met with variable success. Over the recent years there has been renewed interest in 'slow release insemination' (SRI) as a method to improve IUI success rates. This method releases washed sperm into the uterus over a 4-hour period, compared to conventional IUI (cIUI) release, which is usually completed within 1 minute. This study aimed to compare the efficacy of SRI and cIUI.

**Method:** A randomised-controlled cross-over study in three centres specialising in IUI was performed. Sixty-three patients were recruited for ninety-three cycles. Inclusion criteria were: females <35 years with proven tubal patency; males with initial semen parameters of >10 million/ml and >50% progressive motility.

**Results:** Forty-five SRI cycle and forty-eight cIUI cycles were performed. A significantly higher pregnancy rate (+hCG) was recorded following SRI compared to cIUI: 24.4% (11/45) vs. 6.3% (3/48) (Chi-square test,  $P < 0.05$ ).

**Discussion:** Due to the lack of robust evidence to show the efficacy of IUI treatment over expectant management, the NICE Guideline CG156 (2013) recommended that people with unexplained infertility should be directed to IVF as a first-line treatment, rather than IUI. However, if the success rates following IUI can be significantly improved by controlling the slow release of progressive sperm into the uterus, rather than conventional injection of a single bolus within 1 minute, then SRI might offer a viable alternative to IVF. SRI might also be preferred to IVF, as it is a less invasive procedure, avoiding surgery or anaesthesia, reducing the amount of fertility drugs required and lowering the cost. Whilst the preliminary data is promising, further studies are needed to confirm the success of SRI.



**Bryan Woodward**

*IVF Consultancy Services*

Bryan Woodward began his career as a reproductive scientist at Sheffield Fertility Centre. He was then invited to direct the IVF laboratory at the BUPA Hospital in Leicester in the mid-90s. He went on to read for a PhD in ICSI at the University of Nottingham. He now offers international free-lance consultancy on all aspects relating to fertility management, specialising in trouble-shooting clinics to streamline and improve embryology and andrology services. He has helped to establish numerous IVF laboratories in Africa, Asia and the Caribbean, and also offers hands-on clinical embryology and andrology training. Bryan has served as Secretary for the ACE Executive Committee and is an assessor for the ACE Training Committee and for state-registration. He is presently Chair of the Association of Biomedical Andrologists (ABA) and a member of the Editorial Board for the journal Human Fertility.

### B5.5 Multivariate analysis examining the association between infertility, assisted reproduction and pregnancy outcomes in a single centre tertiary referral obstetric unit

**O'Malley Eimer; Reynolds Ciara; Daly Niamh; McKeating Aoife; Farah Nadine; Turner Michael J**  
*Coombe Women and Infants University Hospital*

**Objective:** To examine the association between a maternal history of infertility and pregnancy outcomes

**Design:** Cohort Study

**Population:** All women who delivered an infant weighing  $\geq 500$ g in 2009-13

**Methods:** We compared those who reported a history of infertility at booking with those that did not. Statistical analyses were performed to examine the associations between a history of infertility and maternal characteristics and delivery and perinatal factors using multivariate analysis.

**Results:** Of women reporting infertility ( $n=1,513$ ), 47.4% ( $n=717$ ) reported receiving treatment. Of these, 61.4% ( $n=440$ ) had assisted reproduction. Compared with women without infertility, women with infertility were older (mean 34.7 vs 30.6 years,  $p < 0.001$ ) and more were nulliparous (63.7% vs 39.8%,  $p < 0.001$ ). Among infertile women, the rate of multiple pregnancies was 13.7% compared with 1.5% ( $p < 0.001$ ). Within the cohort reporting assisted reproduction (AR), the rate of multiple pregnancy was 21.9% compared to 4.0% in the group receiving other infertility treatment ( $p < 0.001$ ). Compared to women without infertility, women with infertility had higher rates of overall Caesarean section (CS) (44.3% vs 26.0%,  $p < 0.001$ ), elective CS (22.5% vs. 12.1%,  $p < 0.001$ ) and emergency CS (21.4% vs. 13.6%,  $p < 0.001$ ). Among the cohort receiving AR, compared to those who had non-assisted reproduction treatments, the overall CS rate was 52.1% vs. 33.7%, ( $p < 0.001$ ) and higher than the cohort reporting infertility but not requiring fertility treatment (52.1% vs. 25.4%,  $p < 0.001$ ). Elective CS was performed for 26.6% of the women receiving AR compared to 11.5% of the remaining cohort receiving non-assisted reproduction treatment ( $p < 0.001$ ). The infant birth weight was  $< 2.5$ kg in 15% of women reporting infertility compared to 5.7% of those not ( $p < 0.001$ ), adjusted for multiples and gestation.

**Conclusions:** This study demonstrated that women reporting a history of infertility have a higher rate of multiple pregnancy with a higher rate of obstetric intervention and adverse perinatal outcomes.

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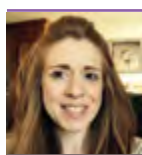
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### Eimer O'Malley

*Coombe Women and Infants University Hospital, Dublin*

Dr Eimer O'Malley completed a first class honours degree in Analytical Science in Dublin

City University prior to studying graduate entry medicine in the University of Limerick, graduating in 2011, achieving first place in obstetrics and gynaecology. She completed her basic specialist training in Obstetrics and Gynaecology in the Coombe Women and Infants University Hospital (CWIUH), a tertiary referral, stand-alone maternity hospital with approximately 9,000 deliveries per year where the research she is presenting was conducted. She is currently in the second year of the higher specialist training programme in obstetrics and gynaecology, working again in the Coombe Women and Infants University Hospital in Dublin, Ireland.

## B5.6 Development of a universal method for the preimplantation diagnosis of $\beta$ thalassaemia and sickle-cell anemia using a novel next generation sequencing approach: A new paradigm for PGD

**Kubikova Nada<sup>1</sup>; Sarasa Jonas<sup>2</sup>; Wells Dagan<sup>1</sup>**

<sup>1</sup>University of Oxford, Reprogenetics UK; <sup>2</sup>Reprogenetics UK

**Background:** Worldwide, the most common inherited disorders are caused by mutation of the beta-globin gene (HBB), responsible for beta-thalassemia and sickle cell anaemia. Traditional PGD protocols involve time-consuming test design. This is problematic in the case of HBB due to a wide diversity of mutations. Consequently, the need to develop customised tests substantially delays treatment and greatly increases the cost of PGD.

**Design:** A large multiplex PCR protocol was designed, allowing simultaneous amplification of multiple overlapping DNA fragments encompassing the entire HBB gene sequence in addition to 22 linked polymorphisms (SNPs) flanking the gene. The resulting DNA was subjected to NGS to reveal the genotype/mutation status. The protocol was validated in samples from 4 families carrying different  $\beta$ -thalassaemia mutations in addition to whole-genome amplified DNA from 24 embryos derived from couples affected by beta-thalassemia.

**Results:** The new NGS-based protocol accurately detected the mutations in the DNA samples tested, confirming all patient genotypes and correctly diagnosed all 24 embryos using the DNA derived from embryo biopsy specimens. The HBB gene plus seventeen SNPs in close proximity of the gene were successfully sequenced. This allowed the inheritance of haplotypes associated with mutant genes to be tracked with high precision, providing a supplementary means of diagnosis, additional to direct mutation detection.

**Conclusions:** The new test displayed 100% concordance when compared to the results obtained from conventional PGD or karyomapping. Importantly, no patient-specific test design or optimization was needed. As far as we are aware, this is the first report of an NGS-based method for PGD of a monogenic disorder. For disorders characterised by large numbers of

different mutations, protocols, such as that described here, provide a simple generic approach, which is substantially less time-consuming and more cost-effective. Lower costs should improve patient access to PGD, especially in less affluent parts of the world.



### Nada Kubikova

*University of Oxford, Reprogenetics UK*

Nada holds a BSc degree in Human Biology from the University of Nicosia and an MSc degree in Clinical Embryology from the

University of Oxford. Shortly after the completion of her MSc, she joined Reprogenetics UK, where she worked on clinical pre-implantation genetic diagnosis (PGD) and screening (PGS) cases until she became a full time DPhil student at the Nuffield Department of Obstetrics and Gynaecology, University of Oxford, carrying out her project under the supervision of Dr Dagan Wells. Her project focuses on development of novel protocols for detection of aneuploidies and genetic defects in human gametes and embryos, with intention to provide innovative solutions for PGD, particularly with utilisation of new technologies such as next generation sequencing (NGS).

## EXHIBITORS SYMPOSIA

### Thursday 5 January

#### Ferring symposium

Debate: Will personalised medicine contribute significantly to improving success rates in IVF?



Join us as we debate the potential contribution of personalised medicine to the success of an IVF cycle.

Chaired by:

#### Dr Nick Raine-Fenning

Associate Professor of Reproductive Medicine & Surgery,  
University of Nottingham

For:

#### Dr Stuart Lavery

Consultant Gynaecologist, Honorary Senior Lecturer,  
Imperial College and Director, IVF Hammersmith

Against:

#### Prof Charles Kingsland

Clinical Director, Liverpool Women's Hospital

### Friday 6 January

#### Merck symposium

Pre-treatment optimisation – uterus and sperm



This symposium explores the characteristics of a healthy uterus and sperm that contribute to successful pregnancy outcomes. Professor Christopher Barratt will address optimising sperm quality whilst Dr Tarek El-Toukhy will propose strategies to investigate and manage uterine pathology.

#### Prof Christopher Barratt

Head of the Reproductive Medicine Group, University of Dundee

Professor Barratt was a member of the WHO Male Fertility Semen Analysis Taskforce and is currently Director of the WHO (2012-2016) Male Fertility Expert Working Group. He was a member of the Human Fertilisation and Embryology Authority for 6 years. Professor Barratt has been on the Editorial Board of Human Reproduction, Human Fertility, Biology of Reproduction, Human Reproduction Update and Journal of Andrology and is currently Editor-in-Chief of Human Reproduction. In 2014, Professor Barratt delivered the Professor Sir Robert Edwards keynote lecture at ESHRE.

#### Dr Tarek El-Toukhy

Consultant in Reproductive Medicine and Surgery and Pre-implantation Genetic Diagnosis (PGD), Guys' and St Thomas' Hospital, London

Dr El-Toukhy is a member of the RCOG, British Fertility Society and The European Society of Human Reproduction and Embryology. Dr El-Toukhy has published over 100 papers, 20 book chapters and lectured widely both nationally and internationally. He is a scientific editor for the British Journal of Obstetrics and Gynaecology. His special interests are recurrent implantation failure, hysteroscopic surgery and PGD.

#### Finox Biotech symposium

From science to practice. Challenging myths



### Changing the stimulation dose in mid-cycle has no scientific basis

#### Prof Richard Fleming

Honorary Professor of Reproductive Medicine (Retired),  
University of Glasgow

### Introduction of the FORWARD grant

#### Prof Julian Jenkins

Finox Biotech

### DHEA study, winner of the FORWARD grant

#### Prof Roy Homburg

Head of Research, Homerton University Hospital

This symposium aims to provoke discussion on current IVF practice with a stimulating faculty of experts. Prof Richard Fleming considers the underlying science around gonadotrophin stimulation suggesting there is no benefit to change the stimulation dose in mid-IVF cycle. Prof Julian Jenkins, introduces the FORWARD grant provided by Finox Biotech to support research in reproductive medicine. Prof Roy Homburg, the first UK recipient of a FORWARD grant, examines the role of DHEA in IVF and presents a study that he is planning to address this.



## POSTER PRESENTATIONS

- 001** The role of selective serotonin re-uptake inhibitor anti-depressants in male infertility  
*Bayan Osmani, Bourn Hall Clinic, Cambridge*
- 002** Role of gonadotropins in improving outcomes for normogonadotropic male subfertility - a systematic review and meta-analysis of randomised controlled trials  
*Rekha Neelakanta Pillai, University Hospitals of Leicester NHS Trust*
- 003** Sperm mitochondrial membrane potential and superoxide production in stallion semen  
*Jane Morrell, Swedish University of Agricultural Sciences*
- 004** Investigation of sperm mitochondrial membrane potential in SLC-selected stallion sperm samples  
*Xander Brown, Oxford Brookes University*
- 005** Sperm morphology assessment without staining is more cost effective and carries minimal clinical risk  
*Jessica Meadows, Nottingham University Hospital*
- 006** A comparative evaluation of two commonly used sperm preparation techniques, density gradient centrifugation and neat swim-up using CMA3 staining and morphology  
*Rebecca King, Wales Fertility Institute*
- 007** Commercial density gradient preparations, DNA fragmentation and reactive oxygen species measured using the MiOXSYSTEM device  
*Mathew Tomlinson, University of Nottingham*
- 008** Migration-sedimentation versus density gradient separation with swim-up method of sperm preparation for in vitro fertilisation: A service evaluation  
*Mhari Eleri Middleton, Leicester Fertility Centre*
- 009** Implementation of diagnostic semen analysis (WHO 2010) into 7 fertility clinics  
*Stacy Wheat, CARE London*
- 010** Sperm DNA damage in men presenting with reproductive and non reproductive cancers  
*Sheena Lewis, Queen's University Belfast*
- 011** The clinical value in assessing sperm DNA fragmentation in couples undergoing failed intracytoplasmic sperm injection (ICSI) and its correlation with semen parameters  
*Timothy Bracewell-Milnes, Imperial College London*
- 012** DNA status and sperm parameters in semen of infertile men  
*Muhammad Riaz, University of Agriculture, Sargodha, Pakistan*
- 013** Quantitative measurement of semen viscosity shows that it affects both sperm function and the accuracy of semen analysis  
*Mathew Tomlinson, University of Nottingham*
- 014** Why we should not disregard seminal viscosity measurements  
*Mathew Tomlinson, University of Nottingham*
- 015** Use of SpermMobil for stimulation of motility in immotile sperm prior to ICSI is not detrimental to clinical outcome  
*Hannah Williams, NHS Tayside*
- 016** Farnesol, a quorum-sensing molecule from *Candida Albicans*, inhibits human sperm motility: Evidence for an effect through inhibition of CAMP signalling  
*Sarah Costello, University of Birmingham*
- 017** Comparison of cryopreservation methods (slow freezing vs. vitrification) using CASA and HALOsperm  
*Maya Nikoloska, University College London*
- 018** Improving sperm cryopreservation: Comparison study with two different freezing media and two cryopreservation protocols  
*Agneszka Florek, City Fertility, London*
- 019** Investigating the impacts of genetic knockdown and environmental exposures on human fetal tissue using a xenograft model  
*Aine Kavanagh, Queens Medical Research Institute, Edinburgh*
- 020** The role of *dmrt1* in human fetal testes development  
*Karen Kilcoyne, Centre for Reproductive Health, University of Edinburgh*
- 021** Referrals into a dedicated tertiary specialist andrology service for microscopic testicular sperm extraction  
*David Mathews, Aintree University Hospital, Liverpool*
- 022** What therapeutic solution can we offer to patients with recurrent total fertilisation failure but normal levels of phospholipase C zeta (PLC $\zeta$ ) protein?  
*Celine Jones, University of Oxford*
- 023** CMV and donor sperm - Is there a risk in using CMV positive sperm?  
*Hannah Hosking, Plymouth Hospitals NHS Trust*
- 024** Does sperm washing select the highest quality sperm?  
*Allan Pacey, University of Sheffield*
- 025** Does the use of hyaluronan sperm binding identify normospermic patients that are at risk of low or failed fertilisation with standard IVF?  
*Emma Balsdon, Wales Fertility Institute*
- 026** Outcome and utilisation of late maturing oocytes following intracytoplasmic sperm injection; is it worth the wait?  
*Kate Johnson, BMI The Esperance, Eastbourne*
- 027** ICSI outcomes with fresh and frozen surgically recovered spermatozoa  
*Jyoti Taneja, Herts & Essex Fertility Centre*

## POSTER PRESENTATIONS

- 028** IVF: ICSI split for couples with unexplained infertility  
*Nicholas Sharp, Bath Fertility Centre*
- 029** The impact of oocyte denudation time after retrieval on ICSI outcomes  
*Osama Naji, Assisted Conception Unit, Guy's and St Thomas' Foundation Trust*
- 030** Association between the number of oocytes retrieved and live birth rate within a stimulated ICSI treatment cycle  
*Hannah Clark, University of Bristol*
- 031** The prognostic value of oocyte dysmorphisms identified prior to ICSI and correlations with controlled ovarian stimulation regimes  
*Jason Kasraie, Shropshire and Mid Wales Fertility Centre*
- 032** Is short IVM before ICSI effective?  
*Shaun Rogers, City Fertility, London*
- 033** Ongoing clinical pregnancy following ICSI of late metaphase II oocyte for PGD-BRCA1  
*Rabi Oda, Centre for Reproductive and Genetic Health, London*
- 034** Live birth after fertilisation of vitrified oocytes: A case report  
*Jannie Michielsen, ReproMed, Dublin, Ireland*
- 035** Novel approach for measuring oxygen consumption of mammalian oocytes  
*Bethany Muller, Hull York Medical School*
- 036** Dynamic changes in human oocyte amino acid and energy metabolism during preantral follicle development  
*Paul McKeegan, Division of Reproduction and Early Development, LICAMM, University of Leeds*
- 037** Nitric oxide donor (SNP) and proteasome inhibitor (MG132) treatment during in vitro maturation impairs bovine oocyte development  
*Haitham Al-Hilfi, University of Nottingham*
- 038** Cumulus cells RNA sequencing: Immature, mature and aged mice  
*Arwa Alageel, University of Oxford*
- 039** Establishing the mechanism of egg activation in *Drosophila*  
*Rob Turnbull, University of Cambridge*
- 040** My elective experience - saving the Northern white rhino  
*Mhari Eleri Middleton, Leicester Fertility Centre*
- 041** Livebirth following two rounds of trophectoderm biopsy, vitrification, and warming: Assessment of the efficacy of retesting PGD and PGS embryos  
*Colleen Lynch, CARE Fertility, Genesis Genetics, University of Kent*
- 042** Predicting oocyte number and ovarian response when there is discordance between antral follicle count and anti-Müllerian hormone level  
*Courtney O'Beirne, Nottingham University Hospitals*
- 043** Impact of direct-to-consumer genetic testing on gamete donation: A survey of gamete donors, recipients and donor-conceived individuals  
*Falak Arshad, Centre for Ethics in Women's Health, University College London*
- 044** Pre-implantation genetic screening can be a better alternative to prenatal diagnosis for the eradication of hemoglobinopathies  
*Hisham Arab, Dr Arab Medical Center, Jeddah, Saudi Arabia*
- 045** Setting up a preimplantation genetic screening (PGS) service: A clinic's experience  
*Natalie Davis, CARE Fertility Northampton*
- 046** Risk of miscarriage and chromosomal abnormalities in pregnancy by transfer of embryos not analysed by CCS (Comprehensive Chromosomal Screening)  
*Joaquin Llacer, Instituto Bernabeu, Alicante, Spain*
- 047** Cumulative live-birth rates following miscarriage in an initial complete cycle of IVF: A retrospective cohort study of 113,870 women  
*Natalie Cameron, University of Aberdeen*
- 048** Intracytoplasmic morphologically selected sperm injection does not improve neither miscarriage rate nor live birth rate in patients with recurrent implantation failure and/or male factor infertility  
*Rabi Oda, The Centre For Reproductive and Genetic Health, London*
- 049** Case study: Double blastocyst transfer leading to a quadruplet pregnancy  
*George Woodhead, CARE Fertility Nottingham*
- 050** Can we decrease multiple pregnancy rates in clomiphene ovulation induction?  
*Raymond Lim, City Hospital Sunderland NHS Foundation Trust*
- 051** Introduction of a different ovarian stimulation protocol and the effect on clinical pregnancy rate (CPR)  
*Stuart Adams, St Bartholomew's Hospital, London*
- 052** Kisspeptin - a safer alternative for triggering oocyte maturation during IVF treatment to reduce the risk of OHSS?  
*Rumana Islam, Imperial College NHS Trust, London*
- 053** Outpatient management of patients at risk of OHSS: Analysis of 497 cases  
*Kugajeevan Vigneswaran, King's College Hospital, London*

## POSTER PRESENTATIONS

- 054** Abdominal compartment syndrome secondary to ovarian hyper-stimulation syndrome (OHSS)  
*Garima Srivastava, Homerton University Hospital, London*
- 055** Is elective frozen embryo transfer better than fresh in patients with a high egg number? A retrospective analysis of 712 cycles  
*Dima Abdo, IVF Hammersmith, London*
- 056** A retrospective comparison of fresh PICS and ICSI treatment cycles between January 2015 and June 2016  
*David Ogutu, Herts and Essex Fertility Centre*
- 057** The art of follicle tracking  
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## POSTER ABSTRACTS

### 001 The role of selective serotonin re-uptake inhibitor anti-depressants in male infertility

**Osmani Bayan; Shaikly Valerie; Blayney Martyn**  
*Bourn Hall Clinic, Cambridge*

**Objective:** In response to patient enquiries a literature review was carried out to assess the effect of commonly prescribed anti-depressants, which act as selective serotonin re-uptake inhibitors (SSRI's), on male fertility.

**Background:** SSRIs are widely used for their treatment in the general population due to their positive effects and efficacy as well as tolerability. Serotonin mediates a series of neuroendocrine functions, including sexual behaviour. In men, SSRI induced serotonin blocks the HPG axis, initiating a drop in LH and thus testosterone development in the Leydig cells. In addition, a reduction in serotonin affects apoptosis of sertoli cells, interrupting spermatogenesis and sperm cell development.

**Methodology:** 17 studies that investigated the effects of SSRIs on male infertility were identified for inclusion in the literature review, these could be further subdivided into the categories of: sexual behaviour (n=4) and sexual function (n=3) sperm function (n=5) Sperm DNA fragmentation and oxidative stress (n=3), and methylation (n=2).

**Results:** The main finding of relevance for patient information purposes in the IVF clinic was evidence of association between the duration of SSRI treatment and sperm DNA integrity. In addition neuroendocrine factors also played a major part in SSRI effects on sperm function. Studies also found that SSRI use is associated with compromised activity in sexual behaviour and the three phases of the sexual response cycle; desire, arousal, and orgasm.

**Discussion:** SSRIs are reported to be associated with fertility problems in men. It is generally accepted that this can be via physical mechanisms such as erection or delayed ejaculation problems. However there is a growing body of evidence to indicate that the effects can also affect the sperm at the genomic level, which in turn could impact fertilising capacity and embryo quality and in turn treatment outcome in IVF.

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Safarinejad MR. (2008a) Evaluation of endocrine profile and hypothalamic-pituitary-testis axis in selective serotonin reuptake inhibitor-induced male sexual dysfunction. *J Clin Psychopharmacol.*;28(4):418-423.

Tanrikut, C., Feldman, A.S., Altemus, M. et al. (2010) Adverse effect of paroxetine on sperm function. *Fertil Steril*, pp. 1021-1026.

### 002 Role of gonadotropins in improving outcomes for normogonadotropic male subfertility -a systematic review and meta-analysis of randomised controlled trials

**Pillai Rekha Neelakanta; Potdar Neelam**  
*University Hospitals of Leicester NHS Trust*

**Background:** Male factor subfertility is observed in 50-60% of subfertile couples. Studies have looked into the benefit of gonadotropins in improving sperm parameters and pregnancy rates in couples with no obvious cause identified for abnormal semen analysis and reported variable results.

**Aims/Objective:** To investigate the role of gonadotropins in improving sperm parameters and pregnancy rates (spontaneous and assisted conception) in couples with normogonadotropic male subfertility.

**Methodology:** The electronic database search included Medline (1946 to September 2016), Embase (1980 to September 2016), Cochrane library and ClinicalTrials.gov. Data extraction and collection was performed based on the eligibility criteria by two authors independently. The risk of bias assessment of the included trials were done using the Cochrane risk of bias assessment tool and statistical analysis performed using the Cochrane systematic review manager 5.31.

**Results:** The systematic review identified 7 eligible randomised controlled trials for the meta-analysis with a total of 523 men. In the gonadotropin randomised group, a significant improvement in sperm count/concentration was noted (mean difference 2.46 (1.65, 3.27); P value < 0.00001) with a significant difference in the spontaneous pregnancy rate (odds ratio 5.54 (2.47, 12.41); P value <0.0001). However, no improvement on sperm motility, sperm morphology and pregnancy rates following assisted conception techniques were observed. A subgroup analysis of two studies that used a higher dose of FSH (300 IU) compared to the traditional dose of 150 IU showed a statistically significant result even for sperm motility (mean difference 7.40 (4.44, 10.35); P value <0.00001) and sperm morphology (mean difference 13.49 (9.28, 17.69); P value < 0.00001).

**Conclusion:** FSH can be used to improve sperm concentration and spontaneous pregnancy rates in normogonadotrophic male factor infertility with no other known cause. There may be a role of using higher dose of gonadotrophins in improving sperm motility, morphology and other outcomes.

1. Cochrane Collaboration (2011). Review manager (RevMan) [computer program]. The Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen.
2. Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, Lopes P, Tabaste JM, Spira A (1991) Incidence and main causes of infertility in a resident population (1 850 000) of three French regions (1988-1989). *Human Reproduction*. Jul 1; 6(6):811-6.

### 003 Sperm mitochondrial membrane potential and superoxide production in stallion semen

**Figueiredo Maria Ines<sup>1</sup>; Al-Kass Ziyad<sup>2</sup>; Johannisson Anders<sup>2</sup>; Rocha Antonio<sup>1</sup>; Morrell Jane<sup>2</sup>**

<sup>1</sup>University of Porto; <sup>2</sup>Swedish University of Agricultural Sciences

Sperm mitochondrial membrane potential ( $\Delta\Psi_m$ ) has been linked to fertility in some species but is rarely used in the evaluation of cooled stallion semen. It might help differentiate between stallions with good and less good fertility. Production of metabolic byproducts could be assumed to increase with increased metabolic activity. The objective was to investigate the relationship between these parameters in fresh stallion semen.

**Materials and methods:** semen was collected from 8 stallions, 3 ejaculates each for 7 stallions and two ejaculates for one stallion (n=23). The semen was extended in EquiPlus (Minitube, Tiefenbach, Germany), cooled and transported to the laboratory at SLU in an insulated box where sperm concentration was measured. Sperm analyses were carried out immediately on reaching the laboratory and after 24h storage at 6°C: sperm motility (SpermVision CASA), membrane integrity

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(SYBR14/PI), production of reactive oxygen species (Mitoxox),  $\Delta\Psi_m$  (JC-1), chromatin integrity (SCSA). Only the relationship between  $\Delta\Psi_m$  and ROS-production is reported here.

Results: two sperm sub-populations differing in their MMP and SO• production were identified. Positive correlations after 24h storage were seen as follows: low  $\Delta\Psi_m$  with SO• production ( $r = 0.892$ ,  $P < 0.001$ ); high  $\Delta\Psi_m$  with no SO• production ( $r = 0.745$ ,  $P < 0.001$ ). Negative correlations after 24h storage were seen between high  $\Delta\Psi_m$  with SO• production ( $r = -0.746$ ,  $P < 0.001$ ) as well as low  $\Delta\Psi_m$  with no SO• production ( $r = -0.892$ ,  $P < 0.001$ ). No correlation was observed between  $\Delta\Psi_m$  and SO• production at 0h.

Conclusions: These two sperm sub-populations can be identified when semen is cooled and stored, e.g. prior to artificial insemination. The relative proportions of these sub-populations may help to differentiate between stallions of differing fertility.

### 004 Investigation of sperm mitochondrial membrane potential in SLC-selected stallion sperm samples

**Morrell Jane; Al Kass Ziyad; Johannisson Anders; Brown Xander**

*Oxford Brookes University*

Equine breeding programs are based on performance enhancement; unlike other species, stallions with poor fertility maybe chosen for breeding if they have performed at a high level, therefore optimising fertility is important. The industry standard is that fresh extended semen will have acceptable fertility for 24 to 48 hours. Colloid centrifugation selects spermatozoa with good motility, viability and normal morphology (1). The aim of this study was to monitor motility, membrane integrity and Mitochondrial Membrane Potential (MMP) every 24 hours for 5 days in controls and sperm samples selected by Single Layer Centrifugation (SLC) through Equicoll. Ejaculates (3 per stallion) were available from 7 stallions at a commercial stud ( $n=21$ ). The sperm samples were transported to the laboratory at the Swedish University of Agricultural Sciences where Single Layer Centrifugation was performed (2). Sperm motility was assessed using computer assisted sperm analysis at 38 degrees. The membrane integrity and MMP were assessed using Flow cytometry, after staining with SYBR14/propidium iodide and JC-1, respectively. There was considerable variation between stallions and between samples. The progressive motility was significantly different ( $P < 0.05$ ) between control and SLC samples at day 5. Membrane integrity was significantly different ( $P < 0.05$ ) from 48 hours onwards, due to a decrease in viable spermatozoa in the control samples (day 0:  $67\% \pm 7$  versus  $82\% \pm 9$  for controls and SLC samples, respectively) whereas viability was maintained in the SLC samples (day 4:  $54\% \pm 25$  versus  $79\% \pm 9$ , respectively). The proportion of spermatozoa with low MMP was higher in controls than in the SLC samples. In conclusion, sperm quality in SLC samples is maintained for at least 96 h after semen collection whereas it deteriorated in controls.

1. Morrell et al. (2011) *Theriogenology* 76, 1424-1432.
2. Morrell et al. (2016) *Reproduction. Fertility and Development*. In press

### 005 Sperm morphology assessment without staining is more cost effective and carries minimal clinical risk

**Pooley Karen; Kohut Tracey; Tomlinson Mathew; Meadows Jessica**

*Nottingham University Hospital*

Some of the most recent robust studies have demonstrated that reporting of % normal forms according to strict criteria is of little or no clinical value (Hotaling et al, 2011; Van der Hoven et al, 2016). Therefore the risk associated with exploring/establishing alternative, simpler methods for assessing % normal forms would appear low as long as severe and clinically significant morphological defects can still be detected.

This study extends our preliminary validation of describing sperm morphology using a wet preparation without staining. This study takes this step further comparing the same sample examined in parallel using both stained and unstained methods. This was performed in 40 patients samples with a minimum of 200 sperm examined in each. Unstained sperm were immobilised in 0.3% formal saline and allowed to settle for 20 minutes before reading ( $\times 400$ , phase contrast). Slides were stained using Diff Quick before mounting and examination at  $\times 1000$  (oil immersion). Scoring was performed by a single trained/competent operator ensuring that 'strict' reporting allowed for 'variation of normal' and that both cytoplasmic droplets and vacuoles are considered 'normal' up to a defined size (WHO, 2010).

Median % normal forms using Diff Quik was 12.5 (range 4.5-23) and 12 (4-26.5) using the 'wet prep' which in both cases was significantly higher than our laboratory mean. Overall mean difference and mean % error was zero (range -65% to 40%).

The overall conclusion was that apart from occasional outliers results/techniques could be considered 'interchangeable'. The only perceived disadvantages of the wet prep method were difficulty in identifying vacuoles which were considered low or unknown risk. In contrast background staining was often significant and particularly in high viscosity/proteinaceous samples. With reduced cost, faster turnaround and low associated risk there appears no clear reason not to adopt the unstained method.

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2. van den Hoven L, Hendriks JC, Verbeet JG, Westphal JR, Wetzels AM (2015). Status of sperm morphology assessment: an evaluation of methodology and clinical value. *Fertil Steril* 103, 53-58.
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## POSTER ABSTRACTS

**006** A comparative evaluation of two commonly used sperm preparation techniques, density gradient centrifugation and neat swim-up using CMA3 staining and morphology

**King Rebecca; Thomas Victoria; Sanders David; Ashley Peter; Balsdon Emma; Lappa Christina; Knaggs Paul**

*Wales Fertility Institute*

**Aims:** This study aimed to compare discontinuous DGC and neat swim-up and determine which method isolated the sperm with overall better quality.

**Content:** This poster/presentation will go through the purpose of this research, which took place in early 2016. The laboratory and statistical methodology used, results obtained and conclusions drawn will be discussed.

**Relevance/Impact:** Despite considerable literature comparing the two most popular techniques, density gradient centrifugation (DGC) and swim-up, still there is no universally accepted better method. This was a split-sample study that included 65 semen samples. Ejaculates were from patients undergoing diagnostic testing or fertility treatment. Along with the more commonly used traditional dependent variables, this study has used additional variables of DNA condensation and TZI analysis.

**Outcomes:** The yield of sperm was significantly higher following DGC (19.0%) than swim-up (2.1%) ( $p < 0.001$ ). CMA3 positivity was significantly lower after DGC (26.4%) than after swim-up (40.3%) ( $p < 0.001$ ). Progressive motility, average motile speed, normal morphology, AI and TZI were not significantly different between preparation groups ( $p > 0.05$ ). In samples with initial concentrations above the 50th percentile, DGC had significantly higher motility (70.1) than those below (51.6) ( $p = 0.002$ ), and significantly faster velocity (54.1  $\mu\text{m/s}$ ) than those below (45.0  $\mu\text{m/s}$ ) ( $p = 0.04$ ). SU was not affected by initial concentration grouping.

**Disussion:** The low yield achieved by swim-up would result in many conversions to ICSI and possibly lower IUI pregnancy rates. Higher CMA3 positivity following swim-up could be detrimental to IVF, ICSI and IUI success, as CMA3 negative sperm are thought to compete with CMA3 positive sperm to achieve fertilisation. DGC appeared to perform better with samples of higher concentration in terms of motility and velocity. SU was not affected by initial concentration. Based on the CMA3 and yield results, it is preferable that clinics use DGC to prepare sperm rather than neat swim-up.

**007** Commercial density gradient preparations, DNA fragmentation and reactive oxygen species measured using the MiOXSYS™ device

**Tomlinson Mathew<sup>1</sup>; Mitchell Clare<sup>1</sup>; Maalouf Walid<sup>2</sup>; Dissing Marianne<sup>2</sup>**

<sup>1</sup>University of Nottingham; <sup>2</sup>Origio

Centrifugation and density gradient sperm preparation (DGC) have been implicated in the generation of reactive oxygen species (ROS) which in turn may lead to poor sperm function and DNA damage. The objective of this study was to measure ROS, semen parameters and DNA fragmentation in different DGC media and at different centrifuge speeds.

Donor samples ( $n=15$ ) were divided between DGC preparations (Suprasperm, Puresperm, and test preparations at pH 7.5 and pH 8.3) before centrifugation (20 minutes) and further washing (300g). ROS (pre and post DGC) were measured using the MiOXSYS™ system which permits reading of the total redox potential (sORP) in a single chip-based assay (Agarwal et al., 2016). Semen parameters were assessed using CASA and DNA fragmentation was measured using the sperm chromatin dispersion assay (SCDA). A second experiment further examined the effect of centrifugation speed on sORP.

DNA fragmentation was reduced after DGC (7.9% v 6.5%) but only significantly so in Puresperm and test media at pH8.3. CASA parameters were no different between preparations. sORP significantly increased post DGC and was significantly correlated with sperm concentration ( $r=0.91$   $p < 0.001$ ) and velocity ( $r=0.35$ ,  $p < 0.05$ ) but negatively correlated with DNA fragmentation. Centrifugation of 5 different washed sperm suspensions at 300g or 1000g showed no difference in sORP (both  $4 \pm 2.9\text{mv}$ ).

In conclusion these experiments demonstrate that most DGC media perform equally well and that the relationship between sORP, sperm function and DNA damage is complex. This agrees largely with Aitken et al. (2012), who describes ROS as having a positive role but also that a 'tipping point' may be reached at which oxidative damage occurs. Further work should define what the threshold is and under what circumstances it exists.

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**008** Migration-sedimentation versus density gradient separation with swim-up method of sperm preparation for in vitro fertilisation: A service evaluation

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**Introduction:** Sperm preparation has developed from single step washing to more sophisticated methods (Beydola et. al., 2013). The techniques must be simple, cost-effective and limit damage to sperm. We propose that migration sedimentation could be used as a minimally invasive, damage reducing, cost- and time-effective method for preparing normozoospermic semen samples for IVF.

**Aims:** To compare benefits of using a migration sedimentation chamber (RI-MSCTM) against density gradient and swim-up (DG-SU); the current method used. The study will investigate whether the RI-MSCTM method can improve IVF outcomes, with the additional benefit of reducing operator time and costs. The primary outcome studied was fertilisation rate, and secondary outcomes included: embryo cleavage; implantation; positive pregnancy; biochemical pregnancy and clinical pregnancy rates.

**Materials and Methods:** Each semen sample was prepared using RI-MSCTM (300?l of ejaculate), and DG-SU (the remaining volume) methods. Oocytes (per patient) were randomised into two groups for insemination with sperm prepared via RI-MSCTM or DG-SU. Embryos that subsequently developed in each group remained separate and their development tracked.

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Results: 50 couples (n=599 oocytes) were included in the study. 302 oocytes were inseminated with DG-SU and 297 inseminated with RI-MSCTM prepared sperm. The fertilisation rate was higher in the DG-SU group at 64.4% (n=163) compared to 57.9% (n=143) in the RI MSCTM group, (p=0.252). Embryo cleavage rates were comparable, 93.9% (n=153) and 93.7% (n=134) in the DG-SU and RI MSCTM groups, respectively (p=0.252). Positive pregnancy rates were comparable in both groups, 66.7% (n=10) RI-MSCTM compared to 63.3% (n=14) DG-SU (p=0.699). The clinical pregnancy rate was higher in the RI-MSCTM group at 53.5% (n=8), compared to 40.9% (n=9) in the DG-SU group, (p=0.536).

Conclusion: The RI-MSCTM method for preparing sperm produced results comparable with the currently used DG-SU method. Further work with a larger cohort is required to confirm the findings.

### 009 Implementation of diagnostic semen analysis (WHO 2010) into 7 fertility clinics

**Wheat Stacy<sup>1</sup>; Babbington Phoebe<sup>1</sup>; Graves Joanne<sup>2</sup>; Montgomery Sue<sup>3</sup>; Eaton Steven<sup>4</sup>; Pastorelli Laura<sup>5</sup>; D'Cruz Ivy<sup>6</sup>; Foley Sarah<sup>7</sup>; Campbell Alison<sup>8</sup>**

<sup>1</sup>CARE London; <sup>2</sup>CARE Nottingham; <sup>3</sup>CARE Manchester;

<sup>4</sup>CARE Northampton; <sup>5</sup>CARE Tunbridge Wells; <sup>6</sup>CARE Dublin;

<sup>7</sup>CARE Sheffield; <sup>8</sup>CARE

Aims: In 2010 the World Health Organisation (WHO) published new guidelines for examination of semen. The guidelines describe the "gold standard" methodology for assessing male factor infertility using Diagnostic Semen Analysis (DSA).

This report will describe how WHO (2010) guidelines were introduced to seven clinics improving semen analysis for around 20,000 patients annually.

Content: In January 2016 a representative from each clinic formed the 'Andrology Focus Group'. Clear objectives and timelines were described in 3 phases.

Phase 1: Research and Education

- Gap analysis against WHO guidelines
- Visits to accredited andrology laboratories
- Training and education sessions

Phase 2: Quality and Equipment

- SOP and laboratory paperwork updated
- Electronic database developed
- Training plan and competency paperwork formed
- Quality control
- Equipment ordered

Phase 3: Introduction to local units

- SOP and training video distributed
- Local training performed
- Competencies assessed

Outcomes: NEQAS distributions were compared before (distributions 87, 88 and 89) and after (distribution 90) implementation of DSA. Five clinics were included in this analysis; two clinics are not implementing DSA to the same timeline.

In each distribution 20 concentration scores were submitted from 5 clinics. NEQAS demonstrated reduction in unacceptable performance scores when comparing distributions 87 (20%), 88 (15%) and 89 (25%) to distribution 90 (5%).

The Intraclass Correlation Coefficient (ICC) was computed to observe if intra-observer variability changed before or after DSA. ICC demonstrated that variability between concentration assessments decreased following implementation of DSA (Before ICC=0.91 (95%CI 0.79,0.97); After ICC=0.97 (95%CI 0.87,1.0)).

Discussion: This review shows improvement in performance of semen concentration assessment within the group.

Introduction of DSA presented numerous challenges. Time to perform semen analysis increased, affecting daily diaries and workload. Further to this training and awareness took longer than anticipated.

This review has demonstrated how to improve andrology services by implementing WHO (2010) guidelines, providing a more accurate semen analysis for patients and referrers.

1. World Health Organisation (2010). WHO Laboratory Manual for the Examination and Processing of Human Semen. UK: World Health Organisation. 287.

### 010 Sperm DNA damage in men presenting with reproductive and non reproductive cancers

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Introduction: The presence of single strand DNA breaks (SSDB), but not double stranded breaks (DSDB), sperm DNA damage has been reported in cancer patients. In this study, we compared the levels of SSDB and DSDB in the same semen samples using three different DNA damage assays: alkaline and neutral Comet and TUNEL in men presenting with testicular cancer (TC) and haematological malignancies (HM) in comparison with fertile donors.

Method: Men presenting with TC (n=19) and HM (n=13) at the Department of Clinical Physiopathology, University of Florence between 2014 to 2015 were recruited into the study. Semen samples were obtained (both patients and donors) after 3-7 days of sexual abstinence. All semen samples were analyzed according to World Health Organisation guidelines (WHO 2010). Fresh semen samples were used for analysis for DNA damage by the TUNEL assay. Semen samples were cryopreserved for the later analysis of DNA damage by both Comet assays.

Results: Sperm DNA fragmentation was significantly higher in TC patients; both in terms of double strand breaks (7.5% vs. 13.4 %; p<0.05) and in the more abundant SSDB (12.4 % vs. 37.4%, p<0.001) than in the fertile donor group. Whereas in HM SSDB was 35.0% compared with 12.4% in the donor group; (p<0.001), and there was 10.7% of DSDB against 7.0 in donor sperm (p<0.05). In contrast, there was no significant difference in sperm DNA damage between patient and donor groups using TUNEL assay.

Discussion: The novelty of this study lies in comparing double with single stranded DNA damage and test sensitivity in men with two types of cancer and ascertaining sensitivities. Longitudinal studies should be designed to investigate these men's fertility following cancer treatment to see if single or double strand breaks reduce in future cycles of spermatogenesis or are more susceptible to damage by therapeutic agents.



## POSTER ABSTRACTS

**011** The clinical value in assessing sperm DNA fragmentation in couples undergoing failed intracytoplasmic sperm injection (ICSI) and its correlation with semen parameters

**Bracewell-Milnes Timothy<sup>1</sup>; Saso Srdjan<sup>1</sup>; Bora Shabana<sup>2</sup>; Thum Meen-Yau<sup>2</sup>**

<sup>1</sup>Imperial College London; <sup>2</sup>Lister Fertility Clinic, London

**Introduction:** A potential cause of male factor infertility is high levels of sperm nuclear DNA damage, or DNA fragmentation. Several studies have compared infertile men to fertile controls and found a higher rate of DNA damage<sup>1,2</sup>. DNA fragmentation has also been associated with a poorer IVF outcome with an increased rate of failure to obtain blastocysts<sup>3</sup>, reduced implantation rates<sup>3</sup>, and increased incidence of miscarriage<sup>4</sup>. DNA integrity has therefore emerged in recent years as a novel parameter of semen quality and a potential fertility predictor, but despite this knowledge, there is a distinct lack of clinical guidelines on DNA integrity assessment.

**Methods:** 116 couples that failed at least one ICSI cycles underwent sperm DNA fragmentation index (SDFI) (n=116). For the SDFI, a threshold of 30% was used to discriminate between samples with normal and elevated levels of DNA-damaged spermatozoa. Comparison was made with seminal fluid analysis (SFA) using WHO 2010 criteria<sup>5</sup>.

**Results:** 116 patients underwent sperm aneuploidy assessment. Karyotyping was performed in 48.3% (n=56) of male patients and was normal in all of them. There was no association found between DNA fragmentation semen quality parameters studied (sperm concentration, Pearson correlation,  $R=0.268$ ,  $p=0.09$ ; sperm motility, Pearson correlation,  $R=0.135$ ,  $p=0.22$ ) and this was consistent when the samples were divided into groups according to World Health Organisation criteria (WHO, 2010). Of the patients studied 28.87% of their sperm had a raised DFDI.

The associations between total aneuploidy rate (TAR) and sperm integrity parameters are revealed a positive and statistically significant 2.5 fold increase in sperm displaying DNA fragmentation with a raised TAR (Pearson correlation,  $R=0.184$ ,  $p<0.05$ ).

**Discussion:** There was no association between a raised DFDI and abnormal sperm parameters. However, a strong association was demonstrated between raised TAR and DFDI. Normal appearing sperm could be selected in this failed ICSI group with a raised DFDI, which could impact the

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**012** DNA status and sperm parameters in semen of infertile men

**Riaz Muhammad<sup>1</sup>; Mahmood Zahed<sup>2</sup>; Shahid Muhammad<sup>3</sup>; Saeed Muhammad Usman Qamar<sup>4</sup>; Munir Naveed<sup>3</sup>; Tahir Imtiaz Mahmood<sup>5</sup>**

<sup>1</sup>University of Agriculture and University of Sargodha; <sup>2</sup>Pakistan

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<sup>4</sup>University of Agriculture; <sup>5</sup>University of Agriculture and Civil Hospital; <sup>6</sup>Government College University, Pakistan

**Introduction:** Recent advances in reproductive biology have proposed evaluation of sperm DNA integrity as an important assessment tool to infer the presence of DNA strand breaks, numerical abnormalities in sperm chromosome complement, and alterations in the epigenetic regulation of the paternal genome. The present study was planned to assess the potential importance of sperm parameters and DNA status in male fertility and their relationship with each other.

**Methods:** A total of forty men were recruited for the study including fertile volunteers (control group; n=20) and infertile patients (test group; n=20) and their semen sample were collected after informed consent. Sperm parameters were assessed by routine semen analysis and DNA status of human spermatozoa was evaluated from chromatin fragmentation index by using Acridine Orange (AO) Staining technique.

**Results and Discussion:** We observed significantly ( $p<0.05$ ) decreased semen quality parameters including semen volume, sperm count and active motility in infertile men. DNA fragmentation of the spermatozoa was increased non-significantly ( $P\geq 0.05$ ) in infertile men compared to fertile men. DNA fragmentation was positively correlated with sperm count ( $r=0.430$ ;  $p<0.05$ ) and active motility ( $r=0.568$ ;  $p<0.05$ ) of spermatozoa. No significant ( $p>0.05$ ) difference was found in DNA fragmentation of the spermatozoa between age groups but slightly increased in men above 40 years of ages. The results suggest that DNA fragmentation may be helpful in evaluating the fertility status of spermatozoa along with semen quality parameters.

**013** Quantitative measurement of semen viscosity shows that it affects both sperm function and the accuracy of semen analysis

**Tomlinson Mathew; Steele Heather**  
*University of Nottingham*

Although it's widely acknowledged that sample homogeneity affects the accuracy and reproducibility of semen analysis, laboratories often measure semen viscosity subjectively or largely disregard it. The objective of this study was to apply accurate quantitative measurements to seminal viscosity to determine whether a: it significantly affects accuracy of semen analysis and b. it has any impact on sperm quality.

Viscosity (cP) was measured in 63 samples using a shearing-rate viscometer and compared to subjective strand length and a semi-quantitative method using filling time of a capillary slide. Trypsin and hyaluronidase were tested at different concentrations to determine their efficacy in reducing viscosity. Quadruple sperm counts were performed in 20 of the specimens using standard haemocytometry and CASA after sampling from each of 4 quadrants (defined by marking the specimen container).



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Viscosity ranged from 2.56 cP to 12.73 cP yet a number of samples were so viscous as not to be considered liquid. Low viscosity was defined at 2-7cP, medium 7-12cP and high viscosity >12cP with excellent agreement between viscometry and capillary-loaded slide methods. There was a significant negative correlation between viscosity and progressive motility and %A grade sperm ( $p<0.01$ ). Although manual and CASA counts were very similar, sperm concentration (and motility) varied greatly between quadrants with CVs often in excess of 10% (median 12.9%, range 5.7-37%). Trypsin and hyaluronidase gave progressive reduction in viscosity with increasing concentration (0.25mg/l-1mg/ml), yet with corresponding reduction in sperm motility/velocity.

Quantitative assessment of viscosity demonstrates that not only does it affect sperm motility but it affects our ability to accurately perform semen analysis. Whilst trypsin and hyaluronidase reduced viscosity they also reduced sperm motility so should only be used to help improve sperm counting consistency. Given these results, semen viscosity should be measured at least semi-quantitatively.

### 014 Why we should not disregard seminal viscosity measurements

**Steele Heather; Tomlinson Mathew**  
*University of Nottingham*

Although it is widely acknowledged that a lack of homogeneity affects the accuracy and reproducibility of semen analysis, in most laboratories, seminal viscosity is either measured subjectively or largely disregarded. The objective of this study was to apply more accurate and quantitative measurements to seminal viscosity to determine whether a: it significantly affects accuracy of semen analysis and b: whether it has any impact on sperm quality.

Viscosity cP was measured in 63 samples using a shearing rate viscometer and compared to standard subjective strand length and a semi-quantitative method using fill time of a capillary loaded slide. Trypsin and hyaluronidase were tested at 3 different concentrations to determine their efficacy in reducing viscosity. Quadruple sperm counts were performed in 20 of the specimens using standard haemocytometry and CASA after sampling from each of 4 quadrants in a sample container.

Viscosity ranged from 2.56 cP to 12.73 cP yet a number of samples were so viscous as not to be considered liquid. Low viscosity was defined at 2-7cP, medium 7-12cP and high viscosity >12cP and there was excellent agreement between viscometry and capillary-loaded slide filling time. There was a significant negative correlation between viscosity and progressive motility ( $p<0.01$ ). Although both manual and CASA counts were closely correlated, sperm concentration (and motility) varied greatly between quadrants with coefficients of variation with 14 of the 20 wells tested having a %CV value in excess of 10% (median 12.9% , range 5.7-37%). Trypsin and hyaluronidase gave a progressive reduction in viscosity with increasing concentration, yet with corresponding reduction in sperm motility.

The quantification of seminal viscosity should not be disregarded as increased viscosity appears to be related to reduced sperm quality and increasing inaccuracy. A semi-quantitative method of assessing seminal viscosity may allow greater precision in defining viscosity.

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### 015 Use of SpermMobil for stimulation of motility in immotile sperm prior to ICSI is not detrimental to clinical outcome

**Williams Hannah; Martins da Silva Sarah; Drew Ellen**  
*NHS Tayside*

The study aimed to investigate the impact of the use of GM501 SpermMobil (Gynemed), containing the non-selective PDE inhibitor theophylline, on clinical outcomes of ICSI cycles where sperm motility is absent.

From September 2015, SpermMobil was used to stimulate motility in 17 samples used for ICSI treatment where only immotile sperm were present. Indications for use of SpermMobil included: recovery of sperm from PESA/TESA/TESE, retrograde ejaculation, or total asthenozoospermia in the prepared sample.

Stimulation of motility by SpermMobil is marketed as a valuable diagnostic tool for assessing sperm viability. In the clinical setting, it could also represent a valuable clinical tool for assessing vitality of sperm prior to ICSI insemination, which could reduce the time taken for sperm selection and thus streamline the ICSI procedure where sperm are immotile. However its reported use in clinical procedures is limited (1,2), and therefore clinical value is unclear.

In this retrospective study, after use of SpermMobil, the fertilisation rate was 56% per oocyte injected (comparable to ICSI+TESE with untreated sperm, 63%). There was one failed fertilisation, however this sample showed no benefit to motility when treated with SpermMobil, therefore immotile sperm were used for injection. Two of the remaining 16 patients (12.5%) had had live births, 6 were clinically pregnant (37.5%), and 5 (31.3%) had negative pregnancy tests. Of the remaining 3 patients, one did not have embryos of good enough quality to transfer, and for two patients the outcome is not yet known.

In conclusion, use of SpermMobil led to an acceptable fertilisation rate and subsequently ~50% of treated patients conceiving, and thus had no significant negative or detrimental effect on the outcome of ICSI cycles where it was employed. The use of SpermMobil would significantly aid efficient workflow through a busy ART laboratory.

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## POSTER ABSTRACTS

**016** Farnesol, a quorum-sensing molecule from *Candida Albicans*, inhibits human sperm motility: Evidence for an effect through inhibition of cAMP signalling

**Costello Sarah<sup>1</sup>; Mattock Jennifer<sup>1</sup>; Bailey Emily<sup>1</sup>; Alsmari Wardah<sup>2</sup>; Lefievre Linda<sup>1</sup>; Pendekanti Venkata<sup>1</sup>; Publicover Stephen<sup>1</sup>**

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Microbial infections of reproductive organs reduce fertility. Rennemeier et al (2) reported that quorum sensing molecules (QSM; microbial communication molecules) directly impair human sperm function and that farnesol (an isoprenoid QSM produced by *Candida albicans*) reduced both motility and viability. We have further investigated the effects of farnesol (1-500µM) on human sperm.

In our experiments, farnesol treatment only slightly reduced viability as assessed by the HOS test. 60 min treatment with 500 µM farnesol reduced HOS positive cells by ≈40% but at 50 and 2 µM the proportion of viable cells fell by <10 %. 1-50 µM farnesol also had significant dose and time-dependent effects on motility, exposure for 60 mins reducing motility by 50-60% (n=6) and progressive motility by ≈90% (n=6) at just 1 µM. Hyperactivation increased for 20-40 mins following exposure to farnesol (5 and 50 µM; n=8). Fluorimetry of fluo4-loaded cells showed that farnesol caused a dose dependent increase in [Ca<sup>2+</sup>]<sub>i</sub>. Farnesol-induced hyperactivation and elevation of [Ca<sup>2+</sup>]<sub>i</sub> were both inhibited by pharmacological block of CatSper channels.

In *C. albicans* farnesol directly inhibits the bicarbonate-sensitive adenylyl cyclase (1) so we investigated whether motility in farnesol-treated cells was rescued by inhibition of phosphodiesterase. After 40 min exposure to 5-50 µM farnesol, IBMX (500 µM) caused recovery of motility to near control rates. 5 µM farnesol 'reversed' protein tyrosine phosphorylation in cells previously incubated under 'capacitating' conditions (n=2).

In conclusion, we have found that low doses of the QSM, farnesol have a significant deleterious effect on sperm motility. Many microbial infections are asymptomatic, however, the presence of these microbial derived quorum sensing molecules may be responsible for reduced sperm quality and contribute to idiopathic infertility.

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**017** Comparison of cryopreservation methods (slow freezing vs. vitrification) using CASA and HALO sperm

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<sup>1</sup>UCL; <sup>2</sup>UCLH; <sup>3</sup>CRGH

Long-term storage of sperm is an essential part of clinical practice and fertility management. In particular, sperm cryopreservation before chemotherapy is critical, due to the gonadotoxic nature of radiation therapy. Cryopreservation is generally acknowledged to cause impairment of sperm quality, notably motility and progression<sup>1</sup>. Despite wide application, however, little progress has been done on the amelioration of freezing protocols in many years. New efficient methods for freezing cells, such as vitrification, have shown to be far more effective than conventional freezing methods<sup>2</sup>. This has, as of yet, been untested clinically with sperm.

The aim of this study was to assess compositions of cryoprotectants based on levels of cryoinjury to vitrified sperm. Once established, slow freezing and vitrification were carried out and compared in order to select the best cryopreservation method to maintain sperm integrity. Motility, progression and DNA fragmentation were compared between groups. Five non-permeating CPAs were tested to determine survival rates post vitrification. Thirty semen samples were vitrified assessing motility, progression and concentration before and after freezing. The CPA yielding highest survival post-vitrification (using Computer Assisted Sperm Analysis (CASA)) was used for the remainder of the study. Interestingly, a CPA used as standard for vitrifying embryos gave the worst survival rates for sperm cells. DNA damage was assessed using a Sperm Chromatin Dispersion test and sperm motility was compared between vitrified and slow frozen samples.

While a decline in sperm motility and progression was seen in both slow freezing and vitrification samples, vitrified semen samples gave far better survival rates and lower DNA fragmentation. While vitrification has been adopted in all other clinical cryopreservation strategies, slow freezing remains the method of choice in all clinics at present. This research shows the need for revision of old protocols for better management of samples, particularly in patients with poor quality sperm.

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**018** Improving sperm cryopreservation: Comparison study with two different freezing media and two cryopreservation protocols

**Florek Agnieszka; Moore Charlotte; Rogers Shaun**  
*City Fertility, London*

**Aims/Objectives:** The present study was set up in order to improve in house procedures of sperm cryopreservation. Two commercially available sperm freezing media Test Yolk Buffer (Irvine Scientific) and Sperm Freezing (Life Global) were tested in combination with two different protocol for sperm freezing.



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**Content:** 20 patients who consented to donate their sperm for research after undergoing semen analysis at City Fertility participated in the study. Both normozoospermic and OATs samples were included. Each sample has been split in two and cryopreserved with two sperm freezing media: Test Yolk Buffer and Sperm Freezing. Additionally each sample was split and cryopreserved according to two protocols: two phase cooling: liquid nitrogen (LN) vapour, at approximately -170°C, and then immersion into liquid nitrogen and three phase cooling: (40°C in a standard refrigerator, liquid nitrogen vapour phase and LN). Pre freezing motility and post thaw analysis were compared to identify trend of the highest recovery of motile sperm after thawing.

**Outcomes/ Discussion:**

| Post thaw motility | Test Yolk Buffer | Sperm Freezing | P value |
|--------------------|------------------|----------------|---------|
| 2 phase protocol   | 7.50%            | 3.80%          | P<0.05  |
| 3 phase protocol   | 20%              | 8.50%          | P<0.05  |
| Statistic test     | P<0.05           | P<0.05         |         |

Obtained data suggest that there is significant improvement in post thaw motility when comparing two different media. Also the results of applying the three phase cooling protocol showed improved rates of recovered motility. This enabled choosing the best media-protocol out of four investigated variants.

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### 019 Investigating the impacts of genetic knockdown and environmental exposures on human fetal tissue using a xenograft model

**Kavanagh Áine; MacDonald Joni; Brown Pamela; Mitchell Rod; Kilcoyne Karen**

*Queens Medical Research Institute, Edinburgh*

**Relevance/Impact:** Previous research in rodents has permitted the understanding of fetal testis development and its perturbation by genetic and environmental factors. However, how these relate to the human remains unknown. We have developed a novel method to recapitulate normal human testis development [1]. Using our xenograft model system, we have investigated environmental exposure effects, e.g. paracetamol and phthalates, on the developing human fetal testis [2][3]. However, there are no established methods for genetically manipulating the human fetal testis.

**Content:** We have designed a novel lentiviral approach to genetically manipulate key genes within the human fetal testis. Combining miRNA knockdown of a gene of interest (GOI) with our xenograft model offers a unique system to investigate human tissue development. To validate this approach, we manipulated several Sertoli cell genes that have been shown, in rodent studies, to be important for testicular cell maintenance and germ cell function in fetal testes.

This system involves obtaining human fetal testis tissue (8–20wks gestation) from elective termination of pregnancy, and exposing tissue fragments to a lentiviral miRNA construct targeting each GOI in a hanging drop culture system. Tissue is exposed to either scrambled (control) or knockdown miRNA

for 24 hours and maintained for up to 7 days. To demonstrate long-term effects of gene manipulation, tissue pieces are xenografted into immunocompromised host mice for up to 6 months. Successful viral uptake by transfected human fetal testis tissue is demonstrated by expression of an mCherry lentiviral reporter (via immunohistochemistry). qPCR analysis demonstrates efficient knockdown of the GOI.

**Outcomes:** Testicular structure and histology are compared between control and knockdown tissue, as are protein and RNA expression. The ability to manipulate gene expression in human fetal tissue using lentiviral vectors allows us to understand the role of these individual genes in the developing human testis.

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### 020 The role of dmrt1 in human fetal testes development

**Macdonald Joni<sup>1</sup>; Kilcoyne Karen<sup>1</sup>; Mitchell Rod<sup>1</sup>; Brown Pamela<sup>1</sup>; Jørgensen Anne<sup>2</sup>**

<sup>1</sup>Centre for Reproductive Health, University of Edinburgh;

<sup>2</sup>Department of Growth and Reproduction Copenhagen University Hospital

TGCC, the commonest malignancy in young men arises during fetal life and is associated with a failure of the germ cells to mature. Germ cell (GC) maturation has been associated with Sertoli cell (SC) maturation and survival. DMRT1 is expressed in SCs (and GCs) during fetal and postnatal life, playing a role in maintenance of the male gonad. SCs in DMRT1 knockout mice transdifferentiate into granulosa-type cells expressing FOXL2. This study investigated whether DMRT1 knockdown via viral transduction in human fetal testes would result in SC reprogramming and inhibit GC maturation.

We performed miRNA knockdown of DMRT1 (labelled with mCherry) in human fetal testis tissue (8–12wks gestation; n=3). Tissue was maintained in hanging drop culture for 14 days and analysed by RT-PCR and immunohistochemistry. To demonstrate long-term effects of DMRT1 knockdown, human fetal testis tissue (12–20wks gestation; n=3) was exposed to 1) Vehicle 2) Scrambled miRNA or 3) miRNA knockdown for 24 hrs. Tissue pieces were then xenografted into immunocompromised host mice. DMRT1 knockdown in 1st trimester human fetal testis hanging drop cultures resulted in a reduction in DMRT1 and an increase in FOXL2 mRNA expression. Several male specific genes including steroidogenic enzymes were also significantly downregulated. Viral uptake by transfected 2nd trimester human fetal testis xenografts was demonstrated by expression of mCherry and the structure and histology of the tissue was comparable between control and DMRT1 knockdown tissue. Cellular



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proliferation (Ki67) was evident in control and transfected tissue. DMRT1 was expressed throughout the seminiferous cords in control xenografts. In contrast, transfected tissues exhibited regions of DMRT1 protein expression loss coinciding with focal dysgenesis of the seminiferous cords.

In conclusion, we show for the first time that miRNA knockdown can be achieved in human fetal testis using an in-vitro system.

### 021 Referrals into a dedicated tertiary specialist andrology service for microscopic testicular sperm extraction

**Mathews David; Starmer Benjamin; Baird Andrew; Lucky Marc**

*Aintree University Hospital, Liverpool*

**Aims/Objectives:** This retrospective study examined all patients who underwent micro-TESE procedures within a tertiary referral centre covering a population of over 5 million over a 40 month period, looking at demographics and possible predictive factors.

**Content:** A current characterisation of patients referred for micro-TESE and an analysis of prevalent associated factors.

**Relevance/Impact:** Micro-surgical testicular sperm extraction is an increasingly popular technique for sperm retrieval in men with azoospermia. Whilst several factors have a known association with the condition, there is a paucity of evidence looking at pre-operative predictive criteria for successful sperm-retrieval in this group.

**Outcomes:** We identified a cohort of 60 patients aged 22 to 53 (mean age of 34). Of these 66.7% were non-smokers and 65.0% had a body mass index (BMI) of greater than 25. The majority (70.0%) had co-morbidities, the most prevalent of which were a history of orchidopexy (16.6%) or malignancy which required chemotherapy (13.3%). There were 8 patients in the latter group and 4 of these were testicular cancers requiring orchidectomy. Klinefelters was unsurprisingly common (10.0%) within the cohort and the most prevalent co-existing condition after this was asthma (6.7%). Other co-morbidities included diabetes (3.3%), vasectomy (3.3%), previous mumps (1.7%) and anabolic steroid use (1.7%). Follicle stimulating hormone (FSH) levels were documented for 48 of the patients and raised in 73% of these.

**Discussion:** Our cohort showed several factors with a known association to azoospermia such as; a direct insult to the testes (from undescended testes, exposure to chemotherapy & previous mumps), a raised FSH and a high BMI. Of note, just 30.0% reported a history of smoking and only 11.7% were active smokers, possibly indicating a motivated and health conscious attitude within the cohort.

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### 022 What therapeutic solution can we offer to patients with recurrent total fertilisation failure but normal levels of phospholipase C zeta (PLCζ) protein?

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*University of Oxford*

There is strong evidence to indicate that mammalian oocyte activation and early embryogenesis are regulated by the sperm-specific protein, phospholipase C zeta (PLCζ). Upon gamete fusion, PLCζ induces the oscillatory release of calcium within the ooplasm which, in turn, regulates oocyte activation and early embryonic development. PLCζ therefore represents a critical biological component of the fertilisation process. Genetic mutations within the PLCζ gene, or abnormalities in the expression or function of the PLCζ protein, are known to be linked to oocyte activation deficiency (OAD) and infertility. Consequently, there is significant interest in the use of PLCζ as a clinical therapeutic agent as a more endogenous alternative to artificial oocyte activating agents (AOAs). Treatment options for total fertilisation failure (TFF) are particularly limited. At present, however, AOAs represent the only clinical option for patients with low fertilisation rates or TFF, but are rarely used by clinics in the UK. While literature continues to support the safety of AOAs, and while no chromosomal abnormalities have been reported as yet following the application of AOAs, further research is urgently required in order to understand the differences between calcium profiles triggered by normal and artificial oocyte activation. Here, we describe the case of a couple with recurrent TFF; one failed cycle of IVF and one failed ICSI cycle. Analysis indicated that the total levels and localisation pattern of PLCζ in the male's sperm were similar to that of fertile controls. However, genetic analysis revealed a mutation in the X catalytic domain of PLCζ, corresponding to the substitution of valine to glutamic acid at position 193 of the amino acid sequence. Computer modelling predicts that this mutation may affect protein folding, stability or even the interaction between PLCζ and other unknown molecules within the oocyte. In this scenario, is AOA really the best way forward?

### 023 CMV and donor sperm - Is there a risk in using CMV positive sperm?

**Hosking Hannah**  
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Cytomegalovirus, donor sperm and assisted conception - Is there a risk in using CMV positive donors? Introduction: Cytomegalovirus (CMV) is the most common cause of congenital infection responsible for neonatal mortality, morbidity and subsequent chronic conditions. It is therefore important to understand and evaluate the risks of CMV being present in donor semen and minimise the likelihood of inducing an infection in the recipient which could then congenitally infect the foetus. Being part of a fertility clinic that recruits its own donors, understanding the importance of screening and donor matching is essential. By exploring the mechanisms behind CMV transmission and reviewing the available literature, the question of whether it is safe to use CMV positive donor sperm shall be clarified. Methods: The Pubmed database was searched

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using the combined terms donor sperm and cytomegalovirus or CMV. The keyword, assisted conception, was also included in further searches. Studies were limited to human rather than animal studies. Articles were also identified by a manual search of relevant references from retrieved articles. The ABA and HFEA guidelines were also considered in the review. Results and Discussion: There seems to be a definite need for further studies within this area. Many studies have been conducted on immunocompromised individuals as opposed to healthy sperm donors. Reliable and current statistics are difficult to obtain regarding percentage risks to pregnant women who have used CMV positive donor sperm. The data that is available within published studies is minimal and there are differences between the molecular techniques used to detect infective virus in sperm samples. With all evidence considered, the current BAS guidelines, to use CMV positive donor sperm solely for CMV positive recipients, seems thoroughly justified.

### 024 Does sperm washing select the highest quality sperm?

**Idrees Sara<sup>1</sup>; Reynolds Steven<sup>1</sup>; Palley Martyn<sup>2</sup>; Pacey Allan<sup>1</sup>; Calvert Sarah<sup>1</sup>**

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**Background:** A male factor contributes to 30-50% of infertility cases and treatment often selects high quality sperm via density gradient centrifugation. This process separates high quality sperm into a pellet with low quality sperm being trapped at the gradient interface. This study wanted to characterise differences between these fractions isolated in PBS to support further metabolic analysis.

**Methods:** Samples from a student population were obtained with LREC approval (n=14) and analysed for volume, concentration and motility, the latter by Computer Assisted Sperm Analysis (CASA) (SCA Evolution by Microptics). Samples were layered on 40%/80% Percoll/PBS gradients and centrifuged at 300g for 20mins. The pellet and interface sperm fractions were collected, washed and re-suspended in PBS. Assessments were done for concentration by haemocytometer, motility by CASA diluted in PureSperm Wash (Nidacon, Sweden), vitality using Live/Dead Sperm Kit, ATP using Luminescent ATP Detection Assay Kit normalised to sperm count and apoptosis using TUNEL Calbiochem fluorescein-FragEL DNA Fragmentation Detection Kit. Student's paired t-test assessed significance between high quality pelleted sperm and interface sperm. (P<0.05) was taken as significant.

**Results:** High quality sperm from the pellet showed significantly higher total motility (55.8%±25.8% versus 25.2%±14.8%), progressive motility (33.7%±20.8% versus 8.6%±6.8%), vitality (65.5%±11% versus 43.7%±10.4), normal morphology (14.1%±6.7% versus 6.5%±3.6%) and ATP (3.3±1.7µM/106 cells versus 2.4±1.7µM/106 cells) and lower apoptosis (2.6%±2.1% versus 6.9%±4.1%) than low quality sperm from the interface, all results (mean ±SD).

**Conclusion:** Sperm from the pellet is higher quality than sperm from the interface, therefore, we may expect different metabolic profiles for these samples and they metabolise substrates differently. Overall, this work supports using only the pelleted sperm in assisted reproduction when there is a choice.

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### 025 Does the use of hyaluronan sperm binding identify normospermic patients that are at risk of low or failed fertilisation with standard IVF?

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<sup>1</sup>NHS; <sup>2</sup>Wales Fertility Institute NHS

Studies have shown that only mature sperm with membrane integrity can bind to Hyaluronan and sperm selected through HA binding have significantly lower levels of DNA fragmentation.

**Objectives:** The aim of this study was to establish whether there was a correlation between the level of HA binding and fertilisation following IVF. Additional parameters including CMA3 staining, TZI and AI scoring were also compared.

**Methods:** 51 consecutive patients undergoing IVF at WFI between January and March 2016 had HA binding performed before and after density gradient centrifugation together with CMA3 staining, TZI and AI scoring. These parameters were analysed for correlation to fertilisation, cleavage and blastocyst formation rate and the percentage of good quality embryos at the time of transfer. The HA scores were also compared in patients that did and did not achieve 50% fertilisation. Mean fertilisation was also compared in patients that achieved 80% HA binding, and those that did not.

**Results:** No significant correlation was found between any of the test variables and the outcome parameters. There was a significant difference in the percentage of CMA3 staining in bound HA samples to the total population in the initial sample, but not the prepped sample. There was not a significant difference in the mean scores in fertilisation or HA binding in the different sub-groups.

**Discussion:** In this study patients at risk of low fertilisation were not detected by HA binding, CMA3 staining or morphology scoring. This is likely, in part, due to the small number of cases not achieving over 50% normal fertilisation.

**Conclusion:** To further establish the clinical use of the HBA Sperm-Hyaluronan binding assay, additional study with selected patients could be beneficial. This could include excluding patients with a history of good fertilisation or patients with a low egg number or ovarian complications.



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### 026 Outcome and utilisation of late maturing oocytes following intracytoplasmic sperm injection; is it worth the wait?

**Johnson Kate; Hall Charlotte; Chui David KC**

*BMI The Esperance, Eastbourne*

**Aim:** A preliminary study was carried out to follow the outcome of Metaphase I (MI) oocytes that required extended culture to permit maturation to Metaphase II (MII) prior to ICSI to determine whether they can be successfully utilised within a treatment cycle.

**Methods:** Oocytes were collected by vaginal - ultrasound guidance 35 hours post hCG and denuded using 80 IU/mL Hyaluronidase (Irvine Scientific) before transferring to 20µl droplets of Continuous Single Culture Medium (CSCM; Irvine Scientific) to permit identification of maturational status. Semen samples were prepared using a two-step Isolate gradient (45/90%; Irvine Scientific) followed by two wash steps in CSCM ± swim up. Where increased proportions of MI oocytes were identified in the cohort, the ICSI procedure was delayed up to a maximum 4 hours to allow any further maturation to take place. Any oocytes exhibiting the presence of the 1st polar body after this time were then injected using ICSI. MI oocytes maturing in the normal time frame between denudation and injection (up to 1 hour) were also included in this study. Embryos were cultured up to day 6 in CSCM without refreshing.

**Results:** Twenty-four MI oocytes (in 11 patients) were identified that had matured to MII in the time frames discussed. Of those oocytes 58.3% (14/24) displayed 2 PN at fertilisation check with 85.7% (12/14) of the 2PN embryos displaying cleavage on day 3 and 21.4% (3/14) forming blastocysts. Fifty percent (7/14) of these embryos were utilised (transferred or vitrified). A positive pregnancy test has been achieved in 1 patient following the transfer of a late maturing oocyte.

**Conclusions:** Oocytes assessed as MI upon initial inspection that are left to mature and then fertilised by ICSI are able to develop normally and be utilised successfully in treatment.

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### 027 ICSI outcomes with fresh and frozen surgically recovered spermatozoa

**Taneja Jyoti; Richardson Lucy; Townsend Nicola; Glover Lynne; Evans Debbie; Ogutu David; Ah-Moye Michael**

*Herts & Essex Fertility Centre*

**Aim:** To compare fertilisation, cleavage, pregnancy and miscarriage rates following Intra-Cytoplasmic Sperm Injection (ICSI) using fresh and frozen surgically retrieved sperm. This included sperm from Percutaneous Epididymal Sperm Aspiration (PESA) Testicular Sperm Extraction (TESE) in azoospermic men.

**Study design:** Retrospective study of 180 Surgical Sperm Retrieval-ICSI cycles over 10 years. 72 underwent fresh PESA, 69 underwent fresh TESE, 24 using frozen PESA (frPESA) and 12 using frozen TESE (frTESE). Groups 1 to 4 consisted of cycles using PESA and TESE and cycles using frozen-thawed PESA and frozen-thawed TESE sperm.

**Setting:** Azoospermic men who had Surgical Sperm Retrieval. The main Outcome measures were fertilisation and pregnancy rates. Statistical significance was determined using Chi-Squared test. Difference was considered significant at  $P < 0.05$ .

**Main results:** Highest fertilisation was achieved using fresh PESA, not statistically significant compared to fertilisation with fresh TESE (63.7% versus 54.4%,  $P=0.2$ ). No statistically significant differences seen using either fresh or frPESA (63.7% versus 54.4%,  $P=0.2$ ). Significantly lower fertilisation achieved using frTESE versus fresh TESE (37.5% versus 54.4%,  $P=0.02$ ). Fertilisation using frPESA was significantly higher than frTESE (54.4% versus 37.5%,  $P=0.02$ ).

Only difference identified in cleavage rate was between TESE and frTESE.

No statistically significant differences in PR across all groups; highest PR was with fresh PESA (PESA 48.8%, TESE 40.62%, frPESA 39.13%, frTESE 33.3%).

No statistically significant differences in miscarriages between fresh PESA and TESE (14.8% versus 18.1%,  $P=0.66$ ) nor with PESA or frPESA (14.8% versus 18.1%,  $P=0.88$ ). There were no miscarriages with frTESE.

**Discussion:** Highest fertilisation and pregnancy rates (PR) are achieved after ICSI with PESA. Statistically lower fertilisation rates are seen after ICSI with frozen TESE although the PR is comparable. There were no statistically significant differences in embryo cleavage, clinical pregnancy or miscarriage rates across all groups.

### 028 IVF: ICSI split for couples with unexplained infertility

**Gadd Stephanie; Walker David; Kendrew Helen; Sharp Nicholas**

*Bath Fertility Centre*

**Aim:** To review our strategy to minimise the risk of failed fertilisation in treatment cycles for unexplained infertility by undertaking a 50:50IVF:ICSI split in these cases.

**Method:** Data were analysed for all IVF/ICSI treatment cycles from May 2013 to June 2016 ( $n=1052$  cycles). Primary outcome measures were fertilisation rate (FR) and failed fertilisation (FF).

**Relevance:** Minimisation of failed fertilisation cycles.

**Outcomes:** IVF:ICSI split was performed in 86 cycles (8%). In 11 cases (13%) fertilisation was secured with ICSI but not with IVF, and 5 of these couples achieved a clinical pregnancy (giving a 6% overall increase in pregnancy rate in this group).

In 74 of split cases (86%) fertilisation occurred with both IVF and ICSI. In 1 case (1%) there was no fertilisation despite the use of ICSI. Fertilisation rates with ICSI in split cycles was higher than with IVF (76% vs 49%).

During this period FR and FF rates for ICSI only cycles were 69% and 1% ( $n=625$ ) and for IVF only cycles were 60% and 4% ( $n=341$ ).



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**Discussion:** Our strategy to undertake a 50:50 IVF:ICSI split in cases of unexplained infertility is vindicated by covering off the risk of FF in a significant proportion of cases (13%). The failure of this strategy is low (1%) and it provides valuable information for potential future cycles of treatment.

Although costs for ICSI treatment are higher than for IVF, these are offset by the higher financial and emotional costs of FF cycles. IVF:ICSI split also helps these couples by providing an explanation for their "unexplained" infertility when ICSI is effective and IVF is not.

### 029 The impact of oocyte denudation time after retrieval on ICSI outcomes

**Naji Osama; Moska Natalie; El-Shirif Awatuf; Khalil Mohamed; Kopeika Yulia; Hosni Mohamed; Bolton Virginia; Khalaf Yakoub; El-Toukhy Tarek**

*Assisted Conception Unit, Guy's and St Thomas' Foundation Trust*

**Aims:** To evaluate ICSI outcomes in relation to timing of oocyte denudation whilst accounting for important confounding variables

**Methods:** A retrospective analysis of 1555 consecutive fresh non-donor ICSI treatment cycles performed between January 2015 and April 2016 was undertaken. Following controlled ovarian stimulation, oocytes were retrieved 36 hours after hCG trigger and denuded either <2 hours (n=847; group I), or 2-5 hours later (n=690; group II). Fertilisation, implantation and pregnancy rates were compared between the 2 groups. StatView software package was used for statistical analysis.

**Results:** Groups I and II were comparable with regard to mean age ( $35.5 \pm 4.6$  vs.  $35.5 \pm 4.3$  years,  $P=0.9$ ), duration of ovarian stimulation, dose of gonadotropins, mean number of total oocytes retrieved ( $11 \pm 6.3$  vs.  $10.9 \pm 6.5$ ,  $P=0.9$ ), mature ( $8.9 \pm 5.3$  vs.  $8.8 \pm 5.5$ ,  $P=0.8$ ) and fertilised normally ( $6.2 \pm 4.1$  vs.  $6.1 \pm 4.2$ ,  $P=0.8$ ). The mean number of embryos transferred ( $1.6 \pm 0.6$  vs.  $1.6 \pm 0.6$ ,  $P=0.4$ ) and surplus embryos cryopreserved at the blastocyst stage ( $3 \pm 2.3$  vs.  $2.7 \pm 2.0$ ,  $P=0.1$ ) were also similar. There was no significant difference between the 2 groups in the rates of fertilisation per egg injected (68% vs. 67%), implantation (29% vs. 27%) and biochemical (39 vs. 38%) or clinical pregnancy (33 vs. 31%),  $P>0.05$ .

**Conclusion:** This is one of the few studies that was carried out on non-donor and fresh ICSI cycles. Oocyte denudation can be carried out at any time up to 5 hours following retrieval without compromising treatment outcomes. This finding is significant with the ongoing increase in assisted conception activities that it will allow flexibility in scheduling laboratory procedures and efficiency in workload management.

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### 030 Association between the number of oocytes retrieved and live birth rate within a stimulated ICSI treatment cycle

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**Aim:** To evaluate the optimum number of oocytes resulting in the best chance of a live birth within an ICSI programme.

**Background and Methods:** A number of prognostic tools are used to evaluate live birth rates following assisted conception treatment. The number of oocytes retrieved following ovarian stimulation has been established as one of the primary indicators of success. A retrospective analysis of anonymized data from our Centre between 2010-2014 was performed, analysing ICSI cycles using fresh partner sperm where at least one oocyte was retrieved and at least one embryo transferred. Four groups were identified based on oocyte numbers: 1-5, 6-10, 11-15 and >15. Statistical analysis was performed using one way ANOVA, Pearson's Chi2 and Kruskal Wallis tests.

**Results:** 3,415 ICSI cycles and 32,255 oocytes were analysed. Significant differences were identified with oocyte maturity and number of embryos transferred decreasing with increasing oocyte number. The number of surplus embryos meeting the freeze criteria increased with increasing number of oocytes. No significant differences were seen between the four groups in terms of normal fertilisation, biochemical pregnancy and miscarriage rates. Clinical pregnancy and live birth rates were significantly decreased between the 1-5 oocytes retrieved group and the other groups.

**Discussion and Conclusion:** Our study indicates that the optimum number of oocytes to result in the best chance of live birth with ICSI treatment is >5. Although the data shows a trend, no significance was reached when >5 oocytes were collected. Results may vary in terms of significance if cumulative live birth rates with frozen transfers were included.

**Relevance and Impact:** This study is reassuring for patients with 6 or more oocytes retrieved as outcomes comparable to those patients with higher egg numbers may be achieved in

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any one fresh ICSI cycle. This may help avoid ovarian hyper stimulation and associated risks.

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### 031 The prognostic value of oocyte dysmorphisms identified prior to ICSI and correlations with controlled ovarian stimulation regimes

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Non-invasive morphological assessment is the most commonly used tool in ascertaining the quality of embryos and thus their selection for transfer in human assisted reproduction cycles. However the morphological features of the preceding oocytes are not commonly considered and could be of use as an additional predictive tool for embryo selection. A number of dysmorphic features have been identified more commonly in certain controlled ovarian stimulation (COH) protocols (5,7) and also been shown to have effects on subsequent fertilisation success and embryo development (1,2,3,6). This study aimed to clarify whether the presence of any out of 17 dysmorphic oocyte features currently commented on prior to intracytoplasmic sperm injection (ICSI) at Shropshire & Mid-Wales Fertility Centre (SMWFC) could be linked to COH regimes and reduced fertilisation rate and pregnancy rate. Oocyte morphology data was collected from 2,006 injected oocytes. Each of the 199 patients underwent ICSI at the SMWFC between October 2013-December 2015 after short, long or antagonist (COH) regimes. Dysmorphic features of denuded pre-ICSI metaphase II (MII) oocytes were recorded and the subsequent fertilisation status, Day 3 & Day 5 development and fate tracked. 7 out of the 17 dysmorphic features were observed to have negative impacts on different stages of embryo development; Darkness ( $P=0.03$ ), Perivitelline (PV) fragmentation ( $P=0.04$ ), enlarged PV ( $P=0.019$ ) (these identified more commonly in short COH  $P=0.021$ ), multiple polar bodies (PB) ( $P=0.023$ ), vacuoles ( $P=0.011$ ), tough membrane break ( $P<0.001$ ), no membrane break ( $P<0.001$ ). No significant results were identified regarding pregnancy rates. Following this study, it is suggested that the number of dysmorphic features commented on prior to ICSI at the SMWFC be reduced to the aforementioned 7 features for further analysis and that use of the short COH regime be minimised.

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### 032 Is short IVM before ICSI effective?

**Rogers Shaun; Finch Katie; Florek Agnieszka**  
City Fertility, London

**Aim:** Retrospective analysis to evaluate efficacy of injecting oocytes that mature to Metaphase II during limited in-vitro maturation.

**Introduction:** We expect the majority of oocytes obtained at egg collection to be mature, arrested at the second Metaphase (MII). Some Metaphase I (MI) oocytes develop during in-vitro maturation to MII after cumulus denudation. It is standard practice for embryologists to perform ICSI on these oocytes to maximise the number of embryos available, but we assume normal embryo development can occur. Reports suggest that a time period of approximately 24 hours is required from nuclear envelope breakdown, in the germinal vesicle, to enable spindle formation, chromosome aggregation and metaphase events to be completed for functional oocytes to be ready for fertilisation. Approximately 8 hours is required for human oocytes to develop sufficiently from MI to MII1. This raises the question of whether our current practice is sufficient.

**Method:** Development of oocytes in late MII's ICSI cases was assessed to evaluate whether normal fertilisation, embryo development, whether embryos generated are selected for transfer or cryopreserved in comparison to oocytes that were mature after cumulus complex denudation.

**Outcomes:**

|                          | MI 35-38hrs post hCG | Late MII's | Statistics |
|--------------------------|----------------------|------------|------------|
| Oocytes Injected         | 792                  | 135        |            |
| Fertilisation Rate       | 68%                  | 45%        | $P<0.05$   |
| Cleavage Rate            | 97%                  | 87%        | NS         |
| Blatocyst Formation Rate | 67%                  | 31%        | $P<0.05$   |
| Utilisation              | 54%                  | 39%        | NS         |

NS not significant

**Discussion:** Fertilisation, embryo development and implantation potential appear to show a trend towards being effected when maturation occurs after denudation. An analysis



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of the significance in the difference between results shows that oocytes should be considered for injection. Only fertilisation and blastocyst development appear compromised. Extended oocyte in-vitro maturation has been suggested to improve the trends of oocyte performance and may affect embryo development to the blastocyst stage. Modifying the policy on handling late MII's and evaluating this change will be the next step in this project.

1 Z. Holubcova et al Error-prone chromosome-mediated spindle assembly favours chromosome segregation defects in human oocytes

### 033 Ongoing clinical pregnancy following ICSI of late metaphase II oocyte for PGD-BRCA1

**Odia Rabi; Loutradi Kalliopi; Cawood Suzane; Ozturk Ozkan; Doshi Alpesh; Serhal Paul**

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**Aim:** To evaluate the efficacy of routinely delaying ICSI of oocytes observed to be immature post-cumulus dissection, in view of creating viable embryos and subsequent pregnancies.

**Relevance/Impact:** culture immature oocytes in-vitro and perform late ICSI, which may result in viable pregnancy.

**Content:** A couple seeking fertility treatment for the avoidance of genetic disorder (BRCA1 Gene). A 38 year old female was stimulated via long protocol and oocytes retrieved at 37 hours post hCG trigger. A total of 8 oocytes were collected and denuded at 40 hours post hCG. There were 3 metaphase II oocytes, 3 metaphase I, and 2 germinal vesicle. At 41 hours post hCG the 3 MII oocytes were inseminated with ICSI (Group 1). 3 MI oocytes were inseminated with ICSI 46 hours post hCG (Group 2), after the extrusion of a polar body indicating maturation to MII (cytoplasmic maturation unknown).

**Outcomes:** At 16-18 hours post ICSI, 2 oocytes were observed to have fertilised normally from group 1, and 3 oocytes from group 2 fertilised normally. Two blastocysts developed on day 5 from group 1, and 1 blastocyst developed from group 2. All blastocysts were biopsied for Preimplantation Genetic Diagnosis (PGD) for BRCA1 gene and simultaneous karyomapping, and frozen post biopsy to await the PGD report. The 2 blastocysts from group 1 were abnormal either due to abnormal mutation at the BRCA 1 site or aneuploidy and therefore not transferable. The blastocyst from group 2 however, showed the BRCA1 S382 mutation site to be normal, with no chromosomal abnormalities detected and was therefore transferable. The patient subsequently returned for a frozen-thawed embryo transfer, and achieved an ongoing clinical pregnancy (presently at 24 weeks).

**Discussion:** It is known that the developmental competence of embryos derived from immature oocytes is reduced, compared with matured oocytes. However, this report shows that it can be good practice to wait for immature oocytes to reach maturation in cases where oocytes numbers and maturation are compromised.

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### 034 Live birth after fertilisation of vitrified oocytes: A case report

**Michielsen Jannie; Guardiola Jordi; Salma Umme; Niblock Laura; Corley Aoife; Baggott Roisin; Keane Declan**

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**Introduction:** Cryopreservation of oocytes have resulted in live births for decades. The slow freezing-rapid thaw method increases damage to the oocytes during temperature transition. [1] Vitrification reduces physical damage and improves survival rates of cryopreserved oocytes. [2] While pregnancies have been reported from vitrified oocytes since 1999 [3] we are reporting on the first live birth achieved from vitrified/warmed oocytes through an Irish clinic.

**Case Report:** A 40 year old single lady attended our clinic for multiple egg freezing cycles due to low AMH (2.6pmol/L) in 2015. Multiple egg freezing cycles accumulate oocytes over several cycles for Intracytoplasmic Sperm Injection (ICSI) treatment. This decreases treatment fatigue for the patient undergoing multiple ICSI cycles with reduced number of possible embryos for transfer at each cycle, and can reduce cost compared to multiple ICSI cycles. In total 4 oocytes were frozen from two cycles and thawed. 3 oocytes survived the thaw and were injected with donor sperm along with 7 fresh oocytes collected on the day of thaw. 3 oocytes fertilised out of 10 oocytes injected with donor sperm. On day 3, two embryos were of good quality, both were from frozen oocytes and both were transferred. A blood test measuring the Human Chorionic Gonadotropin (HCG) level was performed 17 days after embryo transfer and the level was 3154 IU/L. A viability pregnancy scan 21 days after the blood test showed a single intrauterine gestational sac with positive foetal cardiac activity. The patient gave birth to a girl in July 2016 weighing 7 pounds and 8 ounces.

**Conclusion:** This is the first live birth resulting from vitrified/warmed oocytes through an Irish clinic. Multiple stimulation cycles combined with vitrification of human oocytes is a suitable and effective treatment for poor responder patients and should be offered more frequently.

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### 035 Novel approach for measuring oxygen consumption of mammalian oocytes

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Oxygen consumption is an established marker for cellular energy metabolism and an indicator of mitochondrial function. In reproductive biology, it has been correlated to a range of outcomes including oocyte viability and maturation, embryo development, implantation potential and pregnancy rate. However, measuring oxygen consumption is technically challenging and requires specialist equipment. The recent availability of Seahorse Bioanalysers has transformed the study of cellular metabolism in a range of systems, however, this technology has not been used to study oocytes and embryos. We have therefore examined whether Seahorse XFp is capable of measuring oxygen consumption of oocytes.

Bovine oocytes were retrieved from abattoir-derived ovaries and cultured overnight in media supporting maturation (M199 supplemented with hormones, pyruvate, glutamax, and serum). Oocytes were either allowed to mature or treated with cycloheximide to maintain their immature state. They were then placed into Seahorse flux packs containing maturation media in groups of 3 to 6 corona-enclosed oocytes. These groups produced reproducible values for oxygen consumption within the expected range – basal measurements of  $2.37 \pm 0.22$  pmol/oocyte/hour (immature) and  $2.05 \pm 0.77$  pmol/oocyte/hour (mature), without impeding subsequent development. To test further the validity of these data, the mitochondrial uncoupler FCCP, and electron transport chain inhibitors oligomycin and Antimycin A/rotenone were serially injected. These data indicated approximately 60% of total oxygen consumption was coupled to ATP production, with 20% each of non-mitochondrial and proton leak.

These data are the first reported use of the Agilent Seahorse XFp for the direct, non-invasive assessment of mitochondrial function in oocytes. Compared to previously applied assays for oxygen consumption, Seahorse is fast, simple and highly automated, allowing high-throughput investigations of energy metabolism. With increasing recognition of the critical role mitochondria play in supporting healthy reproduction; this tool facilitates investigation into mitochondrial function which has extensive scope for applications within reproductive biology.

### 036 Dynamic changes in human oocyte amino acid and energy metabolism during preantral follicle development

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Division of Reproduction and Early Development, LICAMM, University of Leeds

This study aimed to map metabolic signatures of human oocytes during primordial follicle activation. Preantral follicles were isolated from cryopreserved human ovarian cortex tissue by collagenase digestion and classified as primordial, early primary or primary stages according to diameter and granulosa cell morphology. Oocytes were extracted from the surrounding granulosa and incubated in KSOM for photometric analysis

of glucose, pyruvate and lactate turnover or AAP-IVM media for HPLC Amino Acid Profiling (AAP). All tissue was donated with informed consent by donors < 35yr under ethically approved protocols. Data were confirmed as non-parametric by D'Agostino-Pearson test and for significant differences between groups by Kruskal-Wallis with post-hoc Dunn's test.

Primordial and early primary oocyte pyruvate consumption were significantly different to primary oocytes (n=123 primordial, n=86 early primary, n=47 primary, n=2 secondary, p=0.0005). However there were no significant differences between other groups either on a per oocyte or a per oocyte volume basis.

Oocyte amino acid profiles revealed significant differences in consumption or release between follicle stages (n=177 primordial, n=163 early primary, n=132 primary, p<0.05). These changes included a switch from consumption to release during early primary stage of glutamine (p=0.036), glycine (p=0.026), valine (p=0.001) and lysine (p=0.041), a switch from production to consumption during early primary stage of tryptophan (p=0.017), and a switch from release to consumption during primary stage of arginine (p=0.013), tyrosine (p=0.0006), isoleucine (p=0.04) and lysine (p=0.041).

These data imply a transition from low levels of oocyte metabolic activity in human primordial follicles, to increased oocyte amino acid turnover during activation to the more metabolically active primary stage. These metabolic changes may fuel protein synthesis, mitochondrial replication and oocyte growth.

### 037 Nitric oxide donor (SNP) and proteasome inhibitor (MG132) treatment during in vitro maturation impairs bovine oocyte development

**Al-Hilfi Haitham; Kwong Wing Yee; Fisher Patricia; Alberio Ramiro; Sinclair Kevin**

University of Nottingham

Oocyte quality determines post-fertilisation development. In turn, functional mitochondria determines oocyte quality. Sodium nitroprusside (SNP), a potent nitric oxide donor, operates via the PPARG-coactivator 1 $\alpha$ , Nuclear-respiratory factor 1, Transcription factor A-mitochondrial pathway to initiate mitochondrial replication. The specific and reversible proteasome inhibitor MG132 reduces mitochondrial degradation whilst simulating maturation promotor factor (MPF) activity. We hypothesised that timed combinations of these agents, which have not been investigated previously, could enhance developmental competence of oocytes by increasing functional mitochondria and ATP production. Working with cumulus-enclosed Grade 1 and 2 bovine oocytes, aspirated from 4-9 mm follicles from abattoir derived ovaries, we determined the timing of first polar-body extrusion (PBI) and ATP content during in vitro maturation (IVM). In seven replicated experiments, the proportion PBI peaked (~0.80; P<0.001) by 19 h culture, but PBI was reduced (P<0.01) by both SNP (10  $\mu$ M throughout IVM) and MG132 (10  $\mu$ M from 16 h IVM) ( $0.86 \pm 0.043$ ,  $0.64 \pm 0.056$ ,  $0.61 \pm 0.058$  and  $0.50 \pm 0.060$  for serum-supplemented (10%) TCM199 Control, SNP, MG132 and SNP+MG132 treatments respectively). Consistent with these observations, the proportion cleaved of inseminated oocytes by Day 2 following insemination in four replicated experiments was reduced (P=0.012) for SNP+MG132 compared to Control groups ( $0.26 \pm 0.063$  vs  $0.72 \pm 0.058$ ).

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ATP content of PBI oocytes was also reduced ( $P=0.026$ ) for SNP+MG132 compared to Control groups ( $1.25\pm0.073$  vs  $1.53\pm0.074$  pmol/oocyte). These preliminary findings are somewhat unexpected and, on first inspection, inconsistent with studies assessing these mitochondrial-stimulating agents at the indicated concentrations separately. Final conclusions await ongoing assessments of mitochondrial proliferation and post-fertilisation development to the blastocyst stage for all 4 treatment combinations.

### 038 Cumulus cells RNA sequencing: Immature, mature and aged mice

**Alageel Arwa; Gray Nicki; Repapi Emmanouela;  
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*University of Oxford*

Oocyte development is coordinated by bidirectional communication between the oocyte and the surrounding somatic cells known as cumulus cells (CCs). The CCs play an essential role in the production of competent oocytes, hence, the fate of both oocyte and CCs are tightly linked. Female fertility declines with age which is attributed to the deterioration in egg quality. Due to the tightly linked fate of cells, it is possible that cumulus cells also deteriorate in function with age. Therefore, the aged follicular cells could contribute to the diminished developmental potential of the aged oocyte.

To investigate the impact of age on the transcriptome profile of CCs, we carried out RNA sequencing on cumulus cells using a mouse model. We selected three ages based on important points in the mouse reproductive lifespan: 3 weeks old (prepubertal), 9 weeks old (prime reproductive age) and 52 weeks old (similar to pre-menopausal women). Mice were injected with pregnant mares serum gonadotropin (PMSG) and ovaries collected 48 hours later. Each CCs sample was obtained from an individual follicles and processed using RNAseq.

A number of differentially expressed genes were identified between the different age groups and further investigation is being carried out to define the pathways involved in CCs aging. RNA high throughput sequencing has the potential to provide insight into the effect of age on CCs.

### 039 Establishing the mechanism of egg activation in *Drosophila*

**Turnbull Rob; York-Andersen Anna; Derrick Chris;  
Weil Tim**  
*University of Cambridge*

Egg activation is a universal process by which a mature oocyte is released from its arrest in meiosis and begins a host of developmental events that enable the onset of early embryogenesis. Changes at egg activation include translation of maternal mRNAs, cytoskeletal rearrangements and a transient increase in the concentration of cytoplasmic calcium. In *Drosophila*, it has previously been shown that a single calcium wave occurs at egg activation<sup>1,2</sup>. Our work suggests that the initiation of this calcium wave requires osmotic pressure and we currently testing this by observing a genetic encoded calcium indicator under experimental conditions of varying pressure, osmolality and ionic composition. The

calcium wave has also been shown to require a *Drosophila* calcipressin. This aspect of the calcium signalling pathway is required for translation of specific mRNAs at egg activation. We hypothesise that as the calcium wave passes through the egg, translation is initiated for many stored mRNAs. We observe translation occurring almost immediately after egg activation as mRNA dissociates from Processing bodies, cytoplasmic regions of repression.

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### 040 My elective experience - saving the Northern white rhino

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During training as a Clinical Embryologist on the Scientist Training Programme, each student has the opportunity to undertake an Elective Learning Experience. The elective is designed to allow trainees to explore areas related to their specialism, not taught during the academic or work-based elements. Assisted reproductive technology (ART) in animals was of great personal interest, therefore the decision was made to observe and gain experience in the applications of ART in animals, with a particular focus on conservation.

The white rhinoceros (*Geratotherium simum*) native to Africa, has two sub-species, the southern white rhinoceros (SW) (*C. simum simum*) and the northern white rhinoceros (NW) (*C. simum cottoni*). The population is considered extinct in the wild, and the captive population only consists of 3 individuals based in Kenya (one male two females). Each individual has a medical complication that prevents natural mating, conception and pregnancy. A collaborative group of scientists from Europe and the USA have developed a plan to rescue the NW from extinction using ART. One proposed method is to collect oocytes from the two remaining females and use in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) with fresh or frozen sperm. The subsequent embryos would then be transferred into a surrogate mother, most likely a SW.

Oocyte collection and IVF are in their early stages of development in the rhinoceros, with many difficulties and complications becoming apparent. The oocyte collection technique is being developed and refined by Professor Hildebrandt and his team from the Leibniz Institute, Berlin. Working with the team from Berlin, two oocyte collections took place on a SW in December 2015 and January 2016. The first attempt was unsuccessful. 3 were collected in the second. Further attempts to optimise this technique continue, as well development of new strategies to save the NW from extinction.



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### 041 Livebirth following two rounds of trophectoderm biopsy, vitrification, and warming: Assessment of the efficacy of retesting PGD and PGS embryos

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Current best practise for PGD and PGS is considered to be trophectoderm biopsy and vitrification. Unaffected or euploid embryos can then be used in a frozen cycle. Trophectoderm biopsy provides more material for testing, but some samples still fail to generate results. Retesting of embryos may also be necessitated by contamination events, or sample rejection by the testing laboratory. This necessitates the embryos to be thawed, re-biopsied and re-vitrified.

PGD (Karyomapping) patients are informed that embryos with no result are treated as affected, while PGS patients (NGS) are given the option to transfer with no result or retest. Anecdotal evidence suggests retesting is common in the USA, with a concurrent reduction in implantation compared to standard PGS results. A publication by Zhang et al<sup>1</sup> provides the largest cohort of 10 SETs of re-biopsied and re-vitrified embryos, with a 50% implantation rate, equivalent to their standard PGS results.

We have undertaken warming and a second round of biopsy and vitrification for 55 embryos. Results were obtained for 93% of embryos and 25% of those yielding results were suitable for patient use. The most common reason for retesting in PGS was a failure of DNA amplification from the initial biopsy (73%), followed by failure of initial test results to meet QC criteria (24%). In PGD both these factors occurred at the same incidence (47%).

Six of the suitable retested embryos have been transferred resulting in one livebirth and an ongoing pregnancy, now in the second trimester. There has also been a clinical miscarriage, two negative tests, and a cycle currently awaiting outcome.

The available data demonstrates the efficacy of the procedure in terms of generating a PGD/PGS result, implantation, and livebirth. Data needs to continue to be monitored to assess any effects on expected outcomes.

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### 042 Predicting oocyte number and ovarian response when there is discordance between antral follicle count and anti-Mullerian hormone level

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In predicting ovarian response in assisted conception we usually rely upon Anti-Mullerian Hormone (AMH) and Antral Follicle Count (AFC). However, what is frequently found

are cases where these are largely discrepant, complicating treatment selection. We designed a study to identify those patients and investigate ovarian response in these instances.

This is the first study to use regression modelling to define discordance between AFC and AMH and categorise data pairs into discordant groups to a number of degrees ( $\frac{1}{2}\alpha$ ).

A multifactorial model was created using generalised linear models with oocyte yield and ovarian sensitivity index as outcomes. In addition, prediction of poor response, hyper-response and live birth rate were measured as secondary outcomes using ROC curves.

This study is extremely relevant to this current era of personalised therapy in IVF. This study will provide guidance to clinicians in frequent cases when the adopted ovarian reserve markers are discordant.

Discordant pairs were split into high AMH and low AMH groups. For those with high AMH, the addition of AMH to our model provided 8.3% explanation of the variance in oocyte yield (p

Neither marker was valuable in predicting live birth; whilst AMH was the stronger marker for both hyper-response (AUC 0.768 vs 0.747,  $p < 0.001$ ) and poor response (AUC 0.832 vs 0.815,  $p < 0.001$ ).

Whilst AMH and AFC provided similar predictive use in non-discrepant pairs, this is not true when AMH and AFC are discordant. In these cases, the marker which is followed depends upon whether the AMH is discordantly high or low compared with the AFC.

### 043 Impact of direct-to-consumer genetic testing on gamete donation: A survey of gamete donors, recipients and donor-conceived individuals

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Direct-to-consumer (DTC) genetic testing enables individuals to discover information about their biological makeup and ancestry. As we have previously reported (Harper et al. 2016), this development is a potential factor in gamete donation; individuals unaware of their donor conception might inadvertently discover new aspects about their family narrative, unexpected half-siblings might be identified, and anonymous donors can be traced by their offspring.

The present study explored the views of gamete donors, donor recipients and donor-conceived individuals on the role of DTC genetic testing and disclosure.

An online survey was sent to the online introductory connection site Pride Angel and to the UK Donor Conception Network (DCN). In total, 590 responses were returned, consisting of 194 donors and 212 recipients from Pride Angel, and 163 recipients and 21 donor-conceived individuals from the DCN.

The majority of DCN recipients and donor-conceived individuals were aware of DTC genetic tests, compared to less than half of the Pride Angel recipients. In our cohort, 31% of donor-conceived individuals and 22% of donors had



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undergone some kind of genetic test themselves. The majority of donor recipients favoured disclosure, and this trend was strengthened among those who themselves had undergone DTC genetic testing. A significant number of recipients quoted awareness of DTC genetic testing as a factor in an increased openness towards disclosure. These findings are potentially of value to donor-conceived individuals as the majority in our sample favoured mandatory disclosure.

Our study shows that awareness of DTC genetic testing is contributing to changing attitudes towards gamete donation. Awareness of such testing is correlated with an increased willingness to disclose to a child that they are donor-conceived. It is vital that information about future genetic tests forms part of pre-conception counselling in the context of gamete donation.

Harper, J.C., Kennett, D. and Reisel, D. (2016) The end of donor anonymity: how genetic testing is likely to drive anonymous gamete donation out of business. *Human Reproduction* 31(6), 1135–1140.

### 044 Pre-implantation genetic screening can be a better alternative to prenatal diagnosis for the eradication of hemoglobinopathies

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**Aim:** The main objective of this project was to show that Pre-implantation Genetic Screening (PGS) could be a better alternative when invasive Prenatal Diagnosis (PND) failed to minimize the prevalence of both sickle cell disease and thalassemia (Hb-pathies).

**Content:** This is a review of the first 5 years results of a project conducted to serve the above purpose.

**Relevance:** PND with subsequent termination of pregnancies (TOP) of affected fetuses is an acceptable approach for severe genetic diseases or lethal malformations. However, in certain communities, like ours, genetic disorders like Hb-pathies are considered serious but TOP is not justified. This led to delivering affected fetuses despite PND. Hence, all couples at risk were advised to proceed with IVF cycles supplemented with PGS for Hb-pathies.

**Outcome:** Over 5 years period (2011-2015) our laboratory received 7251 embryonic biopsies from 1170 IVF cycles for different PGS purposes. 199 cases were done for screening for single gene disorder; the majority of which (70%) were for couples at risk of Hb-pathies. Healthy embryos were transferred in 89.4% of the cycles with 37% pregnancy rate.

**Discussion:** The calculated genetic yield of 25% affected fetuses with Hb-pathies diagnosed by PND is unfortunately delivered alive in our community; hence its incidence is not affected. According to our findings, PGS has resulted in 40% reduction in newborns with Hb-pathies. Further improvement in the outcome can be achieved by increasing awareness, reducing the cost, and improving the technologies surrounding IVF procedure and molecular genetics. Moreover, simultaneous aneuploidy screening is an additional advantage of PGS.

### 045 Setting up a preimplantation genetic screening (PGS) service: A clinic's experience

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<sup>1</sup>CARE Fertility Northampton; <sup>2</sup>CARE Fertility

**Aim/Objectives:** In 2015 the decision was taken to offer a preimplantation genetic screening (PGS) service at the clinic, replacing a satellite service to another clinic within the same group which had previously operated. This abstract discusses the setup and implementation of the service, along with initial outcomes.

**Content:** The laboratory aspects of setting up the PGS service are discussed, ranging from purchasing a laser, to validation of both the equipment and process. A description will be provided regarding interdisciplinary staff familiarisation and training for the PGS service and of HFEA licensing which was completed in February 2016. Initial cases have been undertaken and these outcomes are available.

**Relevance/Impact:** As patient uptake of PGS is increasing, more clinics may look to begin offering this service. Our experience is being shared to assist others in this process.

**Outcomes:** Patient uptake has been pleasing, with 41 patients registering an interest in PGS so far. 10 trophectoderm biopsy cases, with vitrification, have been performed and ploidy results have been obtained for all blastocysts tested. 2 patients have reached frozen embryo replacement so far, both with a single euploid blastocyst. Unfortunately, the first resulted in demise of the embryo prior to transfer. The second is awaiting a pregnancy scan, following a positive pregnancy test.

**Discussion:** Introduction of PGS at this clinic has involved a significant multidisciplinary effort, ranging from initial validation, to biopsy training, patient counselling, treatment pathway specification and implementation of finance packages. With the knowledge of the first positive pregnancy test and using staff and patient feedback following our initial cases, we aim to continue to progress and improve the service going forward.

### 046 Risk of miscarriage and chromosomal abnormalities in pregnancy by transfer of embryos not analysed by CCS (Comprehensive Chromosomal Screening)

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**Aims/Objectives:** Embryo chromosomal aneuploidy is the most common cause of unsuccessful pregnancy after IVF. In embryos with chromosomal abnormalities, development becomes blocked, and they ultimately cause miscarriages or produce children with variously syndromes.

The aim of this work was to quantify accurately the risk assumed by couples undergoing in vitro fertilization treatment when embryos are transferred without being analyzed by CCS.

**Content:** A retrospective study was performed. We included the arrayCGH results of 1704 embryos from 594 IVF-cycles

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conducted since January-2013 to September-2016. ArrayCGH analysis of the biopsied trophoectoderm was performed using Agilent SurePrint-G3-8x60K-CGH.

**Relevance/Impact:** CCS applied as a therapeutic tool reduces the risk of miscarriages and children born with chromosomal abnormalities.

**Outcomes:** A total of 1029 embryos (60.4%) were euploid. Of the total of aneuploid embryos, 2.7% carried numerical sex chromosome anomalies (47,XXY; 45,X0; 47,XXX and 47,YYY), 1.3% carried viable autosomal trisomies (chromosomes 13, 18 and 21) and finally a total of 10.8% carried other trisomies (chromosomes 16, 22, 15 2, 7, 14, 8, 9, 4 and 20) producing spontaneous miscarriages in the first trimester.

In the group of women over 35 years, the percentage of viable autosomal trisomies was higher than in younger women (14.4% vs 2.8%). Similarly the percentage of embryos that would result in first-trimester abortions was higher in the older age group (81.2% vs 63.9%).

**Discussion:** Different authors propose not to analyze chromosomal abnormalities in embryos prior to embryo transfer. These authors believe that the CCS reduces the chances of successful treatment. This study reveals that about 39.6% of embryos from patients that undergoing an IVF cycle are aneuploid and 14.8% of them could implant and lead to miscarriages or live births with chromosomal abnormalities. Therefore the CCS is a useful technique in IVF to ensure an ongoing pregnancy and a healthy child.

### 047 Cumulative live-birth rates following miscarriage in an initial complete cycle of IVF: A retrospective cohort study of 113,870 women

**Cameron Natalie; Bhattacharya Siladitya; McLernon David**

*University of Aberdeen*

**Aims/Objectives:** To compare cumulative live-birth rates (CLBRs) in women who miscarry in their first complete cycle of IVF/ICSI with those whose treatments end without a pregnancy or a live-birth.

**Content:** Data from the Human Fertilisation and Embryology Authority (HFEA) register on IVF/ICSI treatments using autologous gametes started from 1999-2008 were analysed. CLBRs were estimated in women who a) had miscarriage (and no live-birth), b) at least one live-birth or c) no pregnancy in their first complete cycle of IVF/ICSI (including fresh and frozen embryo transfers following a single oocyte retrieval).

**Relevance/Impact:** Miscarriage following IVF is a setback for couples who are uncertain about their ultimate prognosis. CLBRs, which are better indicators of overall chances of IVF success, have not previously been reported in couples who miscarry an IVF pregnancy.

**Outcomes:** In their first complete cycle, 9,321 women had at least one miscarriage (and no live-birth); 70,076 had no pregnancies and 33,152 had at least one live-birth. After three complete cycles, conservative CLBRs (which assume that women who discontinued treatment subsequently never had a live-birth) were 40.9%, 49.0% and 30.1%, while optimal CLBRs (which assume that women who discontinue have the same chance of live-birth as those treated) were 49.5%, 57.9% and 38.4% in the miscarriage, live-birth and no pregnancy

groups respectively. Odds of cumulative live-birth for women who miscarried in their first complete cycle were 43% higher than those who had no pregnancy [odds ratio (95% confidence interval) = 1.43 (1.35, 1.52)], and twice as high for live-birth versus no pregnancy [2.10 (1.95, 2.26)]. Significant predictors for live-birth in all women included tubal infertility [0.88 (0.87, 0.93)] and increasing age [18-40 years = 0.94 (0.94, 0.95); >40 years=0.63 (0.60, 0.66)].

**Discussion:** Our findings will provide reassurance to couples who experience miscarriage in their first complete cycle of IVF/ICSI.

### 048 Intracytoplasmic morphologically selected sperm injection does not improve neither miscarriage rate nor live birth rate in patients with recurrent implantation failure and/or male factor infertility

**Seshadri Vidya; Serhal Paul; Doshi Alpesh; Ozturk Ozkan; Loutradi Kalliopi; Saab Wael; Ben Nagi Jara; Cawood Suzanne; Mania Anastasia; Sarna Urvashi; Gaunt Matthew; Heath Carleen; Odia Rabi; Atluri Vidya; Webber Lisa; Duran Montserrat**

*The Centre For Reproductive and Genetic Health, London*

A new approach of Assisted Reproductive Technology (ART) involving real-time and high- magnification technique of spermatozoa together with a micromanipulation system called IMSI has taken place over a decade to improve the efficiency of the conventional Intracytoplasmic sperm injection (ICSI).

The intracytoplasmic morphologically selected sperm injection (IMSI) is based on motile sperm organelle morphology examination (MSOME) which involves the use of differential interference contrast microscopy at high magnification (at least x 6300). This real-time system enables the selection of the best available motile spermatozoa before oocyte injection but requires more human time to perform it in comparison to the conventional ICSI procedure.

Several randomized control trials and other comparative studies have reported better outcomes such as top quality embryos, fertilization, clinical pregnancy, miscarriage and live birth rates, in couples with previous recurrent implantation failure (RIF) and/or male factor infertility (MF) undergoing IMSI versus ICSI.

The aim of the present study is to confirm improved clinical outcomes in light of what has been published. We have populated the outcomes of 501 ICSI cycles and 179 IMSI cycles.

Interestingly, our study shows similar fertilization rates when comparing IMSI versus ICSI (70.6 % vs 70.8% respectively), higher clinical pregnancy rate in the IMSI group (62.5% vs 52.5%) though there were more numbers of miscarriages in the IMSI group. Live birth rate is lower in the IMSI group compared to the ICSI group (28.4% vs 34%).

Finally, our outcomes have not strengthened previous conclusions regarding less miscarriage rate and live birth rate when performing IMSI.

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### 049 Case study: Double blastocyst transfer leading to a quadruplet pregnancy

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<sup>1</sup>CARE Fertility Nottingham; <sup>2</sup>CARE Fertility

Although very rare (1 in 500,000 pregnancies) quadruplets do occur spontaneously but in most cases high order multifetal pregnancies (HOMP) are derived from ART following a double or triple embryo transfer and therefore can be either monozygotic, dizygotic or trizygotic.

The couple (30 year old female and a 32 year old male) had a history of 7 years of primary infertility, 3 previous failed IVF cycles and a successful fourth cycle, resulting in a singleton birth. After a double embryo transfer in their fifth cycle, the pregnancy scan revealed monozygotic twins and dichorionic diamniotic (di-di) twins. Subsequent reduction of the monozygotic twins was performed and led to a twin live birth.

The clinic's multiple birth minimisation strategy (MBMS), stipulated an elective single embryo transfer for IVF/ICSI patients aged <38 with a good quality blastocyst on Day 5, undergoing their first or second treatment attempt. As this was the patient's fifth cycle and had three previous failed cycles, double embryo transfer was justified.

The di-di twins were different genders and the monozygotic twins did not share a chorion with the other twins, so it is likely that the pregnancy was trizygotic originating from a combination of IVF embryos and a naturally conceived embryo implanting simultaneously. However, there is no way to prove or disprove this hypothesis as the monozygotic twins were terminated.

In conclusion, all patients are advised against unprotected intercourse for 2 weeks after ART and the failure to do so can increase the risk of HOMP, as seen in this case study.

### 050 Can we decrease multiple pregnancy rates in clomiphene ovulation induction?

**Lim Raymond; Edmondson Judith; Yossry Abdel-Monem; Gudipati Madhavi**

*City Hospital Sunderland NHS Foundation Trust*

**Aim:** To analyse the multiple pregnancy rate and number of treatment cycles in clomiphene ovulation induction.

**Content:** Retrospective review of case notes of women on Clomiphene Ovulation Induction from 2008-2013 at district general hospital.

**Relevance/Impact:** Clomiphene is the first line treatment option for anovulatory infertility. Side effects include 10% risk of multiple pregnancy. NICE recommends offering ultrasound monitoring during at least the first cycle of treatment to minimise the risk of multiple pregnancy. It also recommends that clomiphene treatment is no longer than 6 months.

**Outcomes:** 222 patients were included in the study. Results show ovulation rate of 92% with pregnancy rate of 48% (106/222). Although the ovulation rate was comparable in under and over 35 year groups, as expected the pregnancy rate was significantly higher in under 35 group (52% vs 25% p<0.05). Majority of patients were on 50-100 mg, however even in 150mg group (n=6), the pregnancy rate was considerable at 23%.

A significant decrease in twin pregnancy rate of 0% was seen as opposed to the 10% quoted in literature. All patients had ultrasound follicular tracking in their first cycle to monitor response to Clomiphene.

86 were treated for longer than 6 months up to a year and the pregnancy rate in this group was 31%.

**Discussion:** Clomiphene treatment has been prescribed by some general gynaecologists and also either has not been closely monitored or serum progesterone used for assessing response, which can contribute to multiple pregnancy. Ultrasound follicular tracking and treatment managed by Reproductive specialists can significantly decrease the multiple pregnancy rate.

As the association between clomiphene and ovarian cancer is with more than 12 months of treatment, along with significant pregnancy rate beyond 6 cycles, it is reasonable to continue treatment up to 12 cycles with patient counselling.

1. NICE Guidance: Fertility problems: assessment and treatment.

2. Ovarian tumours in a cohort of infertile women. *N Eng J Med* 1194;331: 771-6



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### 051 Introduction of a different ovarian stimulation protocol and the effect on clinical pregnancy rate (CPR)

**Adams Stuart; Collins Bonnie; Hernandez Montserrat Amodio; Pundir Jyotsna; Sabatini Luca**  
*St Bartholomews Hospital, London*

**Aim:** To demonstrate the importance of key performance indicators (KPIs) and multidisciplinary team working in IVF setting.

**Content:** Laboratory and clinical KPIs highlighted CPR in 2015 decreased by 4%. The monthly average decreased below the first lower control limit (one standard deviation from the mean) three times in nine months; previously occurring once in three years. No changes in staff, training, gonadotrophins and laboratory materials had occurred.

The clinical protocol for controlled ovarian stimulation had changed in October 2014 aiming at lowering ovarian hyperstimulation syndrome (OHSS); patients' with pre-treatment antral follicle count (AFC) >18 were assigned to antagonist protocol, rather than agonist protocol.

**Result:** 12% of patients' were assigned to antagonist protocol in 2014, compared to 37% in 2015. Antagonist protocol use increased from 15 to 50% in patients <35 years and from 12 to 45% in patients achieving blastocyst transfer.

In patients <35 years, the overall CPR decreased from 41.2% to 33.6% and the blastocyst transfer CPR decreased from 54.1% to 46.5% (P=0.09 and P=0.08 respectively).

The overall CPR for blastocyst transfer fell 4% indicating <35 years were most affected.

The CPR of patients with AFC >18 treated with agonist protocol before October 2014 was compared to that of patients with AFC >18 treated on antagonist protocol after October 2014; The CPR had decreased significantly (46.2% to 35.4%) P=0.014.

Incidence of OHSS was not significantly lower in 2015 (29 cases, 3.2%) compared to the 2014 (35 cases, 3.6%); P=0.4.

The original protocol was reintroduced while clinical methods and staff training were thoroughly analysed.

**Discussion:** The protocol change did not reach the aim expected and, on the contrary affected negatively the CPR.

This abstract aims to demonstrate the importance of KPIs continuous monitoring and multidisciplinary team working.

### 052 Kisspeptin- a safer alternative for triggering oocyte maturation during IVF treatment to reduce the risk of OHSS?

**Islam Rumana<sup>1</sup>; Abbara Ali<sup>2</sup>; Clarke Sophie<sup>2</sup>; Christopoulos Georgios<sup>2</sup>; Comninou Alexander<sup>2</sup>; Salim Rehan<sup>1</sup>; Lavery Stuart<sup>1</sup>; Trew Geoffrey<sup>1</sup>; Dhillo Waljit<sup>2</sup>**  
*<sup>1</sup>Imperial College NHS Trust; <sup>2</sup>Imperial College London*

**Aims and Objectives:** Ovarian hyperstimulation syndrome (OHSS) is a serious iatrogenic condition that is predominantly related to the mode of triggering oocyte maturation during IVF treatment. Kisspeptin is a novel trigger which stimulates

the physiological release of GnRH from the hypothalamus. Kisspeptin has recently been shown to safely trigger oocyte maturation in a population at high risk of OHSS, but has yet to be directly compared with other triggers. Ovarian volume and ascitic fluid are commonly used to categorise the severity of OHSS in diagnostic guidelines. We therefore investigated these parameters in women undergoing IVF treatment with 3 different triggers of oocyte maturation in women at high risk of OHSS.

**Outcomes:** Women at high risk of OHSS (antral follicle count ≥23), aged <35yrs, BMI <30 kg/m<sup>2</sup> with both ovaries intact, were screened sonographically and for symptoms of OHSS at 2-5 days following oocyte retrieval. Patient outcomes were determined when patients were triggered with human chorionic gonadotropin (hCG) (n=8), GnRH agonist (GnRHa) (n=54) or kisspeptin (n=122). Statistical analysis was performed using Kruskal-Wallis test with post-hoc Bonferroni correction.

**Discussion:** Median ovarian volume (MOV) following GnRHa trigger (74.8mls) was significantly lower than in patients triggered with hCG (143.3mls; p <0.05). MOV following kisspeptin trigger (44.0mls) was significantly lower still when compared with GnRHa trigger (p <0.001).

Median ascitic volume was lower after GnRHa (2mls; p<0.01) and kisspeptin (0mls; p<0.001) when compared with hCG (42mls). Symptoms of OHSS were more frequently reported following GnRHa use than kisspeptin and more frequently still following hCG.

**Relevance:** Increased ovarian and ascitic fluid volume consistent with OHSS were less frequent following kisspeptin than GnRHa or hCG in a population undergoing IVF treatment at high risk of OHSS. Kisspeptin may thus present a safer alternative than GnRHa or hCG triggering in patients undergoing IVF at high risk of OHSS.

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### 053 Outpatient management of patients at risk of OHSS: Analysis of 497 cases

**Vigneswaran Kugajeevan; Hoo William; Nussair Bassam; Savvas Michael; Narvekar Nitish**  
*King's College Hospital, London*

**Background:** Ovarian hyperstimulation syndrome (OHSS) is a well-recognized complication of stimulation during IVF treatments, and, can rarely be life threatening. We identify all cases at-risk based on current/previous response to stimulation, and following egg collection, initiate a structured out-patient surveillance program which includes patient education and training, regular staff telephone calls, and, judicious use of clinic review, admission, and abdominal drain.

**Aim:** To assess the outcomes of out-patient surveillance in the management of women at risk of OHSS

**Methodology:** This is a retrospective study of all IVF cycles between March 2010 and May 2015. The primary outcome measures were the incidence of admission and/or drain and the secondary outcome measure were freeze all rate and clinical pregnancy rate (FHR at 6 weeks' gestational scan).

**Results:** There were 2808 fresh IVF cycles performed with a mean age of 34.9 years (Range 20-42). 558/2806 (19.9%) women were identified at-risk of developing OHSS. 61 women were excluded as they were not for planned ET or not local to our catchment area which left 497 women in the final analysis. Patients on average were followed up for 8 (range 1-44) days following egg collection. The incidence of admission was 7.8 % (39/497) and drain 7.4 % (37/497). The average duration of admission and drain were 4.1 and 4.5 days respectively. The freeze all rate was 4.2% (21/497) and, CPR 31.0 % (154/497). There was no difference in outcomes between patients treated with agonist [42.5% (211/497)] versus antagonist [57.5% (286/497)] protocol.

**Relevance/Impact:** We report outcomes of an out-patient surveillance program to manage all at-risk cases of OHSS. Patients can be safely managed on an out-patient basis with recourse to admission and drain for limited periods of time where necessary.

### 054 Abdominal compartment syndrome secondary to ovarian hyper-stimulation syndrome (OHSS)

**Srivastava Garima; Eigener Katrin; Talati Chirag; Borkar Amol; Robert Stefanie; Shah Amit; Gudi Anil; Erskine Katrina**  
*Homerton University Hospital, London*

**Aims:** To make fertility professionals aware of occurrence and management of a very rare complication of IVF.

**Participants and Setting:** A lady presenting with OHSS complicated by abdominal compartment Syndrome

**Case Presentation:** Abdominal compartment syndrome complicated severe OHSS in a 38 year old lady who had IVF cycle in our centre. The patient initially presented with massive ovarian enlargement up to the hepatic border, free fluid in the abdominal cavity and generalised distension. Despite

conservative management and fluid resuscitation, the pain and distension got progressively worse. ITU admission was necessitated because of oliguria, rising creatinine, need for inotropes and fluid management. Heparin was started in ITU for anticoagulation which resulted in an intra-ovarian bleed, haemo-peritoneum and anaemia. A GnRH antagonist was commenced to reduce the ovarian size.

Intraabdominal pressures were excessively raised. Abdominal paracentesis was difficult as abdomen was completely occupied by ovaries. Cul-de centesis and decompression laparotomy were withheld because of tissue fragility, acute renal failure, anaemia, risk of infection and self- limiting nature of OHSS. As the ovarian size reduced in next 48 hours, abdominal paracentesis was possible and 7 litres of fluid were drained.

**Outcome:** There was dramatic improvement after paracentesis demonstrated by a decrease in abdominal pressure, return to normal renal function and discontinuation of inotropes.

**Relevance:** Abdominal compartment syndrome is rarely observed in gynaecological patients. Abdominal compartment syndrome may be a consequence ovarian hyper-stimulation syndrome which clinicians should be aware of.

**Discussion:** There was overlap of OHSS and Acute Compartment Syndrome in the above patient. The ovarian size and ascites led to acute renal failure and reduced cardiac output.

However multidisciplinary management between the Fertility, ITU and the radiology team resulted in a favourable outcome for the patient.

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### 055 Is elective frozen embryo transfer better than fresh in patients with a high egg number? A retrospective analysis of 712 cycles

**Abdo Dima; Jansa Perez Marta; Trew Geoffrey; Lavery Stuart**  
*IVF Hammersmith, London*

**Aims/Objectives:** To evaluate whether frozen embryo transfer (FET) improves clinical pregnancy and implantation rates compared to fresh embryo transfer (ET) in patients where  $\geq 20$  eggs were retrieved.

**Content:** Data was retrospectively analysed from 712 cycles (2010-2015) with  $\geq 20$  eggs where all blastocysts were electively frozen due to high risk of ovarian hyperstimulation syndrome (OHSS) or where patients had a fresh blastocyst transfer, followed by a subsequent FET.



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**Relevance/Impact:** An elective freeze-all policy might improve pregnancy and healthy baby rates and reduce fertility treatment risks such as OHSS. More evidence is needed to assess whether avoiding fresh embryo transfer may lead to higher pregnancy rates.

**Outcomes:** There were no statistically significant differences in clinical pregnancy rate (CPR) and implantation rate (IR) between fresh ET and subsequent FET or FET post freeze-all. When comparing the FET CPR(53.9%) and IR(39.5%) following a failed fresh cycle to FET CPR(37.9%) and IR(32.3%) following a successful fresh cycle there was a stronger trend for a better CPR in the former, although not quite statistically significant( $p=0.0699$ ).

**Discussion:** A freeze all policy might not be necessary for patients not exhibiting symptoms of OHSS. There was no difference in CPR between fresh ET and subsequent FET, although the potential advantage of FET over fresh ET might be masked by the fact that the highest quality embryos in the cohort were transferred in the fresh cycle. The trend for higher CPR in FET following a failed cycle compared to FET following a successful cycle suggests that those patients might be more susceptible to the potential negative effects of the higher hormone levels in the fresh cycle, compared to those who got pregnant, thus having better outcomes in the subsequent FET. More evidence from randomised controlled trials is needed to assess this further.

### 056 A retrospective comparison of fresh PICSI and ICSI treatment cycles between January 2015 and June 2016

**Glover Lynne; Richardson Lucy; Townsend Nicola; McClure Alistair; Bunyan Kelly; Engley Stephanie; Ogutu David; Ah-Moye Michael; Taneja Jyoti**

*Herts and Essex Fertility Centre*

Physiological Intra-Cytoplasmic Sperm Injection (PICSI) was introduced as a new treatment method for patients in March 2014. From the beginning of 2015 there has been a steadily increasing demand from patients requesting PICSI, a modified version of ICSI at the point of sperm selection, which ensures that only mature spermatozoa are selected for injection into mature metaphase II eggs at the time of insemination. This study aimed to look for any difference in the number of patients reporting positive and negative treatment outcomes from fresh ICSI cycles ( $n=421$ ) and PICSI cycles ( $n=120$ ) between January 2015 and June 2016. Patients with a freeze all cycle were excluded from the study, as was a patient who had a mixed ICSI/PICSI cycle due to insufficient sperm to complete the entire procedure using PICSI. The difference between the two groups was statistically significant different using the Chi Squared Test ( $P=0.05\%$ ), with a higher pregnancy rate recorded in the PICSI group. In addition the study aimed to look for any difference in the early outcome of patients who reported a positive pregnancy test by looking at the number of patients with an ongoing pregnancy (FH) vs the number with no ongoing pregnancy (early biochemical loss before scan) for the two groups. The difference between the ICSI and PICSI groups was not statistically significant different using the Chi Squared Test ( $P=0.05\%$ ).

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### 057 The art of follicle tracking

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**Aims:** With the increasing use and success rates of IVF, follicle tracking, with or without ovulation induction (OI) is frequently deemed of low importance within fertility units. However, particularly in anovulatory cases, this can provide effective treatment at a fraction of the cost and intervention. We noted significant variation in the use of follicle tracking at our tertiary fertility unit and sought to investigate this further, to identify factors which may influence success rates and better understand how to optimize this technique.

**Methods:** A retrospective analysis of all patients undergoing follicle tracking, with or without OI between January 2014 and December 2015. Patients undergoing IUI or IVF were excluded.

**Results:** 104 records were available for review. The mean age was 33.5 years and mean BMI 23.2. 96% of cases were done to assess response to OI with clomiphene. In 15% of patients there was no suggestion of anovulation prior to OI. There was wide variation in start date (range 1-14) and number (range 1-10) of scans. Ovitrelle (hCG) trigger was used in 18% of cycles and luteal phase support with progesterone pessaries (Cyclogest) in 12.5%. Pregnancy rate was 15.3% overall. Pregnancy rate in those with anovulatory subfertility was 15% and in those with unexplained subfertility was 33%. Pregnancy rates were higher in cycles receiving Ovitrelle (13.7%) compared to those without (8.9%) but this was not statistically significant ( $p=0.4$ ). Endometrial thickness was significantly higher in conception cycles (10mm vs 8.1mm,  $p<0.05$ ). There was no difference in pregnancy rates in those given progesterone.

**Discussion:** This study has highlighted some of the factors which can influence the success of OI and follicle tracking. Further research is needed to determine optimal timing of scans and to assess whether success rates can be improved with use of an hCG trigger or luteal phase support.

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**058** A comparison of clinical pregnancy and implantation rates obtained with blastocysts cryopreserved on either day 5 or day 6 of development using a closed vitrification system

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**Background:** An effective cryopreservation programme is critical to the success of an IVF laboratory if outcomes are to be maximised for each stimulation cycle, particularly where strategies are required to minimise the incidence of multiple pregnancy. At our centre vitrification is performed using a closed carrier system (Rapid-I) once the blastocyst has fully expanded. Vitrification may therefore take place on day 5 and/or day 6 of development. This study was undertaken to compare the clinical pregnancy (CPR) and implantation rates (IR) with respect to the day of vitrification.

**Method:** All frozen blastocyst cycles where blastocysts had been vitrified using the Rapid-I between 1st Jan 2014-1st Aug 2016 were retrospectively reviewed. Clinical pregnancy was confirmed by the presence of foetal heart by ultrasound. Unpaired t-test and Fishers exact tests were used to assess significance between the two groups.

**Results:** A total of 158 cycles were included. As shown in the table below no significant differences were observed between cycles where blastocysts were vitrified on day 5 compared with those vitrified on day 6.

|                                       | Day 5           | Day 6           | P value |
|---------------------------------------|-----------------|-----------------|---------|
| Number of patients                    | 105             | 53              |         |
| Age (mean)                            | 34.4            | 35.4            | 0.10    |
| No. of blastocysts transferred (mean) | 1.3             | 1.5             | 0.054   |
| Natural/Programmed cycle              | 50/55 (48%/52%) | 31/22 (58%/42%) | 0.24    |
| Survival rate on warming              | 143/149 (96%)   | 83/83 (100%)    | 0.09    |
| Clinical pregnancy rate (CPR)         | 54/105 (51%)    | 27/53 (51%)     | 1.0     |
| Multiple pregnancy rate (MPR)         | 12/54 (22%)     | 7/27 (26%)      | 0.78    |
| Implantation rate (IR)                | 68/140 (49%)    | 34/79 (43%)     | 0.48    |

**Discussion:** A closed vitrification system can be used to successfully vitrify and warm blastocysts on either day 5 or day 6 of development, both obtaining comparable high CPR and IR. A trend towards a lower IR can be seen in the day 6 group which is in line with published evidence but this did not reach significance.

**059** Comparing fresh versus, elective vitrified - warmed embryo transfer outcomes in high responders (Anti- Mullerian Hormone > 25 pmol/l)

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To compare In vitro fertilization (IVF) outcomes between fresh and elective, vitrified- warmed embryo transfer in cases of high responders (AMH > 25pmol/l).

**Content:** A retrospective, observational, cohort study to compare the live birth rates in fresh and elective cohort, vitrification-replacement groups in high responders.

**Participants/materials, setting, methods:** Women between 25-40 years of age with AMH above 25pmol/l. A retrospective, observational, cohort study including 329 women undergoing IVF with or without ICSI were analysed in a government IVF centre in United Kingdom. 167 women who underwent fresh transfer were compared to 162 women undergoing elective cohort freezing and subsequent transfer between June 2014 - January 2016.

**Outcome (s):** The biochemical pregnancy rates and live birth rates were assessed.

**Results:** Baseline characteristics of the 2 groups were comparable. The bio chemical pregnancy rates and the live birth rates of the two groups were compared using chi square test. The biochemical pregnancy rate in the elective cohort vitrification-replacement group was 59.1 % (94/162) as compared to 40.1% (66/169) in the fresh group (Chi square= 11.173, df=1, p value=0.001). ) The live birth rates were 38.5 % (60/162) and 29.0% (47/169) respectively (Pearson Chi-square statistic (X<sup>2</sup>) = 8.74 and the exact p value based on Monte Carlo method for the Pearson's Chi square statistic is 0.025)

**Relevance:** In high responders, elective freezing and subsequent frozen embryo transfer could yield better pregnancy rates.

**Discussion:** The endometrium in stimulated cycles is not always optimal for implantation in high responders and pregnancy rates may increase following elective freezing and subsequent transfer. Also major improvements in the embryo freezing techniques i.e. (vitrification) have now made elective frozen embryo replacement (FERs) a viable alternative to fresh embryo transfer.

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### 060 Successful FET outcome in women following freeze all for high progesterone on the day of egg collection

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Ovarian hyperstimulation increases the number of oocytes collected, but the high steroid levels can have a negative effect on endometrial development and successful implantation. Studies have suggested lower pregnancy rates with high progesterone levels on HCG trigger. We based our study on Serum progesterone level on the day of egg collection based on the study which has suggested significantly lower pregnancy rates of  $\leq 10\%$  per ET if the progesterone level was  $\geq 45$  nmol/L on the day of egg collection (1).

We measured serum progesterone on the day of egg collection and if the levels were  $\geq 45$  nmol/L, we recommended embryo cryopreservation at the blastocyst stage followed by a frozen embryo transfer (FET) into a natural cycle or hormone regulated cycle.

Over a four month period there were 153 egg collections (self-treatment) with 33 women having raised progesterone concentration (21.5%). These women had significantly higher basal AMH concentrations (26.8 Vs 14.5), higher Estradiol levels at the time of hCG administration (13026 Vs 6960) and significantly more eggs were collected (21.5 Vs 9.3). In the freeze all group, the range of blastocyst cryopreserved was between 2–10 with a mean of 3.7 blastocysts. This was significantly higher compared with a mean of 1.1 for those who had a fresh embryo transfer.

In the freeze all group the pregnancy rates were 42% with the first FET rising to 66% after the second FET. During this period a pregnancy rate of 52 % per ET were obtained in women undergoing a fresh embryo transfer, and there were similar pregnancy rates across all levels of progesterone below 45 nmol/L. This study suggests that embryo cryopreservation and subsequent FET increases pregnancy rates in women with higher progesterone levels on the day of egg collection.

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### 061 Should single embryo transfer strategies be applied to frozen cycles too? A retrospective analysis of elective SFET and elective DFET in 1194 cycles

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**Aims/Objectives:** We studied the pregnancy outcomes (clinical pregnancy, live birth, multiple pregnancy and miscarriage rates) in elective single frozen embryo transfer (eSFET) and elective double frozen embryo transfer cycles (eDFET).

**Background:** Optimizing a couple's chance of conception and live birth whilst minimizing pregnancy complications has proven to be challenging. NICE recommends eSET for all women <37 years old for their first fresh IVF cycle. However, the evidence is less clear cut on FET cycles. We performed a retrospective analysis of FET cycles between January 2012 and April 2016. The patient demographics and pregnancy outcomes (clinical pregnancy, live birth, multiple pregnancy and miscarriage rates) were compared in eSFET and eDFET groups.

**Results:** 1019 patients underwent 1194 FET cycles (270 eSFET, 248 SET, 676 DFET). 155 women underwent more than one cycle. There was no significant difference in age at the start of treatment or the number of FET attempts in eSFET and DFET groups. DFET had a significantly higher implantation (48.4 vs.40.4%,  $p=0.03$ ), clinical pregnancy (44.2 vs.34.8%,  $p=0.009$ ) and live birth rate (24.6 vs. 17.8%,  $p=0.03$ ) than eSFET group. sDFET group had a significantly higher twin clinical pregnancy (15.8 vs. 0.7%,  $p<0.0001$ ) and live birth rate (6.2 vs. 0%) than eSFET group. There were no significant differences in miscarriage rates between the eSFET and eDFET groups (8.1 vs. 10.7%,  $p>0.05$ ).

**Conclusions:** We have demonstrated significantly higher pregnancy and live birth rates in eDFET compared to eSFET with a relatively modest multiple live birth rates (6.2%) in DFET cycles. This suggests that a modified approach to eSET should be discussed in the management of couples undergoing frozen embryo transfer cycles.

### 062 Time for a re-sync. The importance of embryo / endometrial synchrony in GnRH antagonist cycles

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Implantation is dependent on both embryo viability and endometrial receptivity. The implantation window is controlled by a myriad of genes whose expression is affected by supraphysiologic estradiol and progesterone levels resulting



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from controlled ovarian stimulation (COS). Both GnRH agonist and antagonist regimens differentially alter endometrial gene expression profiles, albeit to a lesser extent in the latter, compared to natural cycles. The consequent advancement of the implantation window may compromise implantation due to embryo / uterine asynchrony. This may be exacerbated by delayed embryo development where blastocyst formation occurs on day 6 of in-vitro culture.

The aims of this study were to determine the impact of COS using a GnRH antagonist regimen, on fresh embryo transfer (ET) outcome and to explore the potential benefit of elective cryopreservation of developmentally delayed embryos, on day 6, followed by subsequent frozen embryo transfer (FET).

Biochemical / clinical pregnancy and implantation rate data for fresh antagonist and subsequent FET cycles were collected retrospectively from January 2014 to July 2016 and controlled for female patient age. Data was categorised into one of four ET groups; A) fresh day 5 (expanded blastocysts), B) FET day 5 (expanded blastocysts), C) FET day 6 (expanded blastocysts), D) fresh day 5 (early unexpanded blastocysts).

Pregnancy and implantation rates were consistently lower in group A compared to group B suggesting COS had a negative impact on fresh cycle outcome. Pregnancy and implantation rates were significantly higher in group C compared to Group D suggesting extended culture of developmentally delayed embryos to day 6 followed by FET may improve embryo / uterine synchrony.

These results indicate the possible advancement of the implantation window due to COS using an antagonist regimen. Day 6 elective cryopreservation of normal but developmentally delayed embryos may improve pregnancy and implantation rates by correcting embryo / uterine synchrony.

### 063 Endometrial thickness does not correlate with clinical pregnancy outcomes in frozen embryo transfer cycles

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<sup>1</sup>Imperial NHS Trust; <sup>2</sup>IVF Hammersmith; <sup>3</sup>Imperial College London

**Objectives:** Successful implantation relies on a complex interplay between the embryo and endometrium during the 'implantation window'. In this study we examined the role of endometrial thickness on pregnancy outcomes in frozen embryo transfer (FET) cycles.

**Background:** A retrospective analysis of pregnancy outcomes (implantation, clinical pregnancy, live birth, multiple pregnancy and miscarriage rates) in medicated FET cycles between January 2012- April 2016 was performed.

In HRT medicated cycles, patients underwent a GnRH agonist suppression regimen for approximately two weeks. Upon confirming pituitary suppression (thin endometrium less than 5 mm and no large cysts on the ovaries), HRT patches were commenced. The Estrogen patches were applied on alternate days for the initial 7 days, then daily for the next 7 days. Endometrial thickness (ET) was measured by ultrasound on day 11 or 12. Progesterone was started when ET measured  $\geq$  8mm.

**Outcomes:** There were 978 HRT medicated cycles analysed; 475 cycles had an ET of 7-10 mm, 391 had an ET of 10-

13 mm, 88 had an ET of 13-15 mm and 24 had an ET of more than 15mm. The mean age was  $34.3 \pm 4.40$  years. The average number of FET attempts was  $2.48 \pm 1.1$ . The mean endometrial thickness was  $10.4 \pm 2.01$ mm.

The clinical pregnancy, live birth and miscarriage rates in all groups were not significantly different. Twin clinical pregnancy and live birth rates did not significantly differ across the groups.

**Discussion:** We have demonstrated that endometrial thickness has no independent significance in relation to pregnancy or live birth rates in frozen embryo transfer cycles. Future work should focus on the development of novel markers of endometrial receptivity to identify the optimum time for embryo transfer to maximize pregnancy rates.

### 064 Metformin for endometrial hyperplasia: A cochrane systematic review

**Clement Naomi<sup>1</sup>; Oliver Thomas<sup>2</sup>; Shiwani Hunain<sup>3</sup>; Sanner Juliane<sup>4</sup>; Mulvaney Caroline<sup>1</sup>; Atiomo William<sup>1</sup>**

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**Aims/ Objectives:** Endometrial hyperplasia is a precancerous lesion of the endometrium, commonly presenting with uterine bleeding. If managed expectantly it frequently progresses to endometrial carcinoma, rates of which are increasing dramatically worldwide. However, the established treatment for endometrial hyperplasia (progestogens) involves multiple side effects and leaves the risk of recurrence. Metformin is the most commonly used oral hypoglycaemic agent in type 2 diabetes mellitus. It has also been linked to the reversal of endometrial hyperplasia and may, therefore contribute to decreasing the prevalence of endometrial carcinoma without the fertility and side effect consequences of current therapies. However, the efficacy and safety of metformin being used for this therapeutic target is unclear and, therefore, this systematic review will aim to determine this.

**Content:** We searched the following trials and databases with no language restrictions for randomised controlled trials of use of metformin compared with a placebo or no treatment, conventional medical treatment (eg progestogens) or any other active intervention: CENTRAL; MEDLINE; EMBASE; EBSCO Cumulative Index to Nursing and Allied Health Literature; PubMed; Google Scholar; ClinicalTrials.gov; the WHO International Trials Registry Platform portal; OpenGrey and the Latin American Caribbean Health Sciences Literature (LILACS). Initially 127 abstracts were screened with nine being included for full text analysis before a final two studies were included in the final review with the primary outcome being regression of endometrial hyperplasia histology towards normal histology.

**Relevance/Impact:** Through the application of this protocol, an up-to-date systematic review of the existing evidence of the role of metformin in treating women with endometrial hyperplasia will be provided.

**Outcomes:** Preliminary data highlights the lack of large scale, low bias trials analysing the true effect of treating women with endometrial hyperplasia with metformin. We hope to have more data to present in the coming months.



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### 065 Effects of hyaluronan-rich culture media on human embryo attachment and gene expression

**Buck Chelsea<sup>1</sup>; Ruane Peter<sup>2</sup>; Smith Helen<sup>2</sup>; Brison Daniel<sup>3</sup>**

<sup>1</sup>Old St. Mary's Hospital, Manchester; <sup>2</sup>University of Manchester; <sup>3</sup>University of Manchester, Old St. Mary's Hospital, Manchester

**Introduction:** Hyaluronan (HA) is a glycosamine which is up-regulated in the uterus around the time of embryo implantation and is thought to promote embryo-endometrium attachment. Embryo transfer media containing high concentrations of HA have been used to increase pregnancy rates in some IVF units, although the mechanism behind this is unknown. This study aimed to investigate the effect of such media on human embryo gene expression and endometrial attachment in and in vitro model.

**Methods:** Day 6 blastocysts (n=45) were chemically hatched using acid Tyrode's solution, treated with EmbryoGlue or control media for 10 minutes, then co-cultured with an Ishikawa cell monolayer for 48 hours. Attachment was assessed after 1, 2, 4, 6, 24 and 48 hours through gentle agitation of the plate. Gene expression analysis was performed on a separate cohort of blastocysts (n=6), randomly allocated to treatment or control groups on day 3. Blastocyst DNA was amplified using PolyA-PCR, before direct detection of B-Actin, Nanog, NFkB1, MYD88, CD44, MMP2 and MMP9 expression using qPCR.

**Results:** MMP9 and MYD88 gene expression was significantly higher in treated embryos than in controls (p=0.008 and p=0.049 respectively). No significant differences were seen for any other genes tested. Treatment with EmbryoGlue did not significantly affect embryo attachment in the fresh or frozen cohorts. However, a larger proportion of treated embryos were attached by 24 hours (91.3% vs. 76.1%), with fewer embryos exhibiting reversible attachment (8.33% vs. 23.8%).

**Discussion:** Due to the high levels of embryo attachment seen with this in vitro model, it may be too receptive to investigate the impact of EmbryoGlue on attachment. However, EmbryoGlue may increase pregnancy rates by up-regulating genes important for embryo implantation, downstream of its binding receptors, CD44 and TLR4. Implantation remains a rate-limiting step to successful IVF and so greater understanding of the process may improve clinical outcomes.

### 066 Conversion to continuous single culture medium; 2 years of practice (2014-2016)

**Hall Charlotte; Chui David KC**

BMI The Esperance, Eastbourne

**Aims:** In June 2014, a change was made from our existing sequential culture media system (SAGE) to continuous single culture medium (CSCM; Irvine Scientific) with the aim of improved culture performance by reducing embryo disturbance, streamlining product use in the laboratory and assessment of timesaving benefits through less dish preparation, manipulation and witnessing.

**Methods:** Full conversion to the CSCM culture system for IVF/ICSI patients enabled the purchase of only one culture medium for preparation of sperm, egg collection (post-aspiration), fertilisation, ICSI, culture to blastocyst and embryo

transfer (ET); HEPES-based medium was only used for oocyte aspiration. On day 0 (ICSI) or 1 (IVF), oocytes were transferred to 20µl droplets of CSCM medium under oil and remained there until day of ET or vitrification. Embryos were checked but not moved on day 3 (unless ET that day). Performance was measured by blastulation rate (BR %), freeze rate (%), clinical pregnancy rate (CPR %) and implantation rate (IR %).

**Results:** Transfer to CSCM reduced the need to buy multiple types of media which streamlined the operational management of the culture system and minimized the amount of wastage. Consumable requirements were also reduced by removal of the day 3 dish change which also negated the need for a witness at this stage.

Over the 2 year period (June 2014-June 2016), 514 patients' (<40 years) embryos were cultured in CSCM, achieving a 64.4% BR, 34.9% FR, 41.2 % CPR and 35.9 % IR, compared to a 48.4% BR, 22.6% FR, 40.2 % CPR and 34.2% IR for sequential media (<40 years, Jan-June 2014; 97 patients).

**Conclusion:** Culture of embryos in CSCM proved to be a more time useful, cost-effective method to achieve comparable clinical pregnancy and implantation rates to sequential media. Furthermore, culture in this undisturbed environment showed improved rates of blastulation and freezing.

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### 067 Pregnancy and live birth using a combination of 'The Liverpool Solution' and a PDE inhibitor for complete asthenozoospermia: A case report

**Drew Ellen**

ACU Ninewells, Dundee

**Objective:** To report the outcome of a treatment cycle using a combination of 'the Liverpool solution' and commercially available theophyllin, in a case of full retrograde ejaculation with complete asthenozoospermia.

**History:** A couple presented for their first cycle of Assisted Conception, with primary infertility of 1 years duration.

The female partner was aged 29 years old and had no history of note. The male partner was aged 36 years old, and has Type 1 Diabetes Mellitus. He was also diagnosed as having full retrograde ejaculation. He had previously produced a very small ejaculate and complete asthenozoospermia; vitality testing on that occasion showed approximately 3% viable.

**Intervention:** The couple was treated using Intracytoplasmic sperm injection (ICSI). The male partner was treated using 'The Liverpool Solution' 1 to alkalise his urine and hopefully improve the conditions for the sperm. Sperm were still found to be non-motile at the time of ICSI, and were treated with SpermMobilTM, a commercially available, ready to use theophylline preparation.

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**Impact:** We believe this to be the first report of these two treatments being used in combination.

**Outcome:** Sperm motility was achieved in less than 1% of the sperm. Successful fertilisation, embryo transfer, clinical pregnancy and live birth were achieved.

**Discussion:** Pentoxifylline and other caffeine derivatives have long been known to stimulate sperm motility<sup>2</sup>. They are phosphodiesterase, or PDE inhibitors; theophylline is also a member of this group of drugs and is available in a ready to use preparation. At present, there are few reports of theophylline being used in a clinical setting.

We believe this is the first report of a pregnancy with the combination of these two treatments.

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**068** Heterotopic cervical pregnancy; cervical cerclage following aspiration and foley catheter insertion. A novel method for effective management leading term pregnancy. Case report and review literature

**Tsakos Elias; Tsagias Nikos; Gibbon David**

*EmbryoClinic, Assisted Reproduction Unit, Thessaloniki, Greece*

**Objective:** Effective management of a heterotopic cervical pregnancy leading to full term delivery. This is a case report regarding early diagnosis and management of a cervical heterotopic pregnancy.

**Content:** A 41 year old gravida 2 para 0 with premature ovarian failure following successful in vitro fertilization treatment with donor oocytes.

A transvaginal ultrasound scan revealed the presence of a heterotopic pregnancy; one intrauterine and one in the cervical canal. Both fetuses presented with positive heart beats. Aspiration of the cervical ectopic pregnancy was followed by Foley catheter placement and cervical cerclage suturing.

**Relevance/Impact:** Management of a heterotopic cervical pregnancy

**Outcome:** Successful term delivery

**Discussion:** Elective uncomplicated Caesarean delivery at 38 weeks following an uneventful pregnancy. A case of timely diagnosis and successful treatment of a cervical heterotopic pregnancy is presented. A conservative method of aspiration followed by Foley catheter placement and cervical cerclage is described. Since no guidelines exist for the management of heterotopic cervical pregnancy this could be an effective method for the management of heterotopic cervical pregnancy. The value of early diagnosis and management is concluded from the literature, in support of our management principles.

**069** Why are fresh treatment MicroTESEs cancelled?

**Massiah Nadine; Stewart Jane; Choudhary Meena; McEleny Kevin**

*Newcastle Fertility Centre*

**Objectives:** To determine the reasons for fresh treatment Micro-TESE cancellations in our unit

**Content:** A retrospective audit of Micro-TESE cases (January 2010-June 2016) that were cancelled after date for treatment was confirmed.

**Relevance/Impact:** Micro-TESE is the gold standard method of retrieving sperm from men with non-obstructive azoospermia. Successfully cryopreserving recovered testicular sperm can be challenging. In fresh treatments, the ICSI treatment cycle is timed to coincide with the (electively scheduled) Micro-TESE. Treatment cancellation has resource and psycho-social implications.

**Outcomes:** 24/156 Micro-TESEs were cancelled (15.3%) due to:

- Delayed ovarian response preventing synchronised treatment (n=8); 6 cancelled, 2 proceeded with oocyte cryopreservation. 5 of the 8 were on a low dose protocol for OHSS risk, 4 of which were cancelled. Of the group who underwent a 2nd cycle, the Menopur dose was increased and all the women got to the oocyte retrieval alongside microTESE.
- Prolonged downregulation (n=5). Group outcomes were: Treatment cycle continued and oocytes cryopreserved (2). Micro-TESE rescheduled for later in the same cycle (1). Cycle cancelled and a future cycle planned with a longer course of downregulation (2).
- Patient request (n=5) (bereavement, marriage & work commitments)
- Failed (n=3) and rapid (n=1) ovarian response. All failed responders had an AMH <4 pmol/l.
- Abnormal cervical smear (n=1)
- Administrative error (n=1)

Sperm was successfully recovered in 14/18 rescheduled MicroTESEs. 13 patients underwent embryo transfer, 3 patients had a clinical pregnancy, 1 miscarried and 2 had singleton live births

**Discussion:** To improve service efficiency, cost and the psycho-social burden to patients, the cancellation rate should be minimised. Prolonged downregulation and delayed/rapid ovarian response could be anticipated by use of a "trial" stimulation cycle with oocyte cryopreservation, followed by a fresh treatment cycle and MicroTESE or further cryopreservation cycles and later microTESE. Regular communications may reduce patient cancellations.



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### 070 Effectiveness of tamoxifen with low-dose gonadotrophin until human chorionic gonadotrophin trigger for poor responders: A pilot study

**Datta Adrija; Deval Bhanu; Campbell Stuart; Nargund Geeta**

*Create Fertility, London*

**Aims/Objectives:** To determine the outcome of a mild-stimulation protocol comprising tamoxifen plus low-dose gonadotropin administration till ovulation trigger and subsequent fresh and frozen embryo transfer (ET) in women with poor ovarian response (POR).

**Content:** Retrospective analysis of 54 consecutive IVF/ICSI cycles with tamoxifen (40 mg daily) +/-low-dose (150 iu alternate day or daily) gonadotropin till trigger day in women with POR, as defined by Bologna consensus. All patients with fresh and subsequent frozen-thawed ET during 1-year study-period (March-2015 to February-2016) were included to determine cumulative and per ET ongoing pregnancy rates (OPRs). Women's mean age ( $\pm$ SD) was  $40.3 \pm 3.6$  years, mean AMH  $3.8 \pm 4.8$  pmol/l and mean AFC  $6.0 \pm 4.0$  (2-6 mm). Mean total dose of gonadotropin was 844.5 iu and endometrial thickness at trigger  $8.8 \pm 2.3$  mm. Mean number of oocytes and embryos were  $2.5 \pm 1.5$  and  $1.8 \pm 0.6$  respectively, fertilisation rate 64.3%. Grade-1 embryos were obtained in 89.2% cycles. Cycle cancellation rate 5.5%, with no incidence of ovulation. GnRH-antagonist was not required to prevent premature LH rise in 94.5% cycles. OPR per fresh ET was 12.5%. A cumulative OPR of 18.9% was achieved over 1 year, with embryos still cryopreserved from 5 cycles. Two livebirths already reported with others awaiting.

**Relevance/Impact:** This pilot study is the first to show the potential of a mild-stimulation IVF protocol with tamoxifen and low-dose gonadotropin till trigger day in poor prognosis women.

**Outcomes:** The study protocol has resulted in satisfactory outcome among women with POR. The use of anti-estrogen (tamoxifen) until the day of trigger prevented premature ovulation and circumvented the need for GnRH-antagonist.

**Discussion:** Future large prospective controlled trials in patients with POR may confirm tamoxifen+ low-dose gonadotropin without the need for GnRH-antagonist to be a cost-effective strategy compared to high-dose gonadotropin stimulated cycles.

### 071 Percentage drop in serum oestradiol level during coasting is predictive of IVF outcome

**Ugwumadu Lilian; Charalambous Elena; Pulsford Nick; Kalu Emmanuel**

*Kingston Hospital NHS Trust, Surrey*

**Introduction:** OHSS remains a severe complication of IVF. Coasting is a strategy to minimise severe OHSS.

**Aim:** To assess the effect of percentage drop in E2 level and duration of coasting on IVF outcomes.

**Methods:** Data collected prospectively on all IVF cycles where coasting occurred for >2days. The decision to coast was based on E2 levels and HCG trigger was administered when

serum E2 level was <15000pmol/l. Data was analysed based on numbers of days of coasting and percentage drop in E2. Primary outcome was Live birth rate(LBR).

**Results:** 97 coasted cycles between February 2000 and March 2016 were analysed. The mean age of patients, E2 at coasting, peak E2 and E2 at HCG were  $34.82 \pm 3.79$ ,  $18722 \pm 6406$  pmol/l,  $26071 \pm 7582$  pmol/l and  $13299 \pm 4750$  pmol/l respectively. Coasting ranged between 2-11 days(mean  $3.64 \pm 1.68$ ). The mean number of oocytes retrieved, fertilized embryos, overall fertilization, implantation and LBR were  $10.62 \pm 5.53$ ,  $6.80 \pm 4.47$ , 94%, 56% and 44% respectively. Coasting days divided into three groups: group I (n= 4) -coasting<3 days only, group II(n=37) coasting  $\geq 4-6$  days and group III (n=6)  $\geq 7$  days. LBR in group I, II and III were 51.85%, 37.82% and 16.67%(P = 0.04) respectively. Mean no of oocytes retrieved were  $11.81 \pm 5.22$ ,  $9.86 \pm 5.56$  and  $4.50 \pm 2.22$  (P=0.005), fertilisation and miscarriage rate 96.30%, 97.30% and 33.33% (P=0.043) and 9.26%, 21.62% and 16.67%(P=0.39) respectively. Data was further analysed to determine the effect of percentage change in E2. Group A(1-50%), Group B(51-60%), Group C(>61%). LBR were 66.67%, 53.33% and 35.48% respectively(P=0.02). Mean no of oocytes retrieved were  $11.84 \pm 4.48$ ,  $9.53 \pm 5.36$  and  $9.13 \pm 6.09$  (P=0.07), fertilisation and miscarriage rate 94.12%, 93.33% and 96.77%(P=0.08) and 11.76%, 13.33% and 22.58%(P=0.41) respectively.

**Conclusion:** Women who underwent coasting had a reasonable overall LBR of 44%. However this is significantly compromised when coasting is prolonged (over 7days) and even more so when the percentage of E2 drops by 60% and over. This information will be useful for managing patients' expectation.

### 072 Laparoscopy and hydrotubation in assessing tubal patency: Are we following the NICE guidelines?

**Ragi Sreedevi; Acharya Santanu**

*Ayrshire Fertility Unit, Scotland*

**Objectives:** Tubal factors account for 14% of the causes of subfertility in women. Tubal disease includes tubal obstruction and pelvic adhesions due to infection, endometriosis and previous surgery. The results of semen analysis and assessment of ovulation should be known before a test for tubal patency is performed. Either pre-procedure infection screen or antibiotics prophylaxis should be administered (NICE guidelines 2013). The aim was to audit our practice of Laparoscopy and hydrotubation in assessing tubal patency against NICE guidelines.

**Methodology:** Retrospective case note review of the 70 Laparoscopy and hydrotubation (2011-4).

**Results:** The mean age was 31 years (19-42 years) and mean BMI of 31 (18-39). 37 had primary and 33 secondary infertility. Indications for laparoscopy were past history of pelvic inflammatory disease (n=28), suspicion of endometriosis (n=23), history of previous ectopic (n=6) and failed or equivocal hysterosalpingogram (n=13). 91% (n=64) were screened for Chlamydia infection but all received prophylactic antibiotics (100%). 67 women were immune to rubella and 3 non-immune. Semen analysis [results normal (n=65) and suboptimal (n=5), WHO criteria] was carried out in 100% cases. Cervical screening was negative (n=65), abnormal (n=2) and not indicated (n=3). Ovulatory status when indicated, were performed in 100%.



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Laparoscopy and hydrotubation confirmed patency of fallopian tubes, bilateral (n=40) and unilateral (n=19) and bilateral blockage (n=5). In women who had previous unilateral salpingectomy (n=6), the remaining tube was patent (n=4) and blocked (n=2). Surgical ablation of endometriosis (n=10), ovarian cystectomy (n=3) and adhesiolysis (n=1) were performed.

**Conclusion:** Compliance with NICE guidelines on assessing tubal patency in terms of indications for surgery, pre-procedural screening for chlamydia immunity / use of antibiotic prophylaxis and semen analysis were satisfactory.

### 073 What is a good egg number in assisted reproduction

**Ghuman Navdeep Kaur**  
*NHS Tayside*

**Study question:** Does number of oocyte retrieved has an impact on live birth outcome in assisted conception (IVF/ICSI)?

**Summary answer:** Live birth occurrence was found to be associated with number of oocytes retrieved and live birth rate was highest when 10-20 oocytes were retrieved both in IVF and ICSI treatment.

**Participants/duration/methods:** The first fresh IVF and ICSI treatment cycles (96,721 IVF and 58,797 ICSI treatment cycles) from the UK's regulator, HFEA's long term anonymised data registry from 1991 to 2012 were analysed by the binary logistic modelling technique for association between oocyte number as categorical variable and live birth occurrence. The statistical package SPSS (version 23) was used for analysis and results were considered to be statistically significant if the p value was <0.05).

**Results and observations:** Taking >20 oocytes as the reference category, live birth rate was statistically significantly lower when oocyte number retrieved was 1-5 (OR 0.70, CI 0.66-0.75, p value 0.000 for IVF and OR 0.66, CI 0.61-0.71, p value 0.000 for ICSI treatment) and was significantly higher when oocytes retrieved were between 10-20 (OR 1.1, CI 1.03-1.8, p value 0.007 for 10-15 oocyte category in ICSI and OR 1.12 CI 1.06-1.20, p value 0.000 for IVF treatment).

**Limitations, Reasons For Caution:** Although the study was adjusted for female age, number of previous treatment cycles and use of donor gametes and surrogacy, compounding factors like BMI and smoking were not adjusted for as there was no information in HFEA data on these parameters. **WIDER IMPLICATIONS OF THE FINDINGS:** Better live birth rates are associated with oocyte number between 10-15 and hence milder stimulation regimes are optimum.

### 074 Increasing the stimulation dose in poor responding women is effective only in women with normal or high AMH concentrations

**Banks Claire; Gaudoin Marco; Ambrose Pat; Mitchell Paul; Fleming Richard**  
*GCRM, Glasgow*

**Aims/objectives:** AMH is the biomarker of choice to individualise protocols in women undergoing IVF. Following a poor response, we commonly increase the FSH starting dose but there is little evidence of benefit.

This study aimed to examine the effect of a dose increase in women with a poor ovarian response in their first treatment cycle (K1) who underwent a second treatment cycle (K2) within the next year, with the emphasis upon impact of egg yield.

**Content:** The single centre database covered ART cycles between November 2006 to March 2016, all women <43y. In K1, the FSH starting dose and down-regulation were determined by ovarian reserve (AMH) and body weight (additional 75IU when > 80Kg). In women with a poor egg yield in K1 (0 to 4 eggs), the FSH starting dose was often increased for K2, usually by 75IU/day. Diminished ovarian reserve (DOR) was defined as AMH<7 pmol/L.

**Outcomes:** 856 cases underwent a second stimulation (K2), of which 259 (30%) had a poor response in K1; of these, 132 (51%) were predicted by AMH. 13% of women with a predicted normal/high ovarian response retrieved 4 or fewer eggs. The FSH starting dose was increased for K2 in 77 cases.

In women with DOR, increasing the FSH starting dose did not influence subsequent egg yields (mean egg yield: 2.4 vs 3.1, P=NS). However, in the normal/high response group, an increase in the FSH starting dose resulted in higher egg yields (mean egg yield: 2.8 vs 5.5, P<0.001).

**Discussion:** Increasing the FSH starting dose only benefits women with a predicted 'healthy' ovarian reserve who had a poor response in their first treatment cycle. The challenge is to identify these women before their first treatment.

### 075 AMH-based individualised ovarian stimulation improves live birth in a typical IVF programme

**Papathanasiou Athanasios; Lynch Stephen; Ebanks Sherry; Allerton Claire; Mauro Valentina**  
*Bourn Hall Clinic, Cambridge*

**Aim:** The aim of this study was to evaluate the benefit of AMH-based individualisation on performance within a typical IVF programme.

**Materials and Methods:** Data from nulliparous couples undergoing their first IVF cycle from October 2012 to December 2014 were prospectively collected. During the study period, a single blood test for AMH levels was gradually introduced before the first treatment. The choice of stimulation (rFSH dose, protocol) was determined by the physician, taking into account female characteristics and, if available, AMH levels. Comparisons were undertaken between AMH and non-AMH groups, using regression analysis that adjusted for confounders (age, BMI, cause of infertility, year of treatment).

**Results:** Compared to the non-AMH group, the AMH group experienced higher live birth rates per cycle (36% vs 30%, OR 1.332 95%CI 1.057-1.678, 1698 patients).

Fewer women in the AMH group experienced suboptimal stimulation ( $\leq 3$  oocytes)(8% vs 14%, OR 0.480 95%CI 0.338-0.681). The same women were more likely to have high-quality embryos available for cryopreservation (53% vs 41% OR 1.648 95%CI 1.320-2.058).

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No differences were detected in the incidence of ovarian hyper-response ( $\geq 15$  oocytes) or cycle cancellation due to OHSS risk. The incidence of OHSS requiring admission was comparable (0.9% in the AMH group, 1.8% in the non-AMH group).

Lower rFSH doses were used when AMH levels were available ( $<150$ iu daily in 50% AMH vs 30% non-AMH, OR 1.759 95%CI 1.379-2.243 and  $>225$ iu daily in 2% AMH vs 9% non-AMH, OR 0.243 95%CI 0.136-0.435). Interestingly, the antagonist protocol was less popular within the AMH group (5% vs 12%, OR 0.342 95%CI 0.229-0.512).

**Conclusion:** AMH-individualised ovarian stimulation can improve success of the IVF programme, which could be mediated via more appropriate rFSH dosing. Considering that couples welcome individualisation during IVF and there is also potential for reducing cost, individualised ovarian stimulation warrants further study and application.

### 076 Is AMH, independent of age, a prognostic factor for live-birth?

**Goswami Mohar; Nikolaou Dimitrios**

*Assisted Conception Unit, Chelsea and Westminster Hospital*

Our aim is to establish if there is any association of AMH with live-birth (LB) considering the effects of age and other relevant confounding factors in predicting LB. There is good evidence of the positive correlation of AMH with egg reserve and oocyte yield following ovarian stimulation. However, the associations of AMH and clinical pregnancy or LB are not clear. 200 IVF cycles were retrospectively analysed and women's age, AMH, IVF/ICSI, infertility factors, protocols and outcomes were compared between the groups with and without LB in the age groups -group 1: 23-29, group 2: 30-34, group 3: 35-39 and group 4: 40-45 years; median AMH and live birth rates (LBRs) across the groups were compared by Kruskal Wallis and Chi Squared tests respectively. Multinomial logistic regression analysis was performed to evaluate the influence of age and AMH in predicting LB. There were no significant differences in any of the confounding factors analysed between the groups with and without LB. In age groups 1 and 2, there was no significant difference in the median AMH between the groups with or without LB; but in age group 3, the median AMH was significantly higher in the group with LB ( $p=0.01$ ). In age group 4, the LB group had a higher median AMH although not statistically significant. The odds of having a LB was significantly higher in the younger 3 age groups, and when AMH was  $>20$ pmol/l. AMH was not found to be the IVF outcome defining factor in younger women, but was relevant in above 35 years. Older women with significantly higher AMH had significantly higher LBR than their peers with low AMH. Thus AMH would have a role whilst counselling women regarding their likelihood of having a LB from IVF, but women's age would have a major determining role to play.

### 077 Is anti-Müllerian hormone a useful marker of ovarian reserve in young girls and women following childhood cancer treatment?

**Gelson Emily; Prakash Alka; MacDougall Jane**

*Department of Reproductive Medicine and Surgery, Addenbrookes Hospital, Cambridge*

**Aims/Objectives:** To determine if the measurement of anti-Müllerian hormone (AMH) in females who have been treated for cancer during childhood has a role in predicting ovarian reserve.

**Content:** A review of the literature regarding AMH as a marker of ovarian reserve in female survivors of childhood cancer.

**Relevance/Impact:** Over the past four decades childhood cancer diagnosis has increased throughout Europe. In addition, advances in medicine and surgery have dramatically improved survival, with 80 per cent long-term survival now expected. It has been estimated that there are currently more than 33,000 survivors of childhood cancer in the UK. Treatment for childhood cancer may result in subfertility and premature ovarian insufficiency. Those at risk should ideally be identified in an effort to improve fertility by providing the option of fertility preservation or timely pregnancy planning. The SIGN guideline recommends that the risk of treatment to fertility be assessed pre-treatment using several factors including the nature of the predicted treatment and assessment of ovarian reserve in girls/young women. Although a risk estimate of the likelihood of subfertility in female childhood cancer survivors can be made based on the treatment modalities used, individual investigations are likely to be more accurate. The role for AMH in the assessment of ovarian reserve in young patients with cancer remains a subject of on-going research.

**Outcomes:** Ten studies were identified. These included 567 girls treated for cancer before the age of 18 years. A significantly reduced AMH level was seen and was lowest in those treated with abdomino-pelvic radiotherapy and/or alkylating agents.

**Conclusion:** AMH appears to be an early and sensitive test of ovarian reserve in this setting.

### 078 Predictive value of age and ovarian reserve markers on the outcome of fertility preservation treatment for cancer patients

**Ghaffar Ammara; Erritty Matthew; Ilangoan Krithiga; Ding Christina**

*Epsom and St Helier Hospital NHS Trust*

**Objectives:** Cohort study assessing the impact of age and other ovarian reserve markers on the outcome of female fertility preservation treatment.

**Content:** We present the outcome of a 5 year cohort study of 70 female cancer patients undergoing fertility preservation treatment within a NHS unit. The study examines the correlation between ovarian reserve predictors (including age, AMH, FSH) and outcomes of fertility preservation treatment (oocyte/embryo number, fertilisation rate).

**Relevance:** The success of fertility preservation treatments prior to chemotherapy is typically measured by surrogate markers including oocyte / embryo yield and fertilisation rates [1,2,3] instead of pregnancy as the "Gold standard" outcome.

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The ability to predict the outcome of treatment using simple predictors and biomarkers including Age, AMH and FSH is critical to counselling. Quantitative information may improve the counselling quality and informed decision making, which can be challenging for cancer sufferers.

**Outcome:** 70 patients underwent fertility preservation treatment between February 2011 - August 2016. The mean age and AMH levels of patients undergoing treatment are 34 +/-14 years old(20-45) and 15.8(<1-65). The average number of oocytes produced following a fertility preservation cycle is 11.3 +/- 5.3(6-14.75). The mean fertilisation rate and embryo number produced are 79% +/- 6%; 7 +/- 6 (1-13). ovarian reserve predictors.

AMH level and Age positively correlates with oocyte yield but not embryo yield or fertilisation rate.

**Discussion:** Ovarian reserve predictors including Age and AMH correlate with the number of oocytes produced following fertility preservation, and can be used with reasonable confidence in predicting treatment outcomes. However, no significant correlation was found between Age /AMH or FSH and Fertilisation Rate or Embryo yields.

Further research is needed in designing a quantifiable prediction model, aiming to improve the quality of pre-treatment counselling.

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### 079 Ex-vivo oocyte retrieval and transport IVF with culture in a Time-Lapse incubator

**Carby Anna<sup>1</sup>; Abramov Benjamin<sup>1</sup>; Hickman Cristina<sup>1</sup>; Oliana Oriol<sup>1</sup>; Butler John<sup>2</sup>; Lavery Stuart<sup>1</sup>**

<sup>1</sup>Boston Place Clinic; <sup>2</sup>Royal Marsden Hospital, London

**Aim:** A strategy for fertility preservation with ovarian mesothelioma rendering ex-vivo oocyte retrieval a safe option for fertility preservation.

**Content:** A 25-year old underwent ovarian stimulation using a luteal phase random start antagonist protocol. GnRH antagonist commenced 4 days prior to and during FSH stimulation (Gonal-F™) 225iu. Follicular response was monitored until 3 follicles reached >17mm. To minimize the risk of hyperstimulation GnRH trigger (Suprecur™ 2mg) was given on day 12 of FSH stimulation. Transvaginal scans revealed prominent pelvic and ovarian vascularity deeming routine oocyte retrieval unsafe. Egg collection was performed at laparotomy after bilateral oophorectomy. Left ovarian follicles were aspirated in the operating theatre immediately after harvesting due to evidence of ovulation from this ovary. The right ovary was transported to the laboratory in normal saline at a temp of 37°C for oocyte retrieval. Follicular aspirates were inspected under a microscope for presence of eggs. Half the oocytes were cryopreserved and the other half were cultured to day 5 in the Embryoscope™ for blastocyst cryopreservation.

**Relevance:** Transvaginal ultrasound guided oocyte retrieval in the presence of ovarian malignancy may carry a risk of spread and seeding of cancer cells and of haemorrhage. Ex-vivo oocyte retrieval may be a safer and a viable option for patients suffering from ovarian tumors.

**Outcomes:** 28 oocytes were recovered, 18 were mature.9 oocytes were cryopreserved on day 0. Fertilisation rate was normal (7/9). From the first ovary, 2/3 blastulated by day 5 and were cryopreserved. Embryos from the second ovary did not blastulate. Morphokinetics were normal for oocytes recovered after oophorectomy but were suboptimal for oocytes recovered in the laboratory.

**Discussion:** Reports of in-vivo and ex-vivo egg collection performed around the time of laparotomy have been published. This case suggests time from oophorectomy to oocyte retrieval seems important in maximising viability and normalising morphokinetics.

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### 080 Sperm banking for oncology patients: Provision, outcomes and cost effectiveness

**Abdallah Yazan<sup>1</sup>; Croghan Natalie<sup>2</sup>; Jachertz Lisa<sup>2</sup>; Horne Gregory<sup>1</sup>; Fitzgerald Cheryl<sup>1</sup>**

<sup>1</sup>Manchester IVF; <sup>2</sup>Manchester University

**Aim:** This study aimed to establish the provision of male fertility preservation for cancer patients over the last 40 years. We also investigate the outcomes and cost effectiveness of this service.

**Methods:** Data was collected for all men diagnosed with cancer who banked at Andrology laboratory in a UK tertiary reproductive medicine centre from 1976 till 2016. The numbers were compared to cancer national statistics in 2014 to establish the annual referral rate. We investigated the change in referral rates every 5 years, the types of cancers referred and semen analyses at banking. Usage and disposal rates were calculated to establish the cost effectiveness of sperm banking for 10 years.

**Results:** Twenty percent of men aged between 12 and 67 and diagnosed with cancer in the north west were referred. Of 4,341 men referred, 194 attended and 3,756 successfully banked a sample. Testicular cancer was significantly (p<0.0001) the most common cancer referred (38.5%), whilst usage of banked sperm was most common in men with lymphoma (11%) (P=002). Sperm concentration in testicular cancer cases was abnormal in half of cases, and statistically significantly lower than in other malignancies (p<0.0001). Usage and disposal rates were 9.7% and 9.5% respectively, with a majority of 75% still in storage. Most usages and disposals occurred within 5 years of banking.

**Conclusions:** The provision of male fertility preservation has improved over time owing to the advancements in assisted reproduction, improved survival and increasing fertility awareness. Further improvement can be made especially in haematological cancers. Repeating semen analysis at one year after banking increases the disposal and usage rates; and hence improves the cost effectiveness of this service.



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### 081 The demography of referrals and implications for NHS funded assisted conception treatment for health boards due to implementation of Scottish national guidelines, 2013

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<sup>1</sup>Ayrshire Fertility Unit, University Hospital Crosshouse;

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**Aims:** To explore the implications for health boards of NHS funded assisted conception treatment due to implementation of new Scottish national guidelines, 2013

**Content:** The National Infertility Group(Scotland) recommendations were made to promote equality across health-boards for couples accessing assisted conception in line with NICE guidelines 2013.

**Method:** Retrospective case notes review between 1.1.11 to 31.5.12 of couples presenting to the Fertility clinic at secondary care.

**Findings:** Of 465 new couples attending, 115(24%) were referred for NHS funded IVF+/-ICSI. The couples not referred

had none, one, two, three or more reasons documented in 24%, 51%, 23% and 3% cases respectively. Age range 19-49 (mean 31) years. Of the reasons documented 31% had at least one child resident in the family, 19% had BMI>35 (range 35-60), 16% were smokers, 13% age >38 years (38-39: 30%, 40-42: 30%, >42: 40%), 5% either not actively trying or not in a stable relationship for 18 months, 2% were sterilized, 2% had unstable medical conditions, 3% had previous fertility treatment, 1% had child protection issues due to drug addiction/self-harm and 1.5% were already pregnant! 1% couples were in a same-sex relationship who were eligible.

**Impact:** The implementation of new guidelines will not significantly alter the overall referrals for assisted conception. The biggest reason for ineligibility was at least one child resident in the family (amendment in the guidelines from 1.9.16 will allow treatment if one partner has no biological child of her/his own). The new cut-off age of 42 years will allow more couples access IVF. This is offset by the numbers that would be ineligible with new cut-off for BMI<30 and being smokers.

**Discussion:** Improvement in documentation is advised for reasons for non-referrals and prospective audit is planned for referrals based on the new criteria.

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### 082 Audit of primary care subfertility referrals

**Umapathy Sashikala<sup>1</sup>; Kamal Lamya<sup>2</sup>**

<sup>1</sup>Salford Royal Foundation Trust; <sup>2</sup>University of Manchester

**Background:** An integral component of the role of GPs is to provide comprehensive referrals for specialist input in compliance with NICE guidance. Currently there are large delays in the organisation of subfertility follow-up appointments at SRFT and staff are concerned this is due to a lack of preliminary investigations being done at the primary care level. This project aims to audit the primary care fertility referrals to SRFT from October 2014-2015 and determine if they are compliant with NICE guidance.

**Methods:** 491 new patients attended the subfertility unit at SRFT from Oct 2014-15, of which 355 patients met the inclusion criteria for this project. The data analysed to determine overall referral compliance, referral compliance per borough and frequency of investigations conducted per case.

**Results:** 8.73% of the referrals were compliant with NICE guidance while 91% of referrals were below compliance standards. There was large variation amongst referral compliance per borough and within individual GP surgeries.

**Discussion:** To provide patient centered care and improve cost effectiveness, a collaborative effort between primary and secondary care is essential. This project suggests a specific subfertility proforma and patient leaflet pack could standardize referral compliance and improve patient care. A proposed copy of each has been included in this report.

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### Action plan:

- Collaborative meeting with GPs in order to identify and address challenges faced by GPs when managing subfertility
- Implementation of a specific subfertility referral proforma and patient information leaflet to be provided to all GPs.
- Re-audit after changes have been implemented

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### 083 Improving the quality of primary care referrals to an NHS fertility clinic

**Banu Shaila; Husain Fatima; Imsirovic Manik**  
*Heatherwood & Wexham Park, Frimley Health*

**Aims:** We aim for accurate data collection, consent and 100% completion of the tests for couples as basic standards in our Fertility clinic. This was a re-audit following a GP education event held 4 years previously where the pathways were agreed; improve utilisation of existing pathways and reduce the frustration of clinicians and patients alike when patients missed deadlines for age criteria for NHS funded IVF due to primary care delays in referral.

**Method:** Retrospective audit of 43 patient records referred to Fertility clinic as new patients from primary care. Survey of the awareness and use of the local fertility referral pathway, sent to 40 GP practices.

**Results:** First semenalysis result available for only 16%, Rubella; 49%, FSH; 74%, luteal phase progesterone; 84%, pelvic US report; 77%, The majority of referrals (93%) had a medical or gynaecological co-morbidity potentially contributing to their infertility but only 7% of these were referred within 1 year. GP survey; 45% response rate, 61% routinely used the proforma.

**Discussion:** Couples not conceiving within 1 year should be investigated, or earlier if there is a known factor contributing to infertility[1]. Despite the majority of patients having a contributing factor, only 7% were referred < 1 year. Awareness and use of the proforma was suboptimal, leading to delay in management.

**Relevance:** Further GP education needed for referrals and investigations. Triaging of referrals by secondary care; inconsistent due to scarce NHS resources and 18-week pathway. We can modify the detailed patient information leaflets we already send out with appointments, to highlight the importance of completing the tests. Patient engagement may improve the patient experience by allowing timely management and conserve NHS resources by reducing duplication of tests and appointments.

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### 084 Audit of infertility referral letters from primary care to infertility clinic

**Malik Fozia Sarfraz; Hussain Munawar**  
*Southend University Hospital NHS Trust*

**Audit:** Audit of Infertility referral letters from Primary care to infertility clinic.

**Aims & Objectives:** To assess the quality of initial management and investigations in primary care.

To address the areas which needs improvements?

**Type of Audit:** Retrospective.

**Material & Methods:** 200 GP referral letters of sub fertile couples.

A standard preform prepared taking in to consideration local guidelines on management of infertility, and current NICE guideline on Fertility assessment and treatment.

Data was entered results were analysed and compared with the standard guidelines.

**Results:** 200 patients referred to fertility clinic as first consultation reviewed. 14 patients excluded as they were inappropriate referral. All information collected from 186 patient and data analysed. 37.6 % had primary and 31% had secondary subfertility and 31% not stated for type of subfertility. 41% had partners identified but 59% had no mention of partner. 23% couples both partners requested to attend clinic consultation. Regarding female partners 40% had menstrual cycle length stated. 12% had smoking status

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mentioned, 6% had BMI calculated, 4% had alcohol status mentioned, 15% had chlamydia tested, 41% had transvaginal scan, 15% had Rubella antibody test, 46% had progesterone test results in their referral letter from primary trust and 46% had irrelevant investigations. For Male partners only 6% had smoking status mentioned, 3% had BMI calculated, 1% had alcohol intake stated, 37% had semen analysis reported along with referral letter.

**Recommendations:** Teamwork and communication between primary care and infertility clinic.

Local and national guidelines should be adhered while managing infertile couple.

Both partners should be referred and seen in clinic at the same time

Prepared standardized history sheets for infertility referrals.

History and examination of both partners should be properly taken and documented in referral letter

Semen analysis, day-21 serum progesterone and if indicated serum FSH/LH and prolactin levels to be performed

Regular Audit and evaluation of current clinical practice

### 085 Out of working hours patient support

**Moult Debbie; Lytollis Alison; Atkinson Glen; Joy Jolly**  
CARE Fertility Manchester

**Aims:** To assess the concerns which arise outside of clinic hours aiming to improve service/efficiency during working hours.

**Content:** In our clinic, the on-call nurse is available by telephone up to 2230hrs Monday - Saturday and 0730hrs-2230hrs on Sundays with a Consultant available for further advice. Patients undergoing assisted conception often require practical advice, support and reassurance. This was a prospective study which was undertaken from 13th January 2016 to 13th July 2016. A diary of all out of hours calls was recorded for analysis.

**Outcomes:**

- A total of 189 calls were recorded and categorised:
- Pre-treatment queries 11
- Protocol/ medication/ administration of drugs 41
- Drugs storage 3
- Concerns during the stimulation stage 10
- TVOR queries e.g. timing and trigger medication 30
- ET planning and pessaries 11
- Post ET advice 11
- Early pregnancy concerns 24
- Satellite clinics 4
- Appointments 6
- Blood results 2
- Unrelated medical concerns 11
- Staff communication 14
- Embryology information 5
- Miscellaneous 6

**Relevance:** Based on our findings we aim to have teaching sessions for all staff and update patient information leaflets so

that the staff are better equipped to counsel patients at the injection teach so as to avoid stress and are better equipped to answer out of hours queries.

**Discussion:** The out of working hours service is an HFEA requirement to provide support for patients who are undergoing treatment. Although patients come into the clinic to review their protocol and injection teaches, this can be a particularly anxious time when extra support is required in not only understanding the treatment process but being able to actually inject oneself. Early pregnancy problems and management of coexisting medical conditions also cause concern. The nurse on call can offer reassurance and practical advice over the telephone and can follow up in the clinic the following day where necessary.

### 086 One stop fertility clinic - service provision and patient experience

**Mitra Devasree; Borase Himanshu**  
West Hertfordshire Hospitals NHS Trust

Fertility problems and their investigations and treatment can cause emotional stress. Generally, couples appreciate a service that provides rapid and efficient assessment, frank discussion of prognosis and a clearly agreed plan of management. So we have designed a One stop clinic and audited the service provision to assess the couples' satisfaction.

**Aims/Objectives:**

- To assess time gap between the first referral and the definitive management plan before and after initiation of One Stop Clinic
- To evaluate patient satisfaction

**Methods:** A population based retrospective study was conducted in a District General Hospital. Couples were identified from the clinic appointment database. Patient satisfaction was evaluated by using locally designed questionnaire.

**Relevance/Impact:** The effectiveness of the newly designed clinic can be analysed from the couples' experience. This helps in proper utilization of resources without compromising the quality of care.

**Outcomes:** 100 couples, each from old and new design clinic (200 in total) were identified. In the old arm 22/100 (22%) got a definitive management plan in the 1st doctor's appointment as opposed to 96/100 (96%) in the new arm. In the old clinic set-up, 14/100 (14%) couples were given definitive management in 4 months from the time of referral, whereas in the new set up this was 78/100 (78%). In terms of overall patient satisfaction, 29/39 (74%) in the old arm and 94/100 (94%) in the new arm were satisfied with the service. However the clinic wait time in One Stop Clinic is quite significant – 45% couples had to wait between 30 and 90 minutes. We are trying to constantly improve our services, with special note on our clinic wait times.

**Discussion:** NICE says "ensuring that care is safe and that people have a positive experience of care is vital in a high quality service. It is important to consider these factors when planning and delivering services relevant to fertility". Therefore, initiation of One stop clinic has minimized the number of clinic attendance, thereby minimizing emotional stress and at the same time using resources judiciously.



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### 087 Strategies to improve fertilisation rates with assisted conception: A systematic review

**Jeve Yadava; Potdar Neelam; Blower Jane; Gelbaya Tarek**

*Leicester Fertility Centre*

**Introduction:** Successful fertilisation is a key step in assisted conception. Various factors including sperm or oocyte pathology and environmental factors have significant impact on fertilization rates. This systematic review is aimed to evaluate the existing evidence about factors affecting fertilization and strategies to improve fertilization rates.

**Methods:** A literature search was performed using Ovid MEDLINE® (1950–April 2016), EMBASE (1950– April 2016), Ovid OLDMEDLINE®, Pre-MEDLINE, in-Process & Other Non-Indexed Citations database consists of In-Process and PubMed-not-MEDLINE records from NLM, Google scholar, Web of Sciences (1950- April 2016) and the Cochrane Library. Language restrictions were not applied. Relevant key words were used to combine set of results. Total 243 results were screened. Only qualitative analysis was performed as there was major heterogeneity in study design and methodology for quantitative synthesis. The studies were grouped together based on methods used to improve fertilization rates.

**Results:** Factors affecting fertilization were classified into sperm and oocyte related factors. The methods to improve fertilization rates were grouped together based on approach used to improve fertilization rates. Optimising laboratory condition and procedural effects in techniques is associated with improved fertilization rates. Assisted oocyte activation using various techniques showed promising results.

**Conclusion:** The commonest cause of failed fertilization is non-availability of appropriate sperm or failed oocyte activation. Various techniques are described to improve fertilization rates including assisted oocyte activation, PICS and IMSI. This review highlights the promising strategies under research to enhance fertilization rates. Adequately powered multicentre randomised trials are required to evaluate each of these techniques before considering clinical application.

### 088 The challenges with legal parenthood consent: Can we remove the risk?

**White Linsey; Gregoire Rachel**

*Glasgow Royal Infirmary*

**Aims/Objectives:** HFEA consent forms WP and PP must be completed correctly before donor treatment commences to ensure appropriate legal parenthood (HFEA T60/T61). In 2013, the Cobb ruling stated that a UK clinic had not complied with HFEA licence conditions, declaring that the non-birth mother in question was not the legal parent of children born using donor sperm, due to lack of informed consent.

HFEA Chairs letter CE(14)01 was issued in February 2014 instructing all clinics to fully audit any donor treatments performed since 2009 and report discrepancies.

Our clinic identified five major discrepancies in legal parenthood status. This led to an immediate review of the consent taking process and swift changes to practice to ensure compliance.

**Content:** The audit scope and findings reported to the HFEA. The immediate and on-going improvement to clinical practice, and the challenges the clinical service faces.

**Relevance/Impact:** Clinics must use best practice to obtain effective consent to legal parenthood. Over 90 couples throughout the UK have suffered unnecessary distress and uncertainty due to improper consent.

**Outcomes:** Our clinic audited the consents of 59 couples who had completed successful treatment since April 2009 from a total of 415 cycles. Five major discrepancies were found (8%).

Process mapping for consent taking and the offer of counselling; staff competency assessments and training workshops; and improvements to the consent review process, took place over a two month period. Four (ongoing) quarterly audits reported no further major discrepancies and a significant decrease in minor discrepancies: Q1 2/15(13%); Q2 6/21(29%); Q3 2/28(7%); Q4 1/26(4%).

**Discussion:** Introducing a robust process for consent taking and review of consent forms prior to treatment can effectively reduce the risk of discrepancies in legal parenthood consent, removing the unnecessary risk of distress to couples.

### 089 Fertility awareness for family building

**Grace Bola<sup>1</sup>; Shawe Jill<sup>2</sup>; Stephenson Judith<sup>1</sup>**

*<sup>1</sup>University College London; <sup>2</sup>University of Surrey*

**Introduction:** Global health policies have highlighted the importance of optimising women's health and knowledge for contraception as part of pregnancy-prevention and for pregnancy-planning as part of preconception care. However, in terms of general fertility awareness, there is a disproportionate amount of information on pregnancy-prevention versus pregnancy-planning. This study was carried out to assess current state of evidence for fertility awareness with respect to family-building.

**Methods:** Comprehensive review of literature relating to fertility awareness was carried out in a systematic manner using PubMed, Embase, Cochrane databases. Keywords were generated through exploratory searches and by using existing reviews in relevant areas and similar articles. The MeSH terms Fertility AND health knowledge OR attitudes OR practice were utilised for the search.

**Results:** 24 studies with similar themes on fertility awareness were analysed.

**Recurring themes:**

- Significant knowledge gaps and misconceptions regarding fertility, ovulation and conception.
- Common misconception that all women will conceive immediately after they begin to try.
- Impact of age on men and women's fertility decline is typically underestimated by 10 years.
- Less than 25% of women were aware that menstrual cycles can vary.
- Significant overestimation of ART success rates.

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**Conclusions:** Emphasis on pregnancy-prevention means that relatively little attention is being drawn to issues associated with postponement of childbirth and impact of infertility. Although there's still an important need for continuous advocacy of contraceptive methods for family-planning within fertility-awareness campaigns, some balance in the message can help alleviate problems experienced with infertility and family-building. By promoting awareness, we are investing in better outcomes.

### 090 Treatment choices and pregnancy outcomes in same sex couples

**Lowe Melanie<sup>1</sup>; Polson Dave<sup>2</sup>**

<sup>1</sup>University of Manchester; <sup>2</sup>Manchester Fertility

The increasing openness of same sex relationships in society has led to a more couples attending for fertility treatment. There is little published data on their treatment choices or the success rates than can be achieved with donor insemination (DI) or IVF treatment. We have performed a retrospective review of the treatment requests of same sex couples and their subsequent pregnancy rates.

During our 20 month study, 232 couples attended for treatment reflecting 20% of our clinical workload. 57% requested donor insemination and 43% chose IVF as their first treatment. Of these, 15% chose to have IVF using their partner's eggs. Almost 40% of those choosing IVF opted to donate half their eggs to an anonymous recipient, as part of the egg share programme.

The cumulative pregnancy rates over three cycles of donor insemination were 28% (in women  $\leq 35$  years); 20% (36 – 37 years) and 10% ( $\geq 38$  years). The IVF results were significantly higher with a first cycle success rate of 44% for all ages. The cumulative pregnancy rates were 74% (women aged  $\leq 35$  years); 63% (aged 36 – 39 years); and 36% (for those aged  $\geq 40$  years). Women having IVF with partners eggs had similar pregnancy rates to those who did not give their eggs to their partner. The egg sharers had similar pregnancy rates to those keeping all their eggs for their own treatment.

Donor insemination is the more popular treatment choice and these results confirm that this is recommended under the age of 35. Over this age the success rate is lower and IVF should therefore be recommended. Egg sharing does not have any negative impact on success rates and can also be recommended.

### 091 Exploring perspectives of men and clinicians in communicating male fertility results

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<sup>1</sup>University of Sheffield- Dept. of Oncology and Metabolism; <sup>2</sup>University of Sheffield- SCHARR; <sup>3</sup>University of Sheffield- Dept. of Automatic Control and Systems Engineering

**Background:** Although 50% of infertility in couples has a male factor contribution, little is known about how doctors communicate test results and how men understand this information. Due to the complexity of semen analysis results, it was hypothesised that both men and doctors find interpretation of this data to be difficult and confusing.

**Methods:** To determine the experience and opinions of doctors and men about the current methods used to deliver results of semen analysis 27 semi-structured interviews were conducted with four different groups: (i) men in sub-fertile partnerships; (ii) a control group of healthy men; (iii) fertility specialists; and (iv) GPs. All interviews were conversational, addressing six broad topics: (i) public awareness of male infertility; (ii) experience and/or preference for receiving results; (iii) role of the partner; (iv) the level of detail discussed; (v) the availability of printed or digital copies of results; and (vi) what supplementary information is provided. Transcribed interviews were then analysed thematically and common themes identified using focused coding.

**Results:** The interviews revealed four main themes commonly discussed by the study population: (i) low public awareness of the prevalence and issues surrounding male factor infertility; (ii) significant variation in the opinions of GPs and fertility specialists across a number of key areas (such as the value of giving a printed copy of the results or whether the man was seen with his partner); (iii) NICE guidelines for the communication of test results was not routinely followed; and (iv) semen analysis results were not presented in a standardized format.

**Conclusions:** There is a need to improve the method of communicating the results of semen analysis and better support men and their partners through the fertility journey, particularly in primary care. There could be improved guidance and training, particularly for GPs and inexperienced clinicians.

### 092 Donor in vitro fertilization pregnancy and delivery with the use of vitrified embryos in a 49 year old following fibroid uterine embolization and hysteroscopic surgery

**Tsakos Elias<sup>1</sup>; Tsagias Nikos<sup>1</sup>; Wardle Peter<sup>2</sup>**

<sup>1</sup>EmbryoClinic, Assisted Reproduction Unit, Thessaloniki, Greece; <sup>2</sup>Nuffield Hospital, Bristol, UK

**Objective:** Uterine pathology is often associated with female infertility by intervening in the implantation process. In this report we present a case of a 49-year-old woman with leiomyomata, previously treated by uterine artery embolization and operative hysteroscopy, who achieved a singleton pregnancy following IVF treatment with vitrified embryos originating from donor oocytes and husbands' sperm.

**Content:** The patient was first investigated for infertility at the age of 42 years. Her significant medical history included symptomatic multiple uterine fibroids subserosal, intramural and submucous treated with hysteroscopic resection in 2008, uterine artery embolization in 2009. Six months later there was a 76% reduction in fibroid size. A hysteroscopic myomectomy was performed in Greece just prior to IVF treatment. Following hysteroscopic surgery in 2014, fresh embryo transfer was cancelled due to the formation of functional hormone producing follicular cysts in the recipient associated with long down regulation GnRH-a protocol. Seven top quality blastocysts were vitrified and combined oral contraceptive pill treatment was commenced. Two months later, the cysts dissolved and a long down regulation GnRH-a protocol coupled by intensive oestrogen treatment and luteal phase support led to the successful embryo transfer of two thawed blastocysts. A single intrauterine viable pregnancy was



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confirmed by ultrasound scan 3 weeks later. The pregnancy was uneventful and a planned Caesarean section was performed at 38 weeks. A healthy girl was delivered, weighing 2770 grams. The patient suffered a major postpartum haemorrhage due to placental adherence complicated by maternal myocardial ischaemia but she made full recovery.

**Relevance/Impact:** Successful donor IVF in advanced maternal age with uterine fibroids.

**OutcomeDiscussion:** This is world's first report of IVF treatment with the use of donor oocytes and vitrified embryos in a woman of critically advanced reproductive age who had previously undergone uterine artery embolization and hysteroscopic surgery for fibroids.

### 093 Investigating psychosocial attitudes, motivations and experiences of egg sharers: A systematic review

**Bracewell-Milnes Timothy<sup>1</sup>; Thum Meen-Yau<sup>2</sup>; Saso Srdjan<sup>1</sup>**

<sup>1</sup>Imperial College London; <sup>2</sup>Lister Fertility Clinic, London

**Introduction:** Egg share donor numbers were steadily increasing in the UK from 2006, however in 2013 there was a national fall in numbers<sup>1</sup>. With an acute shortage of oocyte donors, the psychosocial aspects behind egg share donation are important for fertility clinics to understand to improve patient experiences and also increase donation numbers.

This study aims to systematically review the psychosocial aspects of oocyte donation from the point of view of egg share donors and their recipients. Its secondary aims are to explore the motives and experiences of donors as well as attitudes towards donor anonymity and disclosure. It is the first such review to be performed.

**Methods:** A systematic search of English peer reviewed journals following PRISMA guidelines of four computerised databases was undertaken, with no time restriction set for publications.

**Results:** 11 studies met the inclusion criteria and were included in the systematic review. One study reported 89% of successful and 90% of unsuccessful egg share donors found the experience positive<sup>2</sup>. 74-94% of egg share donors disclosed the nature of their fertility treatment<sup>2,3,4</sup>, while 86% of egg share recipients planned to disclose the nature of conception to their offspring<sup>5</sup>. Studies consistently demonstrated egg share donors reported altruism and helping another couple to have a child as important motivating factor as receiving cheaper fertility treatment and having a child themselves<sup>6,7</sup>.

**Conclusion:** Overall, the review was reassuring regarding the psychological well-being of egg share donors and does not support ethical concerns previously proposed as assumptions without sound empirical knowledge.

However poor study designs with small patient numbers and short term follow up limited the review. An increased number of well designed studies looking into the psychological issues surrounding egg share donation could allow more directed assessment and counseling of egg share donors, with a resulting potential increase in donor recruitment.

1. Human Fertilisation and Embryology Authority (HFEA). Facts and Figures: Number of sperm and egg donors, 2012-2013.

2. Ahuja KK, Simons EG, Mostyn BJ, Bowen-Simpkins P. As assessment of the motives and morals of egg share donors: policy of 'payment' to egg donors requires a fair review. *Hum Reprod* 1998;13:2671-2678.

3. Kirkland A, Power M, Burton G, Baber R, Studd J, Abdalla H. Comparison of attitudes of donors and recipients to oocyte donation. *Hum Reprod*. 1992 Mar;7(3):355-7.

4. Ahuja KK, Mostyn BJ, Simons EG. Egg sharing and egg donation: attitudes of British egg donors and recipients. *Hum Reprod*. 1997 Dec;12(12):2845-52.

5. Gürtin ZB, Ahuja KK, Golombok S. Emotional and relational aspects of egg-sharing: egg-share donors' and recipients' feelings about each other, each others' treatment outcome and any resulting children. *Hum Reprod*. 2012 Jun;27(6):1690-701. doi: 10.1093/humrep/des085.

6. Blyth E, Speirs J. Meeting the rights and needs of donor-conceived people: the contribution of a voluntary contact register. *Nord Soc Arbeid* 2004;24:318-330.

7. Gürtin ZB, Ahuja KK, Golombok S. Egg-sharing, consent and exploitation: examining donors' and recipients' circumstances and retrospective reflections. *Reprod Biomed Online*. 2012 Jun;24(7):698-708. doi: 10.1016/j.rbmo.2012.02.008.

### 094 The demand and supply of embryo donation for treatment

**Massiah Nadine; Shaw Carol; Choudhary Meena**  
Newcastle Fertility Centre

**Objective:** The objective of our study is to determine whether the demand for donated embryos for treatment is being met at our centre.

**Content:** This was a retrospective study. The index cases of donors and recipients between January 2004 and December 2015 were obtained from the embryo donor register. The outcome measures were embryo donor numbers, embryo recipient numbers, number of donated embryos, clinical pregnancies and donor siblings.

**Relevance/Impact:** Embryo donation for treatment of other couples is altruistic and rare. In the UK, an average of 204 women (range:78-269) are treated each year<sup>1</sup>. This study will aid the development of our embryo donation programme.

**Outcomes:** The rate of embryo donation was 0.91/year with 11 embryo transfer cycles performed in 12 years with an average of 1.8 embryos transferred per cycle. Thirty seven embryos were donated with an average of 4 embryos per donor. The donor to recipient ratio was 3:2 with 9 embryo donors and 6 recipients. Most recipients 4/6 (66%) had more than 1 donor in consecutive cycles. The clinical pregnancy rate per embryo was 10%, per embryo transfer cycle 18%, and per person 33%. Two recipients had success on their second embryo transfer that led to a singleton pregnancy and twin pregnancy. No donor conceived children had donor genetic siblings. Live birth data was not available.

**Discussion:** The supply of embryos fulfilled the demand in a donor to recipient ratio of 3:2. The embryo donor and recipient numbers were low. To increase the donation and uptake of embryos, we need to increase awareness by ensuring that couples with cryopreserved embryos receive donor information and have an opportunity to ask questions. This is an alternative



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option for couples who need both donor gametes, those who wish to avoid long donor egg waiting lists and those considering adoption.

1. HFEA (2014) Donation statistics. [www.hfea.gov.uk/3302.html](http://www.hfea.gov.uk/3302.html) Accessed 10 August 2016.

### 095 Investigating psychosocial attitudes, motivations and experiences of oocyte recipients: A systematic review

**Bracewell-Milnes Timothy<sup>1</sup>; Saso Srdjan<sup>2</sup>; Bora Shabana<sup>3</sup>; Thum Meen-Yau<sup>3</sup>**

<sup>1</sup>Imperial College London; <sup>2</sup>Imperial College London; <sup>3</sup>Lister Fertility Clinic

**Introduction:** Demand for oocyte donors has been on the rise globally, with infertile couples, as well as gay men, increasingly using it as a means to found their families. This study aims to systematically review the psychosocial aspects of oocyte donation from the point of view of oocyte recipients. Its secondary aims are to explore the motives and experiences of recipients as well as attitudes towards donor anonymity and disclosure.

**Methods:** A systematic search of English peer reviewed journals following PRISMA guidelines of four computerised databases was undertaken, with no time restriction set for publications.

**Results:** Eighteen studies met the inclusion criteria and were included in the systematic review. Regarding motives for seeking oocyte donation, the main motivating factors were to have a genetic link between the child and their partner (42%), to experience pregnancy (36%), and a mistrust of the adoption process (22%)<sup>1</sup>. The most significant characteristics requested by recipients were consistently medical history (62%), race (49%), smoking/alcohol/narcotics use (44%), intelligence (39%) and physical appearance (29%)<sup>2,3,4</sup>. Regarding disclosure, most recipients indicated that they would inform family/friends. However, studies consistently report approximately one third of recipients did not intend to disclose the nature of conception to their offspring.

**Conclusion:** The review was reassuring regarding the psychological well-being of recipients during the donation process. The results showing the intended inconsistency of the recipients informing family/friends whilst withholding to offspring were concerning, because it means multiple parties are involved in secrecy and inadvertent disclosure is a risk, which could impact on recipient-offspring relationships.

However the studies reviewed had small patient numbers and short term follow up. An increased number of well designed studies looking into the psychological issues surrounding oocyte recipients and long term follow up, including their relationship with resultant offspring, would allow more directed and informed counseling to potential oocyte recipients.

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### 096 The right to reproduce? Ethics and reproductive medicine from a trainee's perspective

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*Cambridge University Hospitals NHS Foundation Trust*

Advances in reproductive medicine have provided the opportunity to sub fertile couples to have a family of their own, a dream, until recently, few imagined could ever become reality. The beginning of a human life is a miracle, however reducing this to a 'procedure' gives rise to ethical dilemmas. For example, in IVF, the 'healthiest' embryo is implanted while the 'rest' maybe used for stem cell research or abandoned. While this may prove life-saving in many couples with potential genetically inherited conditions, other couples may use this technology to predetermine certain characteristics for non-medical reasons in the future offspring. Also, whilst reproductive medicine provides solace to couples seeking fertility treatments, are we ensuring the best interest of the child being conceived? The HFEA act has clauses which guide the strict NHS funding criteria for assisted reproductive techniques. In this article, we have tried to understand, and indeed question, whether clinicians are best equipped to be judging eligibility on non-clinical grounds.

### 097 DAZL mutations associated with human infertility affect protein activity

**Allen Caroline; Tedim Ferreira Maria; Sousa Martins Joao P; Smith Richard; Gray Nicola**

*University of Edinburgh*

Infertility affects 15% of couples and can arise from defective gametogenesis that has an important genetic component (2). Deleted-in-Azoospermia-like (DAZL) belongs to the DAZ-gene family, which has been associated with human infertility and encodes several germ cell-specific RNA-binding proteins that regulate mRNA translation (1) and poly(A)-tail length (4). Previous studies revealed that DAZL has a role in gametogenesis and, although a role in human fertility remains unclear, a small number of mutations have been identified in sub-fertile patients (3).

The functional consequences of these human (h)DAZL mutations on mRNA translation were determined in vivo using reporter assays in *Xenopus laevis* oocytes. Two mutations (R115G and I37A) alter conserved amino acids in an hDAZL region required for function. These mutations, but not others outside this region, were found to impede DAZL-mediated translational regulation, with the non-conservative R115G mutation abolishing function. This supports the possibility that these mutations may have a causative role in infertility by abrogating DAZL's ability to stimulate translation of mRNAs required for germ-cell function.

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Similarly, the effects of equivalent mutations introduced into the highly conserved murine (m)Dazl protein were studied as a preliminary step before designing a mouse model for Dazl function. We found the effect of R115G to be reduced in this context, and the conservative I37A mutation to have no significant effect. Species-specific differences may result from differences in activity or stability of the homologues, or their relative abilities to bind poly(A)-binding protein (PABP), required for DAZL function (1). The activity of wild-type hDAZL and mDazl in maintaining poly(A)-tail stability were also confirmed as a prelude to testing the effects of infertility-associated mutations on this.

This study extends our understanding of a putative role of DAZL in human fertility, identifying potentially causative mutations that can now be further examined in whole organism studies.

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### 098 Investigating the impact of hyperglycaemia on bovine oviduct epithelial cell physiology and secretions in vitro

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*Hull York Medical School (HYMS)*

A key role of the oviduct, or Fallopian tube, is the creation of the environment in which fundamental developmental processes take place, including gamete activation, fertilisation and early embryo development. Previous studies have partially determined the composition of oviduct fluid. However, the impact of maternal physiology on the oviduct environment is unknown.

The aim of this study was to investigate the impact of hyperglycaemia on the physiology of oviduct epithelial cells and the biochemical and physical properties of oviduct-derived fluid, using an air:liquid in vitro model of the oviduct.

Bovine oviduct epithelial cells (BOECs), harvested from slaughterhouse-derived tissues, were cultured in DMEM-F12(390C,5%CO<sub>2</sub>) for 6 days. Cell identity was confirmed using confocal and Transmission Electron Microscopy imaging. We used fluorescein transport and Trans Epithelial Electrical Resistance measurements to show the barrier properties of the epithelial monolayer in our in vitro system. Glucose was added subsequently to the basolateral surface of the epithelia at normal (7.3mM) and hyperglycaemic (8.5mM, 11mM) levels. After 24h, the cells in our model created a thin film of fluid, which was collected for biochemical analysis and the cells were collected for assessment of gene expression.

After 6 days in culture, the cells produced a functioning monolayer, exhibiting an electrochemical resistance

>700Ωcm<sup>2</sup> (n=4), confirmed by observation that fluorescein was unable to cross the cell barrier. Our data suggest that hyperglycaemic conditions decrease the volume of oviduct-derived fluid and that hyperglycaemia in the basolateral compartment leads to elevated glucose appearance and altered amino acid profile in the apical chamber.

Using an in vitro oviduct model we have shown that hyperglycaemia raises the glucose concentration in oviduct secretions. Future work will focus on the role of insulin on oviduct fluid secretion, as well as evaluating the impact of pathological levels of glucose and insulin treatment of hyperglycaemic samples on early embryo development.

### 099 Assessment of neural toxicity using triangular chart in human embryonic stem cells

**Jeung Eui-Bae; Kang Hee Young; Ahn Changhwan; Lee Jae-Hwan; Kang Song Ai; An Jin Yong; Tran Dinh Nam**  
*Chungbuk National University, South Korea*

Embryonic stem cell test (EST) has been developed to replace animal experimentation and to assess the toxic potential of compounds in early development of fetus. EST was capable of providing more rapid, precise, relevant information than some animal studies and economical approach characterized by a low compound requirement and short duration. Especially, human ESCs have an advantage being able to overcome species-specific differences. In this study, characteristics in neuronal differentiation of human ESCs are used to assess neurotoxicity of six compounds during early development. Cytotoxicity for three anticancer agents (cytosine arabinoside, 5-fluorouracil, and hydroxyurea), two immune suppressing agents (indomethacin and dexamethasone) and a negative control agent (ascorbic acid) were evaluated by CCK assay. Three anticancer agents showed strong cytotoxicity, and two immune suppressing agents showed weak cytotoxicity. Human ESCs were exposed to six pharmacological compounds during neural differentiation up to 28 days. Then expression level of neural markers was examined by real-time PCR and immunocytochemistry. Dose-dependent expression profiles of neural markers in compounds-treated group were expressed to triangular chart with standard expression level, which was determined from expression level in compounds-untreated group. All compounds except ascorbic acid exhibited significant decreases in levels of neuronal specific markers including GAD1, CNP, FABP, and NES. Also, cytosine arabinoside diminished expression of Nestin and β3-tubulin proteins in neural cells differentiated from human ESCs. These findings could extend our understanding of how differentiated human ESCs may be useful in assessment of cell viability or neurogenesis impairment by chemicals that could have an impact on the embryonic stage and relevance of pharmacological compounds to embryonic neurogenesis. Also, GAD1, CNP, FABP, and NES are useful biomarkers to evaluate neural toxicity in early development.

This research was supported by a grant (15182MFDS460) from Ministry of Food and Drug Safety in 2016.

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### 100 Molecular characterisation of HEK 293T cells expressing human DDX4

**Lu Haojiang; Clarkson Yvonne; McLaughlin Marie; Skehel Paul; Telfer Evelyn**  
*University of Edinburgh*

**Aims/Objectives:** Antibody based fluorescent activated cell sorting (FACS) is a method of isolating oogonial stem cells (OSCs) based on the premise that the C-terminus of the germline marker DEAD-box helicase 4 (DDX4), an RNA helicase, is expressed on the cell surface(1). Extracellular localisation of DDX4 is disputed (1,2), therefore our initial aim was to generate mammalian cells expressing DDX4 and then to determine the localisation of the C-terminus of DDX4, using molecular techniques.

**Content:** The mammalian vector pFLAG-DDX4-Myc was constructed by restriction digestion free ligation using Gibson and In-Fusion assembly and expressed in HEK 293T cells. Protein expression was confirmed by Western Blot (WB). Immunocytochemistry was performed on permeabilised and non-permeabilised DDX4-expressing HEK 293T cells to determine if the C-terminus of DDX4 was extracellular.

**Relevance/Impact:** Molecular characterisation of HEK 293T cells expressing DDX4 could confirm the extracellular localisation of the DDX4 C-terminus. This would help to address the DDX4 localisation controversy and validate the use of a DDX4 antibody based FACS as a method of isolation for OSCs.

**Outcomes:** DDX4, with different epitopes on the N and C-terminus, was successfully cloned into a mammalian expression vector and transfected into HEK 293T cells. Non-permeabilised and permeabilised transfected cells were examined by immunofluorescence using antibodies against the tag protein on the DDX4 C-terminus. Fluorescence was detected in both the permeabilised and non-permeabilised cells but no fluorescence was detected in cells transfected with an endoplasmic reticulum (ER) associated protein. These results are consistent with the C-terminus of DDX4 being expressed on the cell surface.

**Discussion:** Highly specific detection methods used in this study confirmed the surface expression of human DDX4. This not only provides evidence to assist the debate on the localisation of DDX4 but also validates the use of DDX4 C-terminus to isolate DDX4-positive OSCs by antibody based FACS.

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### 101 Validation of a kiss1r antibody using kiss1r knockout mice

**Healy James P.<sup>1</sup>; Yeo Shel-Hwa<sup>2</sup>; Colledge William H.<sup>2</sup>**  
<sup>1</sup>University College Cork; <sup>2</sup>University of Cambridge

The G-Protein Coupled Receptor 54 (Gpr54), also known as Kiss1r, is the receptor for the Kisspeptin peptide neurotransmitters or neuromodulators. Gpr54 enables the Kisspeptin-activated release of gonadotropin-releasing hormone (GnRH) which is critical for activation of the mammalian reproductive axis at puberty and the regulation of fertility. For this reason it is thought that Gpr54 is localized on GnRH neuronal cell bodies and nerve terminals but immunohistochemical confirmation has been limited due to the lack of a reliable antibody. Several commercial Kiss1r antibodies are available but none of these are proven to be specific. We recently acquired a non-commercialised Kiss1r antibody.

To validate the Kiss1r antibody, we performed dual immunofluorescent staining using coronal brain sections from adult mice. Specifically, four Kiss1r knockout mice, Kiss1r tm1Coll (Seminara et al., 2003) were compared to three wild types using equal volumes and concentrations of the rabbit polyclonal anti-Kiss1r primary antibody generated against amino acids 348–396 of mouse Kiss1r. The primary antibody was diluted in 1:5000, an Alexa Fluor 568-conjugated goat anti-rabbit secondary immunoglobulin was used for visualization of the Kiss1r immunoreactivity with red fluorescence. We also used a 1:2000 concentration of sheep polyclonal anti-GnRH antiserum followed by Alexa Fluor 488-conjugated donkey anti-sheep secondary immunoglobulin to label GnRH neurons with green fluorescence.

We observed that Kiss1r is concentrated in primary cilia-like structures connected to GnRH cell bodies in the preoptic area of the wild type murine brain while the Kiss1r knockouts were devoid of this staining. These findings are consistent with the published work (Koemeter-Cox et al., 2014) using another Kiss1r knockout mouse line (Kiss1r Gt1Ste1; Dungan et al., 2007.)

It is crucial to validate the reliability of the Kiss1r antibody. This will aid future experiments confirming the distribution of Kiss1r in murine brain, highlighting areas that Kisspeptin may have a previously unknown effect.

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**102** Anti-müllerian hormone (AMH) and antral follicle count (AFC) are predictive markers in the assessment of patients with menstrual disturbance

**Abbara Ali<sup>1</sup>; Clarke Sophie<sup>1</sup>; Roberts Rachel<sup>1</sup>; Vimalasvaran Sunitha<sup>1</sup>; Comminos Alexander<sup>1</sup>; Christopoulos Georgios<sup>2</sup>; Islam Rumana<sup>2</sup>; Franks Stephen<sup>1</sup>; Trew Geoffrey<sup>2</sup>; Dhillon Waljit<sup>1</sup>**

<sup>1</sup>Imperial College London; <sup>2</sup>Hammersmith IVF Unit

**Aims/Objectives:** Anti-Müllerian Hormone (AMH) and Antral Follicle Count (AFC) are both principally used as markers of ovarian reserve. The utility of these markers in the binary diagnosis of Polycystic Ovarian Syndrome (PCOS) by published criteria, such as Rotterdam, has been previously reported.

We evaluated their utility in the evaluation of oligo/amenorrhoea in healthy young non-obese women.

**Content:** Women with both ovaries in situ, under the age of 35 years, with BMI <30 kg/m<sup>2</sup>, seeking fertility treatment at Imperial College Healthcare NHS Trust were included in the study. 186 women were screened with menstrual cycle history, follicular-phase AFC on ultrasound, ovarian morphology (normal, multicystic ovaries MCO, or polycystic ovaries PCO), serum AMH level (pmol/L; Beckman-Coulter 3rd generation assay), and other reproductive hormones. Oligo/amenorrhoea was defined as average menstrual cycle length (ACL) 35days.

**Outcomes:** There was a linear correlation between serum AMH and AFC on ultrasound, with the following equation describing the relationship ( $AFC = AMH \times 0.5 + 12$ ). Rather than AMH and AFC being elevated only in women with oligo/amenorrhoea, there was a gradual increase in these markers with increasing ACL even in eumenorrhoeic women (median AMH 20pmol/L in ACL <27days, 28pmol/L in ACL 28-29days, 47pmol/L in ACL 30-34days, 66pmol/L in ACL >35days).

**Discussion:** There was an increased prevalence of oligo/amenorrhoea with increasing AMH, or AFC, (5% oligo/amenorrhoea in AMH <15pmol/L, 24% oligo/amenorrhoea in AMH 30-45pmol/L, 61% oligo/amenorrhoea in AMH >60pmol/L). Oligo/amenorrhoea was less prevalent in those with at least one normal morphology ovary (0-7%) when compared with those with those with 2 MCO morphology (11%), or 2 PCO morphology (47%) ovaries.

**Relevance/Impact:** AMH and AFC are reliable predictive markers of menstrual cyclicity, even in women currently regarded as eumenorrhoeic. Thus, AMH and AFC are useful adjuncts in the clinical assessment of patients with menstrual disturbance.

**103** Comparable inter-laboratory performance of the two automated platforms for AMH evaluation (Roche® and Beckman Coulter®) permits greater confidence when assessing functional ovarian reserve

**Fairbairn Craig; Lyon Jennifer; Mitchell Paul; Gaudoin Marco; Fleming Richard**

GCRM, Glasgow

**Aims/objectives:** Serum AMH can be used to predict ovarian responses to stimulation. The response spectrum was categorized using ELISA assay formats, establishing pragmatic guideline concentrations values of critical points (Nelson et al, 2007), with values defining AMH < 5 pmol/L as 'reduced' response, and > 15pmol/L for 'excessive' response. However, these original assays showed high inter-laboratory variability and sample storage problems. Two automated assays are now in use (Roche® Elecsys and Beckman Coulter® Access2) which use the same antibodies, but deploy different technologies and calibration. The comparability of these assays needs to be established for clinical use and the critical values need to be re-established.

**Content:** Objective multicentre comparative cohort study of AMH results reported from 8 successive monthly distributions of 40 serum samples were sent to contributing laboratories running either the Access2 or the Elecsys assays within the UK national quality assurance (UK NEQAS) accreditation scheme. The published results from contributing laboratories were analysed to assess variability and concentrations.

**Outcomes:** The reported median concentrations ranged from 0.9 pmol/L to 30 pmol/L, and there was close agreement between the two assay methods ( $R^2$  value = 0.971). The absolute concentrations were determined as: Elecsys =  $0.973 \times$  Access2 + 0.69. The variance between laboratories was low throughout the series (<5.5% for both assay methods) and there was no difference between the platforms. The critical values have been re-evaluated by examination of the age-related changes in AMH.

**Discussion:** Both the Roche® and Beckman Coulter® platforms give consistent, reproducible and comparable AMH results across the normal concentration range. This should result in a return of clinicians' confidence in the method of assessing ovarian reserve.

**104** Gonadotrophin secretion is a useful adjunct in the diagnosis of patients with hyperprolactinaemia

**Abbara Ali; Clarke Sophie; Nesbitt Alexander; Ali Sabreen; Comminos Alexander; Hatfield Emma; Martin Niamh; Sam Amir; Meeran Karim; Dhillon Waljit**

Imperial College London

**Aims/Objectives:** Hyperprolactinaemia accounts for 1 in 7 patients presenting with amenorrhoea. Recent data suggests that prolactin acts at the hypothalamus to reduce GnRH-pulsatility. Conditions in which GnRH-pulsatility is reduced, such as Hypothalamic Amenorrhoea, favour FSH over LH

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secretion from the pituitary gland. We examined gonadotrophin secretion in hyperprolactinaemic patients as a surrogate marker of GnRH-pulsatility.

**Content:** A retrospective analysis of gonadotrophin secretion in patients with hyperprolactinaemia over the gender-specific reference range during 2012-2015 was performed.

**Outcomes:** Of 470 patient records reviewed, 275 (Female 210, Male 65) were identified to have a raised serum monomeric prolactin level concomitant with serum gonadotrophin levels. Frequent diagnoses included Microprolactinoma (n=80), Macroprolactinoma (n=46), Non-Functioning Macroadenoma (NFA; n=72), Drug-Induced Hyperprolactinaemia (DIH; n=22) and PCOS (n=15).

**Discussion:** In PCOS, LH-predominant secretion was observed consistent with increased GnRH-pulsatility (FSH 4.0iU/L, LH 7.2iU/L, FSH-LH -3.2iU/L). By contrast in DIH, FSH-predominant secretion was observed, consistent with reduced GnRH-pulsatility (FSH 5.5iU/L, LH 3.4iU/L, FSH-LH +2.1iU/L; FSH-LH P=0.0006 vs PCOS).

In patients with prolactinoma, there was a progressive increase in 'FSH-LH' differential with increasing serum prolactin level, consistent with a progressive fall in GnRH-pulsatility. However, both FSH and LH secretion were reduced in patients with prolactin levels >4000mU/L, consistent with direct pituitary gonadotroph hypofunction in larger prolactinomas.

In patients with macroadenomas, NFAs were more frequently observed to have extremes of gonadotrophin secretion when compared with macroprolactinomas. This observation was not accounted for by effects of prolactin on GnRH-pulsatility and was more consistent with intrinsic pituitary autonomous gonadotrophin secretion in NFA (100% of FSH+LH >15iU/L had NFA vs 47% with FSH+LH <5iU/L).

**Relevance/Impact:** Raised prolactin acts at the level of the hypothalamus to reduced GnRH pulsatility, and leads to FSH-predominant secretion. In larger prolactinomas, gonadotrophin secretion is reduced due to direct pituitary gonadotroph hypofunction. These data are informative to the clinician interpreting serum gonadotrophin levels in the context of hyperprolactinaemia.

### 105 Can electronic witnessing with RFID tags safeguard patients and mitigate risk in an IVF laboratory?

**Townsend Nicola; Ah-Moye Michael; Bunyan Kelly; Engley Stephanie; Evans Deborah; Glover Lynne; McClure Alistair; Ogutu David; Richardson Lucy**  
Herts and Essex Fertility Centre

**Introduction:** Laboratory errors due to inadequate witnessing can have catastrophic consequences. An electronic witnessing system can eliminate involuntary automaticity and safeguard patients by mitigating the risk of misidentification. Over one million embryos worldwide have been securely monitored with the Research Instruments electronic witness system. Uniquely assigned RFID tags are secured to cultureware containing embryos and gametes. The RFID tags are detected by a reader integrated into the workstation to provide an accurate witnessing record.

**Method:** The RI witness system was installed in the laboratory in 2008 and has successfully assigned 61965 RFID tags and overseen 92543 witness points. The reliability and safety of RI Witness was determined by the retrospective analysis of recorded mismatches and administrator interventions.

**Results:** 154 separate mismatches were documented and categorised as true, primary or secondary mismatches. One true mismatch (0.001% of witness points) due to an embryologist inadvertently transferring two culture dishes to a workstation was successfully intervened. Primary mismatches were identified as the presence of culture dishes or tubes from more than one patient in the workstation. 7.8% were attributed to the presence of a discarded or empty culture dish in the workstation and 6.5% resulted from the cross over of sperm samples awaiting centrifugation. In total 131 secondary mismatches were documented and attributed to failure to remove the witness card from the reader after embryo transfer (44.2%), training errors (11.0%), pre assigned tags (10.4%), donation cycles (9.1%), proximity errors (8.4%) and software failure (1.9%).

**Intervention** by an authorised administrator was required on 171 occasions. Administrator intervention was attributed to the incorrect assignment of the RFID tag (42.1%), clinical decisions (22.8%), systems failure (15.8%), flow chart configuration errors (11.7%), FER cycles (6.4%) and training (1.2%).

**Conclusion:** Electronic witnessing is a reliable system to safeguard patients, minimise distractions to personnel and improve laboratory efficiency.

### 106 A study of whether gradually increasing VOC levels recorded within an IVF laboratory during a period of refurbishment impacts on success rates

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<sup>1</sup>CARE Fertility Manchester; <sup>2</sup>CARE Fertility

**Aims:** Volatile organic compounds (VOCs) are hydrocarbon-based compounds, released by some construction materials. Studies have shown that increasing VOC levels is associated with poor embryo development and reduced pregnancy rates. An extensive refurbishment project is currently underway at our clinic. Gradually increasing VOC levels have been recorded (average level 1.0mg/m<sup>3</sup> to 5.8mg/m<sup>3</sup> over 3 months). To minimise risk, the majority of embryos are cultured in Embryoscope and Miri incubators, with carbon filters for VOC removal, and CODA towers installed. The aim of this study was to determine whether the increasing VOC levels affected success rates.

**Content:** An assessment of correlation between VOC levels and indicators of success will be provided.

**Relevance:** Identification of the potential effects of elevated background VOC levels will help to build knowledge of the impacts of undergoing refurbishment works whilst an IVF clinic operates.

**Outcomes:** A retrospective analysis of ICSI and IVF cycles was performed, with a direct comparison of 127 cycles between two months with the greatest difference in VOC levels. There was no significant difference in the rates of fertilisation, cleavage or hCG/ET for either ICSI (p=0.5600, p=0.3615, p=1.0000, respectively) or IVF (p=0.4139, p=0.1397, p=0.7224). There

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was no difference in the proportion of top grade ICSI embryos cultured in the Embryoscope alone ( $p=0.0946$ ). However, when combining all incubator results, there was a lower proportion at higher VOC levels ( $p=0.0424$ ). Too few embryos were cultured in standard incubators to analyse alone.

**Discussion:** The increasing VOC levels do not appear to have impacted upon success rates and the Embryoscope appears to minimise the effects on embryo grading. However, the outcome of many cycles where VOC levels were highest, is outstanding. VOC levels will be monitored and ongoing results presented in full.

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### 107 An evaluation of the role of early time-lapse embryo assessment in embryo selection

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<sup>1</sup>Southern Health & Social Care Trust; <sup>2</sup>Belfast Heath & Social Care Trust, Northern Ireland

**Background:** Embryo selection remains one of the contentious areas of assisted reproduction. It is believed that improved selection of the "best" embryo should significantly improve pregnancy rates. Recently, various techniques, including EEVAO based on timelapse imagery and assessment of early embryo division patterns, have been introduced in an endeavour to address this issue. However, published evaluation has been limited.

**Aims:**

- To determine the ability of EEVA to predict which embryos will progress to the blastocyst stage
- To determine if there is a correlation between EEVA analysis and pregnancy rate after blastocyst transfer in IVF/ICSI.

**Methods:**

- 488 embryos from 111 IVF/ICSI treatment cycles were analysed by EEVA. The ultimate fate of these embryos in terms of progression to blastocyst stage was then determined.
- 53 single blastocyst transfers were analysed and the pregnancy outcome determined. Retrospectively, the EEVA category of the blastocysts transferred was compared between those blastocyst transfers that resulted in a pregnancy and those that did not.
- Groups were then compared using Chi-square statistical analysis

**Results:**

- There was a significant correlation between EEVA grade and both blastocyst formation and blastocyst grade, ( $P < 0.001$ ).
- 23.5% of embryos in the top grade of EEVA analysis failed to reach the blastocyst stage
- A further 35.9% of embryos in the top grade of EEVA analysis failed to produce a high quality blastocyst, (Grades 5AA, 4AA, 3AA, and 3-5 AB, BA & BB)
- There was no statistically significant correlation between EEVA grade and blastocyst transfer pregnancy ( $P=0.125$ )

**Conclusions:**

- Whilst EEVA analysis is positively correlated with blastocyst formation and grade, the correlation is not sufficiently strong to guarantee embryo progression to blastocyst
- No link was found between EEVA grade and pregnancy in this analysis, bringing the use of EEVA into question. However, this finding will require further analysis on a larger scale to confirm

1 Kirkegaard K. (2015) Choosing the best embryo by time lapse versus standard morphology. *Fertil Steril* 103, 323-32

### 108 Comparison of human embryo development in two different time lapse incubation systems

**Dezi Nuria; Sader Abir; Besi Despoina; Jansa Perez Marta; Abdo Dima; Trew Geoffrey; Lavery Stuart**  
*IVF Hammersmith, London*

**Aims:** To compare the development of embryos derived from sibling oocytes injected by ICSI and cultured in two different time lapse incubators. The primary outcomes were: fertilisation rate, embryo quality on day3 and 5, blastocyst formation and freezing rate. Morphokinetic parameters were also analysed and compared.

**Introduction:** Various time lapse systems are currently available in the market, with the Embryoscope® (Vitrolife) being the most widely used. A new time lapse incubator (GERI-GeneaBIOMEDX) has recently been introduced in our laboratory practice. This incubator allows for microwell group culture of up to 16 embryos, while embryos in the Embryoscope® are individually cultured. In the GERI each dish is kept in a separate compartment, therefore the introduction or removal of other dishes does not disrupt the culture conditions of others, as it does for the Embryoscope®.

**Methods:** 11 patients with more than 10 oocytes available for injection were included and sibling oocytes were split between Embryoscope® (76 injected oocytes) and GERI (71 injected oocytes) immediately after ICSI. The embryos were then cultured in 1-step SAGE-ORIGIO media for up to 6 days. The gas composition was the same in both incubators (6% CO<sub>2</sub>, 5% O<sub>2</sub>).

**Results:** There were no statistically significant differences in fertilisation rate, embryo quality, blastocyst formation and freezing rates. Most morphokinetic parameters for both groups were comparable, apart from tPB2 and tPNa. Embryos in GERI reached these 2 stages significantly faster than embryos in Embryoscope® (tPB2: 3.05vs3.94 ( $p=0.0000015$ ); tPNa: 7.24vs8.37 ( $p=0.001188$ )).

**Conclusions:** The GERI supports embryonic development as effectively as the Embryoscope®. The differences observed in



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the timings of PB extrusion and PN appearance could be due to the paracrine effect that the embryos are exposed to in the GERI dish and for the more stable conditions provided by the GERI. Further data is required to confirm these preliminary findings.

### 109 Reverse annotation to better assess excluded material (EM): Cell or fragment?

**Derrick Ranya<sup>1</sup>; Hickman Cristina<sup>2</sup>; Oliana Oriol<sup>2</sup>; Wilkinson Thomas<sup>2</sup>; Gwinnett Danielle<sup>2</sup>; Rattos Annabel<sup>2</sup>; Christiansen Sandy<sup>2</sup>; Abramov Benjamin<sup>2</sup>; Carby Anna<sup>2</sup>; Lavery Stuart<sup>3</sup>**

<sup>1</sup>Imperial College; <sup>2</sup>Boston Place Clinic; <sup>3</sup>The Fertility Partnership

**Aims/Objectives:** The study objective was to clarify the difference and clinical relevance between two EMs: cells and fragments. EM was defined as any non-polar body, membrane bound structure seen as a separate entity to the blastocyst. EM characteristics analysed included; nucleation, membrane wobbling, cytoplasmic volume, dividing, motility and Oliana strings (OS).

**Content:** Time-lapse imagery from 790 blastocysts were analysed; 595 were of known implantation diagnosis (KID) and 212 of known ploidy. EM was identified around blastulation, tracked in reverse until its origin and analysed for the characteristics above. If EM was originally regarded as a cell, annotations were altered and compared with initial annotations regarding clinical outcome.

**Relevance/Impact:** EM is often observed at blastocyst transfer. Current annotation methods make it difficult to differentiate EM as a cell or fragment. The diagnostic sensitivity and specificity of morphokinetic models for the prediction of embryo viability relies on accurate distinctions between these. This novel assessment methodology has not been previously discussed.

**Outcomes:** Although EM was associated with reduced implantation potential (EM:21%,92/429, without EM:35%,58/166;p<0.001), particularly when 20% or more of the cytoplasmic volume was excluded (<20%:23%,86/369, >20%:10%,6/60;p<0.05), there was no significant impact from ploidy. EM was mostly excluded during the first cell division (44%,250/569) and were mostly anuclear (70%,399/569). Nuclear EM were less likely (p<0.001) to display other features associated with fragments rather than cells (OS, membrane wobbling, increased motility, <40um). 15% of embryos with EM required reannotation. Reannotation highlighted more KID negative embryos as 'bad', compared to the original annotation (25%vs48%,n=52;p<0.05).

**Discussion:** Ploidy and implantation data suggest that assessing EM for nuclearity, strings, membrane wobbling, increased motility and size(<40um) are useful in differentiating between cells and fragments. Reverse annotation is a novel method that improves this distinction, thus improving the efficacy of time-lapse technology in predicting embryo viability.

### 110 Patient specific dissociation of zona pellucida observed in time-lapse culture

**Moran Susan; Gregoire Rachel**  
Glasgow Royal Infirmary

The Zona Pellucida (ZP) is a mesh-like extracellular matrix composed of glycoproteins secreted by the oocyte during follicular development. It protects the embryo and ensures cell-

cell contact prior to implantation. ZP1 glycoprotein is essential for ZP structural integrity<sup>2</sup>. Mouse studies suggest that a lack of ZP1 can cause inclusion of granulosa cells in the Perivitelline Space (PVS) and loose ZP appearance due to abnormal ZP formation<sup>3</sup>. Literature on ZP integrity in humans is limited.

A 36 year old patient with a history of miscarriage underwent a third cycle of ICSI. Eleven oocytes were collected with PVS debris observed in 6/11. Six oocytes were injected, four with PVS debris observed. Four oocytes fertilised, all containing PVS debris. At fertilisation check, one zygote exhibited signs of zona dissociation, with ZP spreading into the culture well. Dissociation increased with culture duration, and by day 3 two further zonae had started to dissociate.

Embryo development appeared unaffected and double embryo transfer was performed on day 4 to reduce risk of blastomere segregation prior to transfer. One blastocyst was cryopreserved on day 5. hCG test was negative.

Zona Pellucida (ZP) dissociation has not been observed in our laboratory and appeared to be a recurring dysmorphism specific to this patient. Retrospective analysis of embryos from the patient's first cycle highlighted initial signs of zona dissociation in one embryo transferred on day 3. Oocytes injected in a second cycle did not illustrate signs of PVS debris or zona dissociation.

PVS debris has been linked to increased doses of exogenous gonadotrophin<sup>1</sup>, which may be the cause in this patient since gonadotrophin dose was increased in each cycle as did incidence of PVS debris. However, here the debris appeared cellular and was associated with zona dissociation, suggesting the possible inclusion of granulosa cells linked with abnormal ZP formation.

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3. Rankin T, Talbot P, Lee E, Dean J. Abnormal zonae pellucidae in mice lacking ZP1 result in early embryonic loss. Development. 1999 Sep;126(17):3847-55.

### 111 Monozygotic twinning footage captured during time-lapse incubation

**Wilkinson Thomas<sup>1</sup>; Oliana Oriol<sup>1</sup>; Gwinnett Danielle<sup>1</sup>; Rattos Annabel<sup>1</sup>; Christiansen Sandy<sup>1</sup>; Abramov Benjamin<sup>1</sup>; Carby Anna<sup>1</sup>; Trew Geoffrey<sup>2</sup>; Lavery Stuart<sup>2</sup>; Hickman Cristina<sup>1</sup>**

<sup>1</sup>Boston Place Clinic, London; <sup>2</sup>The Fertility Partnership

**Aims/Objectives:** Descriptive case report of monozygotic twinning(MT) being identified during Time-Lapse incubation.

**Content:** 33 year old patient, fifth ICSI attempt, 9 oocytes collected, 7 fertilised normally, 6 blastulated: 2 transferred, 4 (including MT) cryopreserved at 139hpi. All embryos were cultured in the GERI. Morphokinetic parameters were compared between the MT embryo and sibling blastocysts (control).

**Relevance/Impact:** MT is a rare occurrence in-vivo (0.4% of all births), although reports suggest an increased frequency within births following IVF (0.9%). Reports of observed twinning before hatching are rare, and time-lapse observations are not

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published to date. This video footage could help clarify how totipotent cells interact as they differentiate into pluripotency.

**Outcomes:** This is the first MT case observed with time-lapse in our clinic out of 4470 embryos time-lapsed to date. The MT oocyte was oval, which may have contributed towards the twinning (reduced cell junction interaction). The MT embryo was ACE graded as 332, 833 and compacting on days 2, 3 and 4 respectively. On days 5 and 6, Blastocyst 1 was graded as cavitating and 3BC, whilst Blastocyst 2 was graded as compacting and 3CC. Both blastocysts collapsed and re-expanded as they competed for limited space (four collapses for Blastocyst 1; three for Blastocyst 2). The slower blastocyst recruited less blastomeres during compaction leading to a smaller inner cell mass and less cells in the trophoctoderm. Both inner cell masses formed at mirror positions to each other. The MT embryo was observed to have a slower cell division.

(t2=32.5, t3=43, t4=46, t5=57, t8=80, tC1=88, tM1=94, tsB1=97, tB1=121 hpi; tC2=94, tM2=103, tsB2=107, tB2=126 hpi) compared to control, although the pace of embryo development seemed comparable.

**Discussion:** The embryo was cryopreserved so that its implantation potential is not yet known. GERI Time-lapse incubation is a useful tool for observing embryo developmental features such as MT which would otherwise have been missed using conventional incubation.

### 112 GERI vs Embryoscope; embryo utilisation and morphokinetic markers

**Finch Katie; Rogers Shaun; Florek Agnieszka**  
*Gennet - City Fertility, London*

**Aims/objectives:** To compare cleavage, utilisation rates and morphokinetic markers of sibling embryos cultured in the GERI and EmbryoScope timelapse incubators.

**Content:** It is widely agreed that Time Lapse offers the embryology lab a detailed analysis tool for embryo selection with several options available on the market. This study looks at two of the leading competitors; the Embryoscope® by Vitrolife and the GERI by Genea and compares development and utilisation rates for each. Furthermore, morphokinetic markers were assessed in each system allowing an in-depth comparison of the two systems from a time lapse point of view as well as the more traditional developmental values.

**Relevance/Impact:** Sibling embryos were cultured in both the GERI and EmbryoScope timelapse incubators over a three-month trial period. In each cohort we assessed day 2 cleavage rate, day 3 cleavage rate, blastocyst formation rate and embryo utilisation rate. With respect to morphokinetics, we assessed key cleavage time points (t2, t3, t4, t5, t8) and the second cell cycle (cc2) and the second synchrony (s2).

**Outcomes:** No significant difference was seen in the t2-t5 cleavage divisions in either cohort. t8 occurred later in the GERI compared to the Embryoscope. cc2 was almost identical between the two groups whilst s2 was extended in the GERI.

**Discussion:** This study highlights the necessity to consider factors other than classic developmental markers when implementing new systems. Whilst no significant difference was noted between the two systems in this case, it is important that each system is evaluated in its own right, creating embryo selection algorithms specific to both individual clinics and individual time lapse systems.

### 113 EmbryoScope IQC

**Norris Elizabeth; Thompson Karen**  
*Leeds Centre For Reproductive Medicine*

The EmbryoScope was designed to aid embryo selection using time-lapse imaging and also encompasses the ability for undisturbed culture. Assessment of embryo development and subsequent embryo selection is still performed by embryologists and is therefore subject to variability. Accuracy and consistency depend on variability within (intra-observer variability) and between (inter-observer variability) embryologists and this is monitored using Internal Quality Control (IQC). EmbryoScope IQC is performed bimonthly in our laboratory. Two embryos are selected and annotated by each embryologist one month, then for the next IQC one embryo is repeated and a new embryo is selected, allowing assessment of both intra and inter observer variability. In order to evaluate our current practice, I have analysed IQC data collected over the past 18 months.

Annotations carried out on 12 embryos by 8 embryologists were analysed to assess inter-observer variability and intra-observer variability was assessed by analysing one embryologist repeated annotations. Specifically tPNf, t2, t3, t4, t5 and t8 were analysed as this data is used to calculate the KIDScore on Day 3, which is the model currently used to aid embryo selection in our laboratory. Intra and inter-observer variability were assessed by calculating the intra-class correlation coefficient (ICC) for the specific time points. At least moderate agreement (ICC 0.5 – 0.6) was found between embryologists for all assessed time points, with agreement ranging from 0.6191 – 0.9913. Almost perfect agreement (ICC >0.8) was found when one embryologist repeated the annotations, with agreement ranging from 0.9933 – 1.

Inter-observer variability could be caused by embryologists with differing levels of experience participating in the IQC and also the quality of the embryos chosen to annotate. The overall agreement of annotations between embryologists is good and the laboratory can be confident that the embryologists are assessing and subsequently selecting embryos consistently.

### 114 EmbryoScope® Vs PLANER benchtop incubator BT37: Comparison of pregnancy and cryopreservation rates

**Rathod Kunal; DiazDiaz Montana; Purohit Prashant; Modarres Maryam; Gibbons Rachel; Mureil Rios Lourdes; Hamoda Haitham**  
*King's College Hospital, London.*

**Aims:** To compare clinical pregnancy and freezing rates between: 5% O2 tension PLANER benchtop incubator BT37PLICS (ORIGIO®) and time-lapse - EmbryoScope® incubator (Fertilitech).

**Methods:** Retrospective analysis of cases between January and September 2015 at a tertiary referral centre. Depending on the incubator used for embryo culture, patients were divided into: (Group A) 5% O2 tension PLANER benchtop incubator BT37PLICS and (Group B) Time-lapse - EmbryoScope®. Freeze all embryos patients due to cancer or OHSS, social reasons, infectious patients and patients undergoing a surgical sperm collection were excluded from the study.



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**Outcomes:** Total number of patients in group A and group B were 234 and 261 respectively. A total of 116 (49.5%) of women in group A had day 5(blastocyst) transfer, compared to 150 (57.4%) women in group B, ( $P=0.07$ ). A total of 96 (41%) women in group A met the criteria single embryo transfer [SET], compared to 178 (68.1%) in group B ( $P=0.03$ ). Clinical pregnancy rates in Group A and group B were 96 (41%) and 127 (48.6%), respectively, ( $P=0.08$ ). Percentage of patients who had blastocyst frozen on Day 5 were 56 (23.9%) and 106 (40.6%) for groups A and B, respectively ( $P<0.01$ ). In  $<35$  years, 33 (30%) women in group A had a singleton pregnancy compared to 58 (43%) women in group B ( $P=0.03$ ), while 6 (5.4%) women in group A had multiple pregnancy, compared to 3 (2.2%) women in group B ( $P=0.18$ ). In  $>35$  years, 29 (23.3%) women in group A had a singleton pregnancy compared to 31 (24%) women in group B ( $P=0.84$ ), while 8 (6.45%) women in group A had multiple pregnancy, compared to 9 (7%) women in group B ( $P=0.84$ ).

**Conclusion:** In our study, uninterrupted culture of embryos and the use of quantitative morpho kinetic parameters for selecting superior embryos using EmbryoScope® resulted in an improvement in our embryo progression to blastocyst, significantly improved clinical pregnancy rates in women under 35 years of age and significantly improved freezing rates.

### 115 Development of a clinic-specific Day 5 embryo selection model using the EmbryoScope® time-lapse system

**Townson Sarah-Louise<sup>1</sup>; Meaney Caitriona<sup>2</sup>; Cutting Rachel<sup>2</sup>**

<sup>1</sup>The University of Sheffield; <sup>2</sup>Jessop Fertility

**Background:** HFEA multiple birth rate targets and the acceptance that eSET reduces risks to mother and child has led to the necessity to improve embryo selection methods. Simple morphological analysis can now be improved upon by Time-lapse imaging: Embryo selection tool which can create algorithms which score embryos according to cleavage timings and morphological criteria (morphokinetics).

**Aim:** This study's aim was to analyse morphokinetic parameters from our centre's own dataset and produce a Day 5 EmbryoScope® model based on the findings.

**Methodology:** The identification of significant morphokinetic parameters was performed through statistical comparison of 262 patient embryos with both positive and negative known implantation data (KID) using Fisher's exact tests and binary regression analyses.

**Results:** A Day 5 additive model was established and showed 62% predictive for positive implantation. Statistical analysis found that deducting PN fading time (tPNf) from the cleavage times showed higher significance. Optimal time ranges for the significant parameters were established which included time to (t) 2 cell t2-tPNf ( $P=0.041$ ), 5 cell t5-tPNf ( $P=0.014$ ), 8 cell t8-tPNf ( $P=0.044$ ), morula tM-tPNf ( $P=0.0008$ ), blastocyst tB-tPNf ( $P=0.008$ ). Furthermore, cc2a (t3-t2) and s2 (t4-t3) were incorporated within the model due to literature suggestions, although they were not statistically significant in this dataset. Negative predictors such as multinucleation, irregular and reverse cleavages were also negatively weighted or included for information purposes.

**Impact and Future Research:** The model has been implemented into the centre's EmbryoScope® and is currently being validated. As 60% of embryo transfers are carried out on day 5, this analysis based on the centres own patient data and culture conditions is of value as the model shows a statistically 'good' chance of selecting the embryos with the best implantation potential. Patient data will continue to be collected thus increasing the cohort enabling improvement and re-defining of the current selection parameters.

### 116 External validation of a new embryo score algorithm

**Gibbons Rachel<sup>1</sup>; Modarres Maryam<sup>1</sup>; Hoo William (Wee-Liak)<sup>1</sup>; Newton Sarah<sup>1</sup>; Rathod Kunal<sup>1</sup>; Purohit Prashant<sup>1</sup>; Barrie Amy<sup>2</sup>; Hamoda Haitham<sup>1</sup>**

<sup>1</sup>King's College Hospital; <sup>2</sup>Liverpool Hewitt Fertility Centre, Liverpool

**Aims:** To externally validate the diagnostic performance of a new Embryo Score Algorithm (ESA) derived from our partner fertility unit.

**Content:** Retrospective study on 614 embryos of known implantation outcome, between January and June 2016. Embryos were transferred based on embryo morphology and development. A new ESA, derived and prospectively validated at our partner fertility centre, was retrospectively tested in our patient population. The new ESA is a hierarchical model of three levels (Primary:  $s2 \leq 1$  hour, Secondary:  $10.9 \leq cc3 \leq 13.3$ , Tertiary:  $46.0 \leq t5 \leq 52.9$ ). The ESA results graded each embryo between A+ and D-.

**Impact:** With the introduction of time-lapse technology, several authors have proposed the use of kinetic markers to improve embryo selection. This led to the formulation of various algorithms based on the timings of embryonic cleavage. Although, many such algorithms have been proposed, there has been a paucity of algorithms that have been externally validated.

**Outcomes:** Embryos were classified as A+ to D- using the ESA. In embryos with positive implantation, 48/118 (40.7%) of embryos had an ESA grade A, 51 (43.2%) embryos graded B, 8 (6.8%) graded C and 11 (9.3%) graded D. Embryos with an ESA score of C- and above (A+ to C-) had a significantly higher implantation rate when compared to embryos that scored below C- (D+ to D-), 34.4% and 16.2% respectively ( $p < 0.001$ ). However, there was no statistical significance between the grading A to C ( $p = 0.965$ ).

**Discussion:** On external validation we showed that the ESA algorithm could predict embryos with a higher implantation potential, however there are limitations in its ability to improve embryo selection when ESA score is above C-. The use of other kinetic markers or in combination with standard morphological grading may be necessary to improve this ESA.



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### 117 Blastocyst succession rate derived from regular, synchronous cleavage of embryonic cells determined by real time imaging

**Simpson Kayleigh; Henderson Ann**

*Nuffield Health, Glasgow Hospital, Assisted Conception Services*

**Aims/Objectives:** I identified whether synchronicity has an effect on early cleavage rate in determining a successful blastocyst outcome, with the aid of time-lapse technology.

**Content:** A retrospective study using time-lapse imaging of embryos cultured in Embryoscope. The embryos were divided into three groups based on their cleavage patterns; a synchronous (1-2-4 cells) group, an asynchronous (1-2-3 cells group) and an undetermined group; in which cell cleavage was difficult to determine.

**Outcomes:** A higher occurrence of embryos with  $\geq 10\%$  fragmentation was seen in the asynchronous group compared to the synchronous group ( $P=0.0094$ ), indicating that asynchronicity may be associated with an increased incidence of fragmentation. Multinucleation and blastomere heterogeneity had no significant effect on blastocyst formation rate ( $P=0.1335$  and  $P=0.2555$  respectively).

**Discussion:** The identification and selection of embryos in vitro that demonstrate the uppermost developmental potential remains a difficult task in assisted conception. Embryo fragmentation, multinucleation and blastomere heterogeneity are known to be determining factors for selecting the most viable embryo to transfer. An increased incident rate of more than 10% fragmentation in embryos that divide asynchronously may indicate inferior blastocyst development.

**Relevance:** The introduction of time lapse imaging has provided an insight into various patterns of embryo development. The use of Embryoscope to identify synchronicity, fragmentation, multinucleation and blastomere heterogeneity as embryo quality markers allow embryologists to accurately depict the 'optimal' blastocyst for embryo transfer.

### 118 Does group embryo culture improve embryo development in single step media?

**Hughes Trisha<sup>1</sup>; Jansa Perez Marta<sup>2</sup>; Abdo Dima<sup>2</sup>; Vlismas Antonios<sup>2</sup>; Lavery Stuart<sup>2</sup>; Trew Geoffrey<sup>2</sup>**

*<sup>1</sup>IVF Hammersmith, Imperial College London; <sup>2</sup>IVF Hammersmith*

**Aims:** To assess if there is any difference in embryo development between embryos that are cultured in a group or individually and cultured either in time-lapse or standard mini-incubators, while using single step media. **Introduction:** Embryo culture systems have a significant effect on embryo development. There is contradicting evidence on the advantages of group versus individual culture. Group culture may have the benefits of embryotrophic paracrine factors but individual culture allows for traceability. In addition, time-lapse adds the ability to trace all morphokinetic parameters. We compared embryo development parameters of these three embryo culture systems.

**Methods:** We conducted a pilot prospective study of 203 embryos from 13 couples undergoing ICSI or IVF over a 3 month period. Embryos were cultured in Sage 1- Step™ media and

assigned to either group, individual or time-lapse culture. The parameters analysed were days 3 and 5 (D3 and D5) embryo quality, as well as blastocyst formation, transfer, cryopreservation and utilisation rates. Chi-squared tests were performed with multiple comparison adjustments. A p value of  $<0.0083$  for three-way comparisons was considered to be significant.

**Results:** There was no statistical difference between the arms of the study for fertilisation rate, D3 and D5 quality, blastocyst formation, cryopreservation and utilisation rates. However, on day 5 there was a non-significant trend for a higher proportion of good and average quality embryos in the Embryoscope™. There was no significant difference between the three arms of the study in final embryo quality for D5 and D6. The proportion of embryos transferred from the Embryoscope™ was significantly higher compared to the other two arms ( $p=0.0069$ ).

**Conclusions:** These three culture systems may not have a significant impact on preimplantation development parameters, which suggests comparable effectiveness in the use of group culture with Sage 1- Step™ media for the first time.

### 119 Pregnancy outcomes following fresh or vitrified embryo transfer of non-top quality embryos. Should we change what we freeze?

**Beaton Catherine; Gregoire Rachel**

*Assisted Conception Service, Glasgow Royal Infirmary*

**Aims/Objectives:** Development of a Multiple Birth Minimisation Strategy (2014) to reduce our multiple pregnancies from 24% has encouraged discussion regarding embryo suitability for vitrification. As a growing team, internal discrepancies regarding classification of 'top quality blastocysts' (TQB) and 'non-top quality blastocysts' (NTQB) have become apparent. Historically, vitrification was reserved for TQB i.e. inner cell mass (ICM) and trophoctoderm (TE)  $\leq$  Grade B. Literature on the implantation potential of NTQB after vitrification is limited.

The aim of this retrospective study was to investigate clinical outcomes of fresh ET and vitrified/warmed ET with TQB versus NTQB.

**Content:** Fresh (305) and vitrified/warmed (131) Day 5 single ETs were compared, utilising TQB and NTQB (i.e. morula/cavitating morula/blastocysts with ICM/ TE maximum Grade C) over a 1 year period (July 2015-2016).

The outcomes were positive pregnancy test (+hCG) and clinical pregnancy rate (CPR).

**Relevance/Impact:** The results presented should encourage review of embryo suitability for vitrification.

**Outcomes:** After fresh ET of TQB, +hCG and cPR rates were 60% and 49% respectively. After fresh ET of NTQB, +hCG and cPR rates were 54% and 39%.

After vitrified/warmed ET of TQB, +hCG and cPR rates were 43% and 23% respectively.

After vitrified/warmed ET of NTQB, +hCG and cPR rates were 45% and 32%.

**Discussion:** These data show no statistical significant difference in +hCG or CPR following transfer of TQB compared with NTQB in either fresh or vitrified/warmed ET.

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These results support a review of criteria for vitrification to include NTQB, and suggest a requirement for clear definition of TQB and NTQB to ensure those patients at risk of multiple pregnancies can be clearly identified.

These data further support the requirement for routine performance review for those performing embryo grading to improve internal quality control, especially important as teams grow and incorporate expertise from other clinics.

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### 120 Use of Thermocoins in laboratory quality control temperature monitoring

**Benn Allison; Armstrong Ellen; Jenner Lucy; Campbell Alison**

*CARE Fertility Nottingham*

**Aim/Objective:** Temperature validation is an important part of laboratory quality control (QC) ensuring that essential equipment is functioning within limits that are optimal. Previously temperature monitoring was performed using thermocouple probes but these were found to be inconsistent and time consuming to use. In an attempt to find a reliable method, Thermocoins (Thermodata) provided by Mitrone Healthcare LTD were selected to perform our regular QC temperature monitoring.

**Content:** Thermocoins are small temperature monitoring devices, calibrated annually to  $\pm 0.1^\circ\text{C}$ , which allow configuration of logging interval, initiation time and temperature limits, to be customised to specified equipment use.

To mimic practice, monitoring of incubators and heated stages were performed with thermocoins placed in mineral oil filled dishes pre-warmed overnight, which were moved to defined locations at test initiation. Thermocoins in empty dishes were used for monitoring fridges. Recording occurred for a time period reflective of equipment use and the logged data analysed using Loggixther Thermodata IVF, an online data downloading and analysis system.

**Relevance/Impact:** QC allows alteration of the set temperature of temperature variable equipment to ensure the acceptable limits are being achieved.

**Outcome:** Monitoring resulted in optimisation and adjustment of the set temperature of tested equipment. Detailed temperature mapping of one flowhood eluded that only a particular area maintained acceptable temperatures. Thus, a safe zone was marked as fit for use. Similarly a fridge shelf exceeded the acceptable limit and was deemed unfit for use.

**Discussion:** Thermocoins allow for reliable, robust temperature monitoring which is more reflective of laboratory practice than the use of thermocouple probes, as they can be left in a stable position, mimicking the location of eggs/embryos during procedures on the heated stage. Overall they are easier to use and less time consuming, as they record autonomously and can be reviewed regularly.

### 121 Determining a sample size for storage tank audit

**Collins Daniel; Gregoire Rachel**

*ACS Suite, Glasgow Royal Infirmary*

**Aims/Objectives:** The ACS unit has more than 15 000 samples from over 3400 patients in storage. As part of the HFEA licence requirements, stored samples must be reviewed at least every two years. Auditing an entire population (census) of this size places a significant burden on workload management and increases risk to the stored material. We set out to derive the appropriate number for a smaller sample population during the auditing process.

**Content:** The sampling size was determined using the method of Cochran (1963), to provide an appropriate number for audit. A confidence level of 95% was selected as a minimal threshold for the process.

**Relevance/Impact:** This approach can benefit many units that have large numbers of samples in storage; providing a workable sample size calculation for necessary auditing purposes.

**Outcomes:** From a population of 3400, the sample size for auditing purposes is 346 individuals with a 95% confidence level. With a proportional split of 63% sperm and 37% embryos, this yields a requirement for 218 sperm samples and 128 embryo/oocytes to be audited over the two-year period. An increase in confidence level to 99% would require a sampling size of 2822 individuals.

**Discussion:** The number of samples required for audit can be determined from the entire population using a statistical equation. The sample size value of 346, randomly sampled, from a population of 3400 with a 95% confidence level provides a workable solution to the issues of workload management and risk reduction during auditing schedules. Raising the confidence level to 99%, would require an audit of 2822 samples, and so diminish any advantage for workload and risk reduction.

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2. Fisher, RA. (1925) Statistical methods for research workers, Oliver and Boyd, Edinburgh, London,
3. Pearson, K. (1900) On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling, London,
4. Till, R. (1974) Statistical methods for the earth scientist : an introduction, Macmillan, London

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### 122 Vitrification versus slow freezing; a comparison in success rates between two techniques for the cryopreservation of blastocysts

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The ultimate goal of the cryopreservation of embryos is survival and viability of the embryos following thawing. Three important factors that determine the success of any cryopreservation technique are the cooling and warming rates of the embryos and the prevention of intracellular ice crystal formation.

The objective of this retrospective study was to evaluate the effectiveness of vitrification and slow freezing for the cryopreservation of blastocysts. The primary end points of this study were: the number of patients achieving a frozen embryo transfer, positive test rate, clinical pregnancy rate and biochemical loss rate of slow frozen-thawed blastocysts and frozen-warmed vitrified blastocysts.

The blastocysts were cryopreserved using vitrification or slow freezing techniques. Statistical analysis was performed using the Chi Squared Test where  $P < 0.05$  was considered to be statistically significant.

The number of patients achieving a frozen embryo transfer was significantly higher following the warming of vitrified blastocysts (95.96%) when compared to the thawing of slow frozen blastocysts (71.28%).

The number of patients achieving a positive test following the warming of vitrified blastocysts (51.01%) was higher when compared to the thawing of slow frozen blastocysts (45.63%), however this was not a significant difference.

The number of patients achieving a clinical pregnancy following the warming of vitrified blastocysts (38.42%) was significantly higher when compared to the thawing of slow frozen blastocysts (28.64%).

The biochemical loss rate following the warming of vitrified blastocysts (27.72%) was not significantly different when compared to the thawing of slow frozen blastocysts (37.23%).

These data demonstrate that vitrification is an efficient method for cryopreservation of blastocysts. Vitrification results in a significantly higher number of patients achieving a frozen embryo transfer, improved pregnancy rates and significantly improved clinical pregnancy rates when compared to the traditional slow freezing method.

### 123 A newly developed universal warming kit can be used to warm embryos previously vitrified in existing vitrification kits

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**Objective:** The aim of this study is to verify compatibility of a new universal warming kit (RapidWarm Omni) with existing vitrification kits.

**Content:** Mouse embryos at different developmental stages were vitrified using currently available kits for vitrification (RapidVit Cleave and RapidVit Blast) while for warming either the original kit (Control group: RapidWarm Cleave or RapidWarm Blast) or the new warming kit (test group: RapidWarm Omni) were used. Embryos were vitrified using Rapid-i at the 1-cell, 2-cell, morula or blastocyst stage. Three replicate tests were performed for each condition involving a total of 90 embryos per group.

**Relevance:** Vitrified embryos may be stored for several years prior to utilization. Therefore it may be necessary to use a different product with a somewhat different formulation when the embryos are to be warmed. Specifically for cryopreservation, this can have practical implications and potentially impacting survival and development rates. It is therefore important to know if such a change is compatible with previously used methods and products.

**Outcomes:** For 1-cell, 2-cell and morula stage embryos survival rates were 100, 100, and 100 % for the test group and 100, 100, 100 % for the control group respectively. After warming, blastocyst formation rates were respectively 100, 92, and 93 % for the test group and 100, 91 and 96 % for the control group. Cell counts of expanded blastocysts ranged between 118 and 125 cells for all groups. For blastocysts, survival and re-expansion rates were 100 and 100 % for the test group and 100 and 99 % for the control group respectively. No significant differences were observed.

**Discussion:** This study confirms that for certain product compositions, when considering certain principles about cryopreservation, warming of previously vitrified embryos is possible when using a universal kit for warming.

### 124 Cryostorage of gametes and embryos: Vapour versus liquid nitrogen tank

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**Aim:** To compare the cryopreservation efficacy between vapour and liquid nitrogen storage.

**Content:** Patients in a private IVF clinic with FET cycles had embryos stored in either vapour (MVE816-2T, upper or lower level) or liquid nitrogen (MVE47/11) storage. Both treatments had no difference with regards to patient age (proportion data age <38/38-39/40+: 58%/12%/30% vs 57%/12%/31%, respectively), embryo quality (proportion 3BB or above: 27/33=82% vs 31/49=63%) or number of embryos transferred (mean±standard deviation: 1.5±0.6 vs 1.5±0.6). Both treatments were retrospectively compared for capacity, temperature, pregnancy rate (urinary, BPR), clinical pregnancy rate (foetal heart, CPR), biochemical loss (BL) and miscarriage rate (MR).

**Relevance:** Traditionally, IVF clinics have stored gametes and embryos in liquid nitrogen vessels. Higher embryo utilisation rates, better cryopreservation methods and increased elective freezing and fertility preservation has led to a relative increase in embryos and gametes being stored, leading to spatial and logistical challenges. Vapour phase tanks have improved the footprint space required for cryostorage per sample, increasing



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the organisation of the cryostorage inventory. There is a need for increased publications demonstrating the efficacy of using vapour tanks compared to liquid nitrogen.

**Outcomes:** Vapour can store more samples per floor space compared to liquid storage (3380goblets/0.52m<sup>2</sup>=6500goblets/m<sup>2</sup> vs 150goblets/0.2m<sup>2</sup>=750goblets/m<sup>2</sup>). The temperature in the lower vapour (-196±0.1°C), upper vapour (-193±0.2°C) and liquid (-196±0.1°C) storages were within acceptable limits.

BPR (17/33=52% vs 18/49=37%), CPR (17/33=52% vs 18/49=37%), BL (4/23=17% vs 5/27=18.6%) and MR (2/23=9% vs 4/27=15%) were equivalent between vapour vs liquid storage respectively. BPR (14/23=61% vs 8/9=89%), CPR (10/23=43% vs 6/9=67%), BL (2/14=14% vs 2/8=25%) and MR (2/14=14% vs 0/8=0%) were equivalent between upper vs lower vapour storage respectively.

**Discussion:** The higher storage capacity and equivalent clinical outcome data from vapour phase compared to liquid nitrogen makes vapour phase storage an attractive alternative for IVF clinics with limited space.

### 125 Clinical pregnancy following the transfer of embryos twice frozen and thawed with the slow freezing method

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**Introduction:** Patients with three or more frozen cleavage embryos have the option to consider a conservative thaw, retaining some embryos in storage, or thawing more embryos for extended culture. This second strategy gives better clinical success per embryo transfer and greater opportunity to select the single best embryo from the cohort. However, following extended culture and transfer, good quality embryos can still be available. In these cases, embryo re-freezing is offered to patients who are counselled that the associated risks and implications are uncertain. Re-freezing was undertaken in 4% (6/165) of frozen embryo transfer (FET) cycles in 2015.

**Objective:** To review outcomes of re-frozen embryos, assess the efficacy of re-freezing and the clinical benefits of twice frozen-thawed embryo transfer.

**Case:** Following a live birth from an ICSI cycle, where a single cleavage embryo was transferred, a 33-year-old woman returned for a FET cycle. She had in storage three slow frozen day-2 cleavage embryos. She elected for blastocyst culture and consideration of another elective single embryo transfer. All embryos were thawed and developed into blastocysts. One blastocyst was transferred and the remaining two were re-frozen by slow freezing on day-5. This transfer resulted in a biochemical pregnancy only. In the next cycle, the remaining two blastocysts were thawed and transferred resulting in an ongoing singleton pregnancy.

**Relevance:** This strategy gives patients greater confidence to request the thawing of more embryos than required for transfer without jeopardising the fate of an individual embryo. An alternative strategy of 'conservative thaw' may entail more treatment cycles, is less clinically effective and more costly.

**Conclusion:** Embryos cryopreserved by the slow freezing method can withstand a second freeze and thaw, and be capable of implantation. If supernumerary good quality embryos are available for re-freezing after FET, these may be cryopreserved again for a future transfer.

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2. Daneshmand, S.T., et al, 2012. Twice-frozen embryos have implantation potential similar to once-frozen embryos. Fertil Steril. 98(3): S128
3. Estes, S.J., et al, 2003. Successful pregnancy resulting from cryopreserved pronuclear and cleaved embryos thawed and cultured to blastocysts, refrozen and transferred. A case report. J Reprod Med. 48: pp. 46-48
4. Koch, J., et al, 2011. Twice-frozen embryos are no detriment to pregnancy success: a retrospective comparative study. Fertil Steril. 96(1): pp. 58-62
5. Kumamoto, Y., et al., 2009. The efficacy of the transfer of twice frozen-thawed embryos with the vitrification method. Fertil Steril. 91: pp. 383-386
6. Murakami, M., et al. 2011. Perinatal outcome of twice-frozen-thawed embryo transfers: a clinical follow-up study. Fertil Steril. 95(8): pp. 2648 - 2650

### 126 Interrelationships of frozen embryo disposition

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Newcastle Fertility Centre, International Centre for Life

**Objectives:** To investigate whether there was an interrelationship between embryo disposition rate, storage length, embryo numbers, embryo purpose and cost; and to determine whether there was a significant difference in disposition choice.

**Content:** This was a retrospective cohort study of 1531 embryo cryopreservation cycles (5039 stored embryos) on our centre's embryo storage register between January 2004 and December 2015. The data was reviewed and subgroups made to compare interdependence of storage length, disposition choice, funding source and number of embryos in cryostorage.

**Impact/relevance:** The embryo disposition decision can be difficult and distressing. Unutilised cryopreserved embryos may be discarded, donated to other couples, to research or to training. The information from this study will be useful for cryopreservation resource planning and consultations with couples considering embryo storage.

**Outcomes:** The embryo disposition rate decreased with storage length. Most discarded embryos (61%) and embryos donated to research (68%) were within the first 2 years of storage. At each time point, most couples that disposed of embryos were self-funded. The discard rate among those with 1-5 embryos was greater in the first 2 years of storage. There was no difference in the discard rate of those with >5 embryos. Storage length and embryo numbers were not linked to disposition choice. Fifteen percent (230/1531) women discarded embryos, 9.5%(146/1531) donated to research, 0.6% (9/1531) to another couple, 0.1%(1/1531) to training, 69.4%(1063/1531) utilised for their own treatment and 5.4%(82/1531) still have cryopreserved embryos.

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**Discussion:** This study highlighted that disposition is most common within the first 2 years of storage and linked to low embryo numbers and self-funding. The preferred embryo disposition choice was either discard or donation to research. Qualitative studies to investigate cost as a disposition reason would be beneficial, since regret for disposition may be heightened if cost was the mitigating factor.

1. Bruno, C et al. (2016) Survey of 243 ART patients having made a final disposition decision about their surplus cryopreserved embryos: the crucial role of embryo representation. *Hum Reprod.* 31(7), 1508-14.

### 127 The impact of age and body mass index on outcomes following single versus double embryo transfer

**Supramaniam Prasanna<sup>1</sup>; Mittal Monica<sup>1</sup>; Bevan Aysha<sup>2</sup>; Child Tim<sup>2</sup>; Lim Lee Nai<sup>1</sup>**

<sup>1</sup>Oxford University Hospitals NHS Foundation Trust; <sup>2</sup>Oxford Fertility Unit

**Aims:**

- To evaluate live birth rate (LBR), and multiple pregnancy rate (MPR) from the transfer of a single versus double cleavage or blastocyst stage embryos with age specific ranges across all BMI categories.
- To define the optimal subgroup (age/BMI) within which a sET/dET would yield the highest LBR without impacting the MPR.

**Content:** Retrospective cohort study of all fresh IVF cycles conducted from January 2009 to October 2015, in a single fertility unit. A total of 10696 cycles were analysed for age specific outcomes based on stage of embryo transfer with an overall LBR of 32.2% (n=3448). Of those, 7315 cycles had both age and BMI data recorded.

**Impact:** Multiple pregnancy is associated with a 2.5 fold increase in maternal mortality. Whilst clinicians practicing assisted reproductive techniques aim to achieve an optimal LBR, one should bear in mind the increase in MPR with a dET.

**Outcomes:** In women aged <39, a dET at the cleavage or blastocyst stage does not result in a significant increase in the singleton LBR but does result in a substantial increase in the MPR. For this subgroup of patients BMI is not seen to have either a synergistic or negative impact on the LBR or MPR. However, in women > 40, a cleavage dET results in a higher singleton LBR with a nominal increase in MPR across all BMI subgroups.

Across all ages, for women with a BMI ≤30, cleavage stage dET does result in an increase in the singleton LBR, with a parallel increase in the MPR, but for women with a BMI >30, this stage of transfer results in a significant increase in the singleton LBR without a significant impact on the MPR.

For blastocyst transfers, all BMI categories have not been shown to have a significant influence on the singleton LBR regardless of whether a sET or dET was performed, irrespective of age. A drop in the singleton LBR is seen across all BMIs with a blastocyst dET. In contrast, women undergoing blastocyst dETs have an increased MPR rate with an increasing BMI.

**Discussion:** From our study, blastocyst stage sET yields the highest singleton LBR regardless of age or BMI without a benefit from a blastocyst dET on the singleton LBR. A negative impact is noted on the MPR with a blastocyst stage dET irrespective of Age and BMI.

A cleavage stage dET however, does show a beneficial effect on the singleton LBR with a minimal impact on the MPR. This may be the only group of patients in which a true dET is beneficial.

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2. Prados N, Quiroga R (2015) Elective single versus double embryo transfer: live birth outcome and patient acceptance in a prospective randomised trial. *Reprod Fertil Dev.* 2015 Jun;27(5):794800. doi: 10.1071/RD13412

### 128 Does fertilisation rate affect the multiple pregnancy and live birth rate following day two, double embryo transfer

**Swann Rebecca; Bevan Aysha; Spencer Jenny; Turner Karen; Child Tim**

*Oxford Fertility*

**Aims/Objectives:** To identify patients, with only two embryos available, who may benefit from Day2 elective Single Embryo Transfer (eSET) based on their fertilisation rate (FR). Thereby, reducing the multiple birth rate (MBR), without affecting the live birth rate (LBR).

**Content/Relevance:** Within the clinic, regardless of aetiology, patients with 2 normally fertilised embryos are recommended a Day2 double embryo transfer (DET). However, this is associated with a 20.0% risk of a multiple pregnancy in patients <38 years old.

This retrospective study of 323, non-elective, Day2 DET cycles were grouped according to FR:

Group 1, 210 cycles: Patients having a poor response to stimulation (≤4 mature oocytes) but normal FR (≥50%)

Group 2, 113 cycles: Patients having a normal response to stimulation (≥5 mature oocytes) but reduced FR (<50%)

**Outcomes:** Outcomes: Group 1 were significantly more likely to have a positive pregnancy result (73/210; p<0.05) than Group 2 (27/113). However, there was no significant difference in clinical or multiple pregnancies (p>0.05), LBR (p>0.05), or MBR (p>0.05). Live birth data demonstrated expected trends, with multiple pregnancies more likely resulting in low birthweight (p=<0.0005) and premature births (p=<0.01), irrespective of FR.

Further analysis within these groups for patients <38 years old, also concluded no significant difference in MPR (Group 1: 37/49; Group 2: 15/20, p>0.05).

**Discussion:** This study was unable to identify a group of patients who, based on their FR, might benefit from eSET on Day2. However, the unit Multiple Birth Minimisation Strategy (MBMS) has been reviewed and altered, with all embryos cultured routinely to Day3, with ≥2 good quality Day3 embryos recommended blastocyst culture and Day5 ET. Cycle outcomes will continue to be monitored to determine the impact following these changes.



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### 129 Is there an association between endogenous anti-mullerian hormone levels and embryo morphokinetics?

**Barrie Amy; Schnauffer Karen; Kingsland Charles; Troup Stephen**

*The Hewitt Fertility Centre, Liverpool*

Morphokinetic development of pre-implantation embryos can be affected by in vitro factors such as culture media. They may also be affected by the in vivo environment as oocytes. This analysis aimed to determine if morphokinetics were affected by endogenous anti-mullerian hormone (AMH) levels in the environment from which they originated.

In this retrospective data analysis, 754 embryos from 223 patients (January 2015 to December 2015) were analysed using the EmbryoScope®. The number of oocytes collected, patient age and nineteen morphokinetic parameters (time to 2-cell (t2), t3, t4, t5, t6, t7, t8, t9, time to morula (tM), time to start of blastulation (tSB), time to blastocyst (tB) and their intervals (cc2, cc3, cc4, s2, s3, t9-tM, tM-tSB, tSB-tB) were analysed using linear regression. Assumptions of this statistical test were met in each case.

Patient age ( $32.5 \pm 4.45$ ) was not significantly correlated with AMH level ( $p=0.065$ ) however AMH was significantly predictive of number of oocytes collected ( $13.9 \pm 6.9$ ) ( $p<0.0001$ ). Of the nineteen morphokinetic parameters, tM, tSB, tB and the intervals between them (t9-tM, tM-tSB, tSB, tB) were found to be statistically significantly affected by the AMH level in the environment from which they originated ( $p<0.0001$ , 0.013, 0.001,  $<0.0001$ , 0.023, 0.012, respectively).

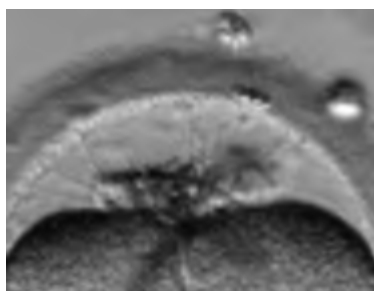
These data suggest that embryo morphokinetics can be altered by in vivo environmental factors. When assessing embryo morphokinetic development it may be important to consider in vivo influences especially when a one-size-fits-all approach is used for embryo scoring algorithm application.

### 130 Observation of commonly occurring zona-cytoplasmic threads (ZCTs) in early embryo development

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Analysis of time-lapse images has revealed the appearance of transient thread-like structures spanning the perivitelline space, connecting the zona pellucida (ZP) and the cytoplasmic membrane in the early embryo. This report attempts to describe

these zona-cytoplasmic threads (ZCTs). It is believed this is the first report of these structures, their incidence and possible function in human embryo development.

**Content:** Analysis of time-lapse videos of 125 embryos from 2012-2016 at 2 IVF clinics. Each video was selected at random, regardless of fate, from 125 different fresh IVF/ICSI cycles and analysed from pronuclei formation to day 6. Patient age ranged from 23-46 years, autologous and donor eggs included.

**Outcomes:** ZCTs were observed in 58.4% of embryos (73/125) and ranged from 1 or 2 individual threads to an abundance spanning a large area of the inner ZP. ZCTs appeared to form from contact points between the cytoplasmic membrane and the ZP prior to cleavage. 90.4% were observed at first cleavage, the latest during blastocyst collapse and re-expansion. In 16.4% of embryos, ZCTs were sighted more than once during development. 82.2% of ZCTs (60/73) were associated with the appearance of fragments.

**Discussion:** This observational study provides evidence of structural zona-embryo interactions, which despite common occurrence are currently unreported in human embryos. Similar structures have been reported to play a role in mouse embryos at compaction<sup>1</sup>. However, data reported here suggests ZCT's participate in the mechanism of fragmentation. The actual frequency of ZCTs may be higher than data suggests as the orientation of the embryo, cleavage planes, multiple blastomeres/fragments, may all obscure viewing. ZCTs have been observed in abnormally fertilised embryos, suggesting their role is not governed by pronuclear status.

Further studies are required to define ZCT ultrastructure and relevance to polarity, fragmentation and implantation potential.

1. Fierro-González, J.C., White, M.D., Silva, J.C., & Plachta, N. Cadherin-dependent filopodia control preimplantation embryo compaction. *Nat Cell Biol.* 2013 Dec; 15(12):1424-33

### 131 Can morphokinetics enhance the selection of euploid embryos and improve clinical pregnancy rates?

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<sup>1</sup>CARE Manchester; <sup>2</sup>CARE Fertility

**Introduction:** The transfer of a euploid embryo has been shown to increase pregnancy rates per embryo transfer (Majumdar et al, 2016). When a euploid embryo does not implant, it is not known whether this is due to uterine or embryonic factors.

**Aim:** To assess if morphokinetic classification can be used to select the euploid embryo that is more likely to result in a clinical pregnancy.

**Methods:** 43 euploid blastocysts transferred between January 2013 and June 2016, with a known implantation outcome (KID) were assessed for morphokinetic model score. This score was based on an algorithm (from over 1000 live births) used clinically to rank embryos on their likelihood of achieving a live birth, dependent on morphokinetic timings at key stages of development. The scores range from 0 (lowest) to 3 (highest). Due to the number of available euploid embryos in this study, the embryos were divided into two groups: all those that scored a 3 (top score euploid) and all other scores (low score euploid).

**Results:** The implantation rate for top score euploids was 100%, with a clinical pregnancy rate of 91.6% (11/12). In



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total, 27 euploid embryos resulted in a clinical pregnancy and in this group there were significantly more top score euploids (11/27) than in the negative group (0/11) at 40% and 0% respectively ( $p=0.016$ ). A further 5 euploid embryos resulted in a biochemical pregnancy only and 80% of these embryos (4/5) only scored a 1 with the morphokinetic model.

**Conclusion:** This is the first study to demonstrate clear morphokinetic differences between euploid blastocysts that can produce a live birth, to those that do not. Morphokinetic classification may enhance the selection of euploid embryos that are most likely to result in a live birth. Further work is needed to increase the number of euploid embryos included.

1. Majumdar G, Majumdar A, Lall M, Verna IC and Upadhyaya KC. (2016) Preimplantation genetic screening for all 24 chromosomes by microarray comparative genomic hybridization significantly increases implantation rates and clinical pregnancy rates in patients undergoing in vitro fertilization with poor prognosis. *J Hum Reprod Sci.* 2016 Apr-Jun;9(2):94-100. doi: 10.4103/0974-1208.183512

### 132 Does the duration of exposure to EmbryoGlue® affect embryo implantation potential?

**Diaz Diaz Montana<sup>1</sup>; Hoo Wee-Liak<sup>1</sup>; Barrie Amy<sup>2</sup>; Gibbons Rachel<sup>1</sup>; Muriel Rios Lourdes<sup>1</sup>; Newton Sarah<sup>3</sup>**

<sup>1</sup>King's Hewitt Fertility Centre; <sup>2</sup>The Hewitt Fertility Centre, Liverpool; <sup>3</sup>King's College Hospital NHS Foundation Trust

**Aims:** To assess the effect of the duration of embryo exposure to EmbryoGlue® on implantation rate.

**Content:** Data were collected retrospectively using the IDEAS™ database for all patients undergoing fresh embryo transfer between January and June 2016. Embryos were exposed to EmbryoGlue® immediately prior to embryo transfer and the duration of exposure was calculated using the witnessing time points. The primary end point was implantation rate calculated as the total number of fetal hearts resulting from the total number of embryos transferred.

**Relevance/Impact:** EmbryoGlue® is a medium with a higher concentration of hyaluronan suggested to improve implantation rates. The manufacturer recommends an exposure of at least 10 minutes, with no upper limits clearly defined. In practice, this recommendation may not always be achievable and the effect of extended exposure to EmbryoGlue® on implantation is largely unknown.

**Outcomes:** EmbryoGlue® exposure of less than 10 minutes (range 2 to 9 minutes, average patient age  $37.8 \pm 3.3$ , average eggs collected  $9.2 \pm 7.1$ ) resulted in a lower implantation rate of 15.4% (8/52) when compared to exposures of 10 minutes or more (range 10 to 125 minutes, average patient age  $35.1 \pm 4.0$ , average eggs collected  $9.1 \pm 6.0$ ) 28.6% (173/604) ( $p=0.04$ ). When prolonged exposures were assessed, exposure of more than 30 minutes (range 31 to 125 minutes, average patient age  $34.9 \pm 4.0$ , average eggs collected  $8.9 \pm 5.0$ ) had a similar implantation rate of 28.6% (69/241) compared to an exposure of 10 to 30 minutes (average patient age  $35.2 \pm 4.1$ , average eggs collected  $9.1 \pm 5.8$ ) 28.7% (104/363) ( $p=0.996$ ).

**Discussion:** These results suggest that an exposure to EmbryoGlue® of less than 10 minutes results in a lower implantation rate, therefore, every effort should be made to

adhere to the manufacturer's recommendations. Moreover, prolonged exposure to EmbryoGlue® did not have a negative effect on implantation rates.

### 133 A retrospective follow-up study comparing implantation rate to blastocyst grade in ART cycles from January 2010 - December 2015

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CARE Fertility Nottingham

**Aims/objectives:** To investigate the comparative relevance of blastocyst ICM and trophectoderm grade in relation to the implantation rate (IR) in fresh ART cycles.

**Content:** Data from 5146 SET cycles including all age groups from January 2010-December 2015 were analysed. Blastocysts were graded at the time of embryo transfer using an in-house system, based on published guidelines, scoring the ICM and the trophectoderm separately either 1, 2 or 3 where 1 is highest.

**Relevance/impact:** The use of single blastocyst stage embryo transfer is now well established, increasing positive outcomes and minimising multiple pregnancy. Criteria to further improve embryo selection are continuously sought.

**Outcomes:** From 5146 single blastocyst transfers 2727(53.0%) implanted; confirmed by a foetal heart. With ICM grade 1 the IR was 53.6% (313/584), grade 2 53.4% (1651/3094) and grade 3 38.1% (40/105), where the trophectoderm grade was constant at 2. Where the trophectoderm grade was 1 IR was 61.4% (161/262), grade 2 53.4% (1651/3094) and grade 3 46.6% (166/356) where the ICM grade was constant at 2.

**Statistical analysis,** using a chi-squared test ( $p<0.001$ ) found that trophectoderm grade was close to being significantly related to IR when the ICM grade was 2 ( $p=0.0013$ ) but that the ICM grade was not significant when the trophectoderm grade was 2 ( $p=0.0082$ ).

**Discussion:** This data follows up and supports a study by Dale et al (2013) and those of Hill et al (2013) and Ahlstrom et al (2011) in the importance of trophectoderm grade related to implantation compared to ICM grade. A large variation in the numbers of embryos in each group could affect the statistical analysis. The data could be further enhanced by reviewing the live birth rates.

1. Ahlstrom A. (2011) Trophectoderm morphology: an important parameter for predicting live birth after single blastocyst transfer. *Hum Reprod.* 26(12), 3289-3296.
2. Dale SM. (2013) A retrospective study comparing implantation pregnancy rate to blastocyst grade in ART cycles from July 2010-May 2012. *Fertility* 2013
3. Hill MJ. (2013) Trophectoderm grade predicts outcomes of single-blastocyst transfers. *Fertil Steril.* 99(5), 1283-1289

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### 134 A preliminary, observational study to determine the prevalence, quality and utilisation of embryos exhibiting micro-PN formation

**Jaques Sophie; Scott Natalie; Barrie Amy; Schnauffer Karen; Kingsland Charles; Troup Stephen**  
*The Hewitt Fertility Centre, Liverpool*

With the advent of time-lapse technology there is a plethora of embryological parameters that can now be annotated. Recently, at the Hewitt Fertility Centres, embryos exhibiting micro-pronuclei (PN) formation at the pronucleate stage became part of routine annotations. The presence of a micro-PN was confirmed if its size was less than 20% of the two larger PNs and contained no more than one nucleoli. This change in practice occurred in an attempt to establish best practice for their subsequent utilisation due to the ambiguity surrounding their developmental competence. This preliminary investigation details the prevalence, embryo quality and utilisation of embryos showing micro-PN formation.

Data were collected retrospectively (May 2016-September 2016) using the EmbryoScope®. Of 3809 embryos cultured, 28 embryos exhibited micro-PN formation at the pronucleate stage; a prevalence of 0.74%.

Sixteen of the 28 embryos were discarded as they failed to meet the criteria for cryopreservation and an unaffected embryo was available for transfer. Eight embryos were able to be cryopreserved and an unaffected embryo was available for transfer. Four embryos exhibiting micro-PN formation were transferred due to unavailability of unaffected embryos. Three day five transfers resulted in negative hCG tests. One day three transfer resulted in an ongoing clinical pregnancy. The blastocyst formation rate (BFR) of affected embryos was 52%. Of these, 35.7% were good, 14.3% average and 50% poor quality blastocysts.

These data suggest that embryos exhibiting micro-PN formation are able to produce good quality blastocysts, although the BFR is lower than the Hewitt Fertility Centre average. Although the population is small, it appears these embryos may be able to produce viable pregnancies however, the live birth outcome is, as yet, unknown. Continued annotation of this developmental parameter is imperative until sufficient data is collected to assess the potential benefit of utilising such embryos.

### 135 Is there space for the 1PN 2PB embryos in a clinical embryology laboratory?

**Andreou Kyriaki; Maguiness Steve; Leary Christine**  
*The Hull IVF Unit*

Monopronuclear zygotes occur in both IVF and ICSI treatments with an approximate prevalence of 2.7-12.5%. Despite a lack of confirmation of normal fertilisation, practises differ on the clinical usage of such embryos. Identification of mononuclear embryos, with two polar bodies (1PN 2PB) at the time of fertilisation check may be followed by further observation for early cleavage or late formation of a second pronucleus. Depending on observations embryos may be discarded or cultured further; but the benefit of this for the patient/ clinic is debatable.

Between January 2014 and July 2016, 1PN 2PB embryos were cultured and monitored throughout their development at the same intervals as normally fertilised embryos. A total of 76 1PN 2PB embryos were observed in 6.7% of treatment cycles (n=66/992 cycles). An equal proportion of embryos were derived from IVF and ICSI cases (42 and 34 respectively; p=0.2). 64 of the 76 embryos were cultured until day 5, only 9 developed into blastocysts (14.1%); 3 formed high quality blastocysts and all were derived from IVF treatment. This compares to a blastocyst rate of 48.8% for 2PN 2PB embryos during the study period (p<0.001). On 3 occasions 1PN 2PB embryos were transferred as no other embryo was available for treatment, all cycles resulted in a negative clinical outcome.

The time consumed observing 1PN 2PB embryos is limited, but nevertheless the time a dish is kept outside the incubator to observe/ manipulate monopronuclear embryos poses a disadvantage to the culture conditions of other embryos. The significantly low rates of blastocyst formation observed here, and recent literature findings suggesting even those reaching this stage are prone to high rates of chromosomal abnormalities would indicate these embryos are of limited viability. Patients should be counselled accordingly.

### 136 Can the time between pronuclei fading and the start of the first cytokinesis predict the implantation potential of embryos?

**Sevillano Martinez Estefania; Fernandez Ponce Alejandro; Palomino Gomez Elena; Barrie Amy; Schnauffer Karen; Kingsland Charles; Troup Stephen**  
*Hewitt Fertility Centre, Liverpool*

The mitotic phase (M-phase) of the first cell cycle begins with the fading of pronuclei (PNf) and lasts until completion of the first cytokinesis. It has been suggested that the length of the first M-phase is an indicator of an embryo's developmental potential and viability.

The aim of this project was to determine whether the first M-phase can be used to predict embryo implantation. Time-lapse imaging data were retrospectively acquired from the EmbryoScope® incubator between August 2011 and July 2016 for 1,824 embryos with known implantation (KID).

Four groups of M-phase timings were assessed: ≤ 2.33h (group 1), 2.34 – 2.51h (group 2), 2.52 – 2.83h (group 3) and > 2.83h (group 4). The mean timings of the M-phase were also compared between embryos that implanted (KID+) and those that failed to implant (KID-). The student t-test and the Chi-square test were used for statistical analysis and p-values of <0.05 were considered statistically significant.

An increased implantation rate (55.0% versus 49.6%) was observed in the embryos where the first M-phase took 2.34-2.51 h, compared with those that took more than 2.83 h, however the quartile analysis suggested that there were no significant differences (p = 0.22344). Nevertheless, statistically significant differences (p < 0.0001) were found in the mean time of the first M-phase when comparing all embryos that implanted with all embryos that did not where the first M-phase was found to be reduced for implanted embryos (2.60h versus 2.67h).

These results suggest that the length of the first M-phase may correspond to an embryo's ability to implant as implanted



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embryos had a shorter M-phase when compared to non-implanted embryos. However, further research is necessary to define the optimal time frame for the first M-phase.

### 137 Embryo morphokinetics: Correlation with maternal and paternal characteristics

**Mascarenhas Mariano; Fox Sarah; Thompson Karen; Balen Adam**

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**Aim:** To analyse the effect of maternal age and body mass index (BMI) and paternal age on embryo morphokinetics

**Methods:** Retrospective data from an infertility unit from January 2014 to October 2015 assessing the following embryo morphokinetic timepoints: time of pronuclear appearance (tPNa) and disappearance (tPNf), time to reach two cells (t2), three cells (t3), four cells (t4), five cells (t5), six cells (t6), seven cells (t7), eight cells (t8), nine cells (t9), morula (tM), start of blastulation (tSB), blastocyst (tB), expanded blastocyst (tEB) and hatching of the blastocyst (tHB). IVF and ICSI embryos were analysed separately. Maternal age categories of 38-40, 41-42 and >42 years were compared with a reference standard 21-37 years. Maternal BMI categories of <19, 25-29.99, 30-34.99 kg/m<sup>2</sup> were compared with reference standard 19-24.99 kg/m<sup>2</sup>. Paternal age categories were 21-40 and 41-60 years.

**Results:** A total of 1433 IVF embryos(336 cycles) and 1707 ICSI embryos(324 cycles) were analysed. IVF embryos with maternal age 38-40 years reached tB and tEB faster. ICSI embryos with maternal age 38-40 years reached t7 and t9 later. ICSI embryos with maternal age 41-42 years reached tPNa, t3, t4 and t6 later. Maternal BMI and paternal age analysis were restricted to the maternal age group 21-37 years to reduce confounding. IVF embryos with maternal BMI < 19 kg/m<sup>2</sup> reached tPNa, tPNf, t2, t3 and t7 stages faster. IVF embryos with maternal BMI 25-29.9 kg/m<sup>2</sup> reached t9 and tM later. IVF embryos with paternal age 41-60 years reached tPNf, t2, t4, t5, t6, t7, t8 and t9 faster

**Conclusion:** These results suggest that maternal age and BMI and paternal age can impact embryo morphokinetics. This data is from a single centre and further research is needed. While faster embryonic development is a good prognostic marker, fast early cleavage has been associated with epigenetic disturbances.

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### 138 Sound vibrations can promote fertilisation and embryo development

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Fertilised oocytes are cultured in CO<sub>2</sub> incubators that replicate the temperature, humidity and gas concentration of the uterus. Although there is a large number of important culture media components the real environment of embryo in the female reproductive tract is still not clear. In vivo, the embryo migrates from the fallopian tube to the uterus and is exposed to different vibrations by daily life movements of the female. We investigated if sound vibrations can improve embryo development in vitro. In this research the vibrations were transmitted from a computer directly to the Petri dish which was placed on the wireless speaker in a CO<sub>2</sub> incubator.

100 egg donors were included in the study. In total there were 1516 oocytes fertilised by ICSI: 758 oocytes from the group cultured with sound vibrations and 758 oocytes cultured without sound in another CO<sub>2</sub> incubator of the same model. Sound (techno music) was produced 24 hours a day by the wireless speaker in the range of frequency 20 – 20000Hz with the noise level up to 80dB. Embryos were cultured individually in 15ul microdroplets of Global media for 6 days in a humidified incubator at 36.7°C with 7.3%CO<sub>2</sub>.

All donors included in the research signed informed consent. Statistical differences between the values were made using analysis of variance.

The results showed that fertilisation and blastocyst rates were significantly higher (p<0.01) in the group of embryos cultured with sound vibrations in compare with those cultured in silence (fertilisation rate: 84%vs78%, blastocyst rate: 48%vs40% respectively).

It was found that sound vibrations applied to the embryos have a positive influence on fertilisation and formation of blastocysts. Although the exact nature of this effect is still not clear, it is possible to assume that these vibrations equalise the concentrations of media compounds surrounding the embryo and promote embryo development.

### 139 Tight junction assembly mediated by CPEB2 is essential for mouse blastocyst formation

**Jeong Yelin; Choi Inchlul**

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Cytoplasmic polyadenylation element binding protein 2 (CPEB2) regulates cytoplasmic polyadenylation of mRNA in mouse haploid germ cells, but nothing is known about its expression and biological function during zygote embryo. Here, we show expression patterns of CPEB2 and its role in blastocyst formation. CPEBP2 is dramatically upregulated from the eight cell onwards. More interestingly, CPEB were detected in nuclei at the two-cell stage, but after the compaction the expression was not homogenous in the cytoplasm. To determine the biological role of CPEB2, we abolished transcripts of CPEB2 using siRNA and found that the transition rates between morula and blastocyst significantly decreased



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(<40%,  $P < 0.05$ ), and more permeability in the KD blastocysts assessed by FTIC dextran assay. Interestingly, we observed direct interaction between CPEB2 and TJP1, indicating TJP localization may be affected by CPEB2, and further TJ assembly. Outgrowth assay support abnormal development of TE region, and embryo transfer experiments confirmed our hypothesis that defects of TJ finally affect maintenance of pregnancy. In conclusion, CPEB2 is directly associated with TJP1, subsequently affect TJP assembly for the blastocyst formation and further development. This work was supported by "Next-Generation BioGreen 21 Program" (PJ011213), Rural Development Administration, Republic of Korea

### 140 Impact of endometrial decidualization on human blastocysts development

**Aberkane Asma<sup>1</sup>; Lee Yie Hou<sup>2</sup>; Adriaenssens Tom<sup>1</sup>; Tournaye Herman<sup>3</sup>; Brosens Jan<sup>4</sup>; Van de Velde Hilde<sup>1</sup>**

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Decidualization denotes the transformation of undifferentiated endometrial stromal cells (EnSCs) into specialized decidual cells (DECs), which sustain a supportive microenvironment for the implanting embryo in early pregnancy. Decidualization is a sequential process, characterised initially by a transient pro-inflammatory secretory response, which spans the window of implantation. This is followed by an anti-inflammatory response and acquisition of a mature decidual phenotype. In this study we hypothesize that the decidualization status of the endometrium impacts on human blastocyst development. To test this hypothesis, late day 5 human blastocysts were cultured for 24h in conditioned media (CM) of EnSCs or DECs in the pro-inflammatory (day 4) or anti-inflammatory (day 10) phase of differentiation. Only high quality cryopreserved blastocysts, which became available for research after a legally determined storage period and with the patients' informed consent, were used. Following incubation with CM, the growth of the blastocysts was scored based on morphological criteria and the embryo-derived secretion of 45 cytokines and growth factors in the microdroplets measured using a multiplex suspension bead immunoassay. Analysis of the embryo growth rates demonstrated that the secretome of EnSCs compromised blastocyst development, exemplified by a growth score 0 (indicative of poor development) in 8 out of 17 (47%) embryos. By contrast, the growth rates were not compromised when blastocysts were incubated in CM of DECs [growth score 0 in 1 the 14 (7.1%) embryos (Chi-square test:  $P = 0.02$ )], irrespectively of the phase of differentiation. Cytokine analysis revealed that human blastocysts secrete CCL2/MCP-1 in response to signals from EnSCs but not DECs. Taken together, our findings to date demonstrate that the secretome changes associated with undifferentiated EnSCs transitioning to fully decidualized cells profoundly impact on blastocyst growth and cytokine responses. A blastocyst-specific response triggered by signals from an unreceptive endometrium may contribute to failure of implantation.

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### 141 Investigating a paternal RNA contribution to maternal clearance during the egg-to-zygote transition (EZT) in the mouse

**Miller David; Dostis Panos; Iles David**

*University of Leeds*

**Aims/Objectives:** Spermatozoal RNAs have been linked to male fertility (1), maternal RNA and protein clearance (2) and the establishment of paternal memory of germline gene expression (3). We aimed to clarify potential paternal effects on pre-zygotic processes in a mouse model and in due course, translate the study outcomes to human fertility.

**Content:** Deep RNA sequencing (RNA-Seq) was employed to characterise parental and zygotic transcriptomes at the single cell level. A total RNA library preparation, sequencing and analysis pipeline was employed. Bioinformatics approaches and tools were used to investigate the role of identified, parental transcripts participating in specific metabolic pathways potentially involved in maternal RNA clearance.

**Relevance/Impact:** Less than 50% of all ART procedures leads to a clinical pregnancy, yet little is known about paternal effects on the most critical stage of early embryonic development following fertilisation and prior to zygotic genome activation.

**Outcomes:** Four paternal 'candidate' RNAs were revealed with a potential to play a role in maternal RNA clearance. These RNAs are encoded by genes participating in maternal metabolic pathway and provides further information on the molecular mechanisms underlying the EZT from a paternal perspective.

**Discussion:** Our study supports existing mouse egg and zygote RNA-Seq data (4) and provides compelling evidence for potential paternal mRNA targets that could be further investigated in relation to idiopathic male infertility. Functional studies focusing on these particular paternal RNAs could further elucidate their roles in very early embryo development.

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**142** A consistent set of imprinted gene transcripts are expressed in human blastocysts: Preliminary evidence for an imprinted gene network operating in human preimplantation development

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There are surprisingly few studies that have compared the nature of homogeneity/heterogeneity in gene expression between individual human preimplantation embryos. In mammals, the imprinted genes (IG) are important in regulating growth and development of the fetus particularly via the placenta and are expressed predominantly or exclusively from one parental allele only. An imprinted gene network (IGN) is known to be active in early mouse development and the network is regulated by key regulatory imprinted genes including H19 and ZAC1 as examples. We therefore hypothesised that a similar network could operate in human early development. It is proposed that human preimplantation embryos that are successful in reaching late preimplantation development will each express a common network of imprinted genes that will be important for controlling growth and development of the embryo and for preparing for implantation and development in utero. In this preliminary study we used a series of archived cDNA libraries from i) individual human blastocysts (n=8) and ii) pooled blastocysts (n=26 in total) to investigate gene expression using a custom real-time PCR array including 53 known or putative imprinted genes and appropriate control genes. Our data indicates that imprinted genes including GNAS, DLX5, H19, CDKN1C, PHLA2, MEG3, UBE3A, BLCAP, DDC, GRB10, SGCE, PEG10, MEST, DLGAP, INS, WT1, MAGEL2 and PEG3 are frequently detected in human blastocysts. These include 7 members of the IGN that is active in mouse development and closely reflects the imprinted genes that are known to be expressed in the mammalian placenta. Based upon the commonality in IG expression between human embryos, we propose that these genes represent members of an IGN that is active in human preimplantation development, possibly with H19 as a key regulatory member. Interpretations are limited by the small sample size and the platform used for analysis.

**143** The hormone environment of pregnancy partially mitigates the effect of hyperandrogenaemia on the ovary

**Zahed Nazia<sup>1</sup>; Nicol Linda<sup>1</sup>; Rae Mick<sup>2</sup>; Duncan W. Colin<sup>1</sup>**

<sup>1</sup>MRC Centre for Reproductive Health, University of Edinburgh; <sup>2</sup>Edinburgh Napier University

Context: Hyperandrogenism is the cardinal feature of polycystic ovary syndrome (PCOS) and is responsible for associated changes in ovarian morphology. Gonadotrophins regulate androgen action and it is possible that they are in part culpable for these effects.

**Objectives:** We hypothesised that androgen effects on the ovary are augmented by gonadotrophins. As gonadotrophins are normally suppressed in pregnancy we investigated whether androgens cause equivalent changes in ovarian morphology during pregnancy.

**Methods:** Scottish Greyface ewes, in the follicular phase of the ovarian cycle, and pregnant ewes (D60 of 147 gestation) were administered either 100mg testosterone propionate (Follicular n=4, pregnant n=5) or vehicle-control (Follicular n=4, Pregnant n=5), twice-weekly for two weeks. Ovaries were then collected for histochemical and immunohistochemical analysis of ovarian morphology and antral follicle dynamics.

**Results:** Androgen treatment during pregnancy did not affect ovarian follicular dynamics. There were no differences in the size, number of follicles and antral follicle proliferation or atresia. In non-pregnant animals there was tendency for increased antral follicle numbers but this did not reach significance. There were no significant differences in antral follicle health but androgen treatment caused a shift to smaller antral follicles with reduction of larger (>3mm) follicles in the non-pregnant ovaries (P<0.05). As polycystic ovaries have thickened capsules we assessed the effect of androgens on capsular thickness. There was a significant increase in ovarian capsular thickness during pregnancy in the TP-exposed cohort (P<0.01). There was the same magnitude of increase in non-pregnant animals but this didn't reach statistical significance.

**Conclusion:** Androgens thicken the ovarian capsule and this is not altered by the hormonal milieu of pregnancy. The androgen effects on antral follicle size distribution in the non-pregnant state is not seen during pregnancy. The environment in pregnancy partially protects the ovary from the effects of androgens.

**144** Every pain in IVF is not ovarian hyperstimulation - a rare case of ovarian torsion in follicular phase of stimulation during IVF

**Borkar Amol; Srivastava Garima; Watson Sandra; Shah Amit; Gudi Anil**

Homerton University Hospital, London

**Aims/Objectives:** To make fertility professionals aware of the rare complication of ovarian torsion in follicular phase of stimulation during IVF.

**Case Presentation:** A 32 year old patient presented with generalised abdominal pain, nausea and abdominal distension on day 13 during IVF stimulation. A provisional diagnosis of mild OHSS (Ovarian Hyper-stimulation Syndrome) was made and patient was discharged. She re-presented on day 15 with increasing abdominal pain. On examination she had tachycardia, abdominal distension. Pelvic ultrasound showed bilateral enlarged ovaries and free fluid in the abdomen. Her blood markers were not indicative of OHSS.

On review after few hours, she was persistently tachycardic despite fluid management and the tenderness was localised to the left iliac fossa. Urgent Doppler's were conducted which failed to reveal any blood flow in the left ovary. Left ovarian torsion was strongly suspected and patient was immediately prepared for diagnostic laparoscopy.



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**Outcome:** A significant amount of hemoperitoneum was noted. Left ovary was torsed thrice on its pedicle and was necrosed and friable. In view of unsalvageable ovary, mini laparotomy and left salpingo-oophorectomy was performed.

**Relevance/Impact:** The first diagnosis during IVF stimulation in patients presenting with pain is generally OHSS. However OHSS is of very rare occurrence before the trigger injection is given as VEGF-Angiotensin II pathway is not activated.

Hence clinicians should be aware of different possibilities of abdominal pain during IVF.

**Discussion:** Torsion of the ovary is a Gynaecological emergency. It occurs with ovarian cysts especially dermoid or with enlarged ovaries due to OHSS.

There are negligible cases of ovarian torsion, during the follicular phase of IVF reported in the literature. Early suspicion and timely intervention is vital to conserve the ovary as oophorectomy is devastating to young infertile patient.

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### 145 The effects of phthalate on 4-Vinylcyclohexene diepoxide (VCD) induced ovarian failure model.

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*Chungbuk National University, South Korea*

Phthalate are commonly used as plasticizers in a wide range of consumer products such as plastic products, baby bottles, epoxy resin, medical and personal care products. Phthalate exposure causes early onset of puberty in females, abnormal of reproductive tract, infertility. VCD has been shown to alter follicle development, growth and impair follicular function, alter steroidogenesis, reduce the primordial, disrupt estrous cycle lead to ovarian failure, reduce fertility in a variety of animals including humans. In this study, we assessed the effects of phthalates on the ovary under the co-treatment with VCD. In control group, Female Sprague-Dawley rats (8 weeks of age, 160-180g bodyweight) were treated with corn oil 0.3ml via interperitoneal, DEHP (25mg/kg), BBP (250mg/kg) and DBP (250mg/kg) via oral gavage during 3 weeks.

Simultaneous treatment with VCD (80mg/kg) in VCD group via interperitoneal. Estrous cycles were assessed daily throughout experiment by vaginal smear test. Uterine, ovaries and blood were collected after 24 hours final injection. There were no differences in body, ovarian and uterine weight. However, there were differences in oestrus cycle between the groups. VCD group was no difference in percentage time of time spent pro-estrus, estrous and di-estrus. In DEHP and VCD+DEHP group spent more time in pro-estrus, estrus. In group BBP and DBP, the time in di-estrus is longer than control group. Particularly in VCD+BBP and VCD+DBP, there were significant more time in di-estrus. The levels of FSH serum in combination groups were significantly increased compare with placebo and alone treatment. Follicles loss occurred in both combination and alone treatment groups but is highly in combination groups. These results demonstrate that effects of phthalates on the ovary under the co-treatment with VCD were more harmful to ovarian of animals compare to exposure only phthalate.

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### 146 Androgen receptor genotyping: A promising tool for identification patients that they will benefit of androgen treatment

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**Aims/Objectives:** Androgens and their receptors have been shown to play an important role in ovarian physiology. Recently, clinicians have attempted to improve the ovarian response in poor ovarian responders by using androgens or androgen modulators prior to IVF treatment. However, there is still some controversy about the evidence that pre-treatment with transdermal testosterone may improve the clinical outcomes for poor ovarian responders. The human androgen receptor (AR) gene contains a highly polymorphic CAG repeat sequence. The aim of this work was to investigate if androgen receptor (AR) polymorphism could be used for selection patients that they will benefit of androgen treatment in previous cycle.

**Content:** A retrospective study was performed. We included 54 ovarian stimulation cycles performed by 27 patients diagnosed as poor responders and genotyped for AR polymorphism. All patients carried out two cycles: one without androgens pre-treatment and the second one with androgen preparation. AR polymorphism statistical differences were shown in oocyte yield and MII. Patients that carried CAG repeats in AR gene between 22 and 24 showed an increased in the number of MII oocytes when were pre-treated with androgens.

**Relevance/Impact:** Androgen receptor genotyping could help us to identify poor ovarian responder patients that will be benefited of transdermal testosterone pre-treatment.



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**Outcomes:** The main outcomes were the number of retrieved oocytes and MII.

**Discussion:** The use of androgens as a strategy to increase the number of retrieved oocyte in poor ovarian responders remains controversial. Our data suggests that the AR genotype could clarify the effectiveness of the androgen pre-treatment. Advance identification of patients who will elicit an improved ovarian response to androgen treatment would be of great clinical advantages for such patients.

### 148 The effect of liver fluke TGF-like molecules on bovine luteal cells in vitro

**Green Rebecca; Thompson Robert; Flynn Robin; Woad Katie; Robinson Robert**

*University of Nottingham*

**Background:** Liver fluke (*Fasciola hepatica*) infection in dairy cows is an increasing economic problem. Chronic liver fluke infection is associated with poor growth, delayed puberty and reduced fertility, however the underlying mechanism is unclear. Secreted transforming growth factor-like molecule (TLM) from fluke has similar properties to transforming growth factor B (TGFB) and is detected in bovine follicular fluid. Since TGFB suppressed luteal angiogenesis and progesterone production in vitro, it is feasible that fluke TLM would have similar effects. Thus, it was hypothesised that recombinant fluke TLM would adversely affect luteal angiogenesis and progesterone production in vitro in a similar manner to TGFB.

**Methods:** A bovine luteal endothelial co-culture system was utilised. Cells from early bovine CL were treated with either control, TLM (0.5 or 5ng/ml) or TGFB (1ng/ml) in the presence of pro-angiogenic growth factors for 5 or 9 days. Endothelial cell (EC) networks were quantified using image analysis of von Willebrand Factor immunohistochemistry and progesterone production determined using ELISA.

**Outcomes:** In control wells, large undeveloped EC islands were present on day 5, which formed extensive intricate EC networks by day 9. There was a large decrease in EC network formation in TGFB-treated cells on both days 5 (12-fold) and 9 (3-fold) compared to controls ( $p < 0.001$ ). TGFB decreased progesterone production at both time points (2.6 fold;  $p < 0.001$ ). There were no significant effects of TLM at both low and high doses upon EC network formation and progesterone production ( $p > 0.05$ ).

**Discussion:** This study demonstrated that TGFB treatment can reduce bovine luteal angiogenesis and progesterone production in vitro. However, TLM treatment has no significant impact upon luteal endothelial cell network formation and steroidogenesis in vitro and is unlikely to be the mechanism by which liver fluke reduces fertility in cattle.

### 149 Case series of 55 patients who underwent laparoscopy for ovarian tissue cryopreservation at a large regional centre, with long term follow up

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**Aims:** To determine whether patients who underwent laparoscopy for ovarian tissue cryopreservation were appropriately referred, long term outcomes, and consider if reinstating this service would benefit patients.

**Content:** Ovarian tissue cryopreservation may offer a viable solution to the increasing numbers of patients who face gonadotoxic cancer treatment during reproductive age (1). The Edinburgh criteria includes patients under 35 years with a high risk of premature ovarian failure, and a realistic chance of survival (2).

We describe the experience of a large centre which offered this experimental treatment between 1995 and 2006, until licensing changes came into force.

**Relevance:** As one of the largest UK cohorts with long term outcomes, this study will help inform the need for and design of this service nationally.

**Methods:** Retrospective analysis of case notes of all patients who underwent ovarian tissue cryopreservation at a large tertiary hospital between 1995 and 2006, with telephone follow up of outcomes.

**Outcomes:** 55 patients underwent laparoscopy with no complications, mean age 25 years (1 – 42). Indications were cancer of breast (31%), cervix (15%), endometrium (7%), other malignancy (16%), disorders of sexual development (7%), other benign disease (11%), and unknown (15%). 1 patient failed biopsy due to adhesions, and 2 patients did not have cryopreservation due to inadequate sample quality. 9% of patients have since died. No patients have since had tissue transplanted, although 1 did request this. Several patients conceived naturally, the remainder either wanted to keep tissue for future treatment or were happy for tissue to be donated for research.

**Discussion:** Patients who underwent ovarian cryopreservation spanned a large age range and suffered from a variety of benign and malignant conditions. Long term survival was good, and overall this treatment was offered to an appropriate cohort. Low numbers of patients requested implantation due to several factors, such as age, general health, natural conception and social reasons.

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## POSTER ABSTRACTS

### 150 The effects of an in vitro culture system on human ovary follicle health and development

**Matthews Rebecca; Liu Jin; Lopes Federica; Morgan Stephanie; Telfer Evelyn; Anderson Richard; Spears Norah**

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**Background:** In vitro culture systems are an invaluable method to investigate ovarian function. The aim of this study was to analyse the degree to which an in vitro system supports the health and development of follicles in human cortical biopsies.

**Methods:** Human ovarian cortical fragments were obtained with informed written consent from women undergoing elective caesarean section (n = 9). Ethical approval was received from the Lothian Research Ethics Committee (10/S1101/24). Tissue was cut into small (0.5 x 1 x 1mm) fragments and each piece placed on a floating polycarbonate membrane in McCoy's culture medium supplemented with human serum albumin, penicillin, streptomycin, human insulin, transferrin, sodium selenite, L-glutamine and ascorbic acid. Half of the medium was replaced with fresh medium every 48 hours, and cultures were maintained for 6 days. Uncultured and cultured fragments were sectioned and stained with H&E.

**Results:** The culture system had no effect on total follicle density. The culture period led to a 77% and 64% decrease in the percentages of primordial and transitional follicles respectively ( $p < 0.001$  and  $p < 0.01$ ), alongside a 360% increase in the percentage of primary/secondary follicles ( $p < 0.0001$ ), showing that follicle development was supported by the culture system. The culture system was also found to have led to an 11-fold increase in unhealthy follicles ( $p < 0.0001$ ), due to an increase in unhealthy primary/secondary follicles ( $p < 0.001$ ).

**Conclusion:** The culture system was found to support growth from the primordial/transitional to the primary/secondary stage over the 6 day culture period. Although there was some compromise in follicle health, the majority of follicles remained healthy. Overall, this technique should provide a useful method to examine the development and regulation of early stage human ovarian follicles.

### 151 Neonatal age does not affect follicle development in reaggregated ovaries

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**Introduction:** Oocyte-somatic interactions can be studied by using the reaggregated ovary (RO) technique, since they can be generated using germ and somatic cells from different sources. To produce an RO, the germ and somatic cells are separated using differential plate adhesion, and reaggregated into a pellet. In vivo RO development involves transplantation of the pellet beneath the kidney capsule of an immunocompromised mouse for 21 days (21d). We have developed an in vitro technique that supports RO development and allows for continuous observation for 14d.

**Aims/Objectives:** Previous published studies with neonatal ROs involved the use of ovaries from P0-P2 mice. Since primordial nest breakdown has not been completed by P2, we investigated whether ROs generated from P6 mice would have better follicle development compared to those generated from P2 mice when cultured for 14d (in vitro) or transplanted for 21d (in vivo).

**Methods:** This study was approved by the Local Ethical Review Panel. ROs generated from 4 neonatal mice (aged P2 and P6) were cultured in Waymouth media containing FSH, insulin-transferrin-selenium, ascorbic acid and FBS, for 14d. ROs were also transplanted beneath the kidney capsule of immunocompromised mice for 21d. ROs were embedded, sectioned, H&E stained and follicle development assessed.

**Results and Discussion:** ROs cultured for 14d (P2: n=4; P6 n=4) contained primary, secondary and preantral follicles. ROs developed in vivo for 21d contained primary, secondary, preantral and antral follicles (P2 n=3; P6 n=3). Follicle development was similar between P2 and P6 ROs both in vivo and in vitro.

These results indicate that ovaries from P6 neonates are no more effective than P2 ovaries for RO generation. Although further studies are needed to optimise follicle development in RO culture, it allows us to observe follicle development over time, which is invaluable for understanding follicle function.

### 152 Proteomic analysis of porcine follicular fluid reveals the differential expression of apolipoproteins and plasminogen associated with pre-mating diet and later fertility

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Glts fed a high fibre (HF) diet during the first 19 days of their third oestrous cycle showed improved fertility compared to glts fed a control (Con) diet. Improvements included an increased proportion of metaphase II oocytes and blastocysts with more cells following in vitro maturation (IVM) and fertilisation (IVF) respectively<sup>1, 2</sup>. We hypothesised that follicular fluid (FF) protein composition is altered by the diet and that these alterations confer the reproductive benefits.

The aim of this study was to compare the protein composition of pooled FF from 12 HF-pigs and 12 Con-pigs. Additionally, within each dietary group, the composition of pooled FF from pigs whose oocytes produced blastocysts following IVF (Con-BI and HF-BI) was compared with FF from pigs whose oocytes did not produce blastocysts (Con-No and HF-No respectively; n=6 per group).

Proteins in each sample were enriched, labelled by di-methylation and detected by liquid chromatography tandem mass spectrometry. There were 180, 478 and 389 differentially expressed proteins (DEPs) detected between Con and HF, Con-No and Con-BI, and HF-No and HF-BI FF respectively. Quantitative western blotting on pooled samples confirmed the differential expression of selected candidates. Plasminogen was lower in HF-FF compared to Con-FF ( $P < 0.05$ ). Apolipoprotein A4 ( $P < 0.01$ ), apolipoprotein M ( $P < 0.05$ ), and plasmin ( $P < 0.05$ ) were higher in Con-BI-FF compared to Con-No-FF. Plasmin was lower in HF-BI-FF compared to HF-No-FF ( $P < 0.05$ ). DEPs were submitted into Ingenuity

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Pathway Analysis, which revealed their association with several canonical pathways including acute phase response signalling, complement system and LXR/RXR activation.

In conclusion, we detected DEPs in porcine FF associated with different pre-mating diets and IVF outcome, four of which have been validated. The DEPs were associated with canonical pathways which uncover mechanism(s) by which the HF diet improves fertility and can potentially be used to refine IVM culture conditions.

Funded by AHDB Pork.

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### 153 Role of Wnt/beta-catenin signal transduction pathway and a crosstalk with Notch system in the proliferation of ovarian cancer cell lines

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Notch and Wnt/beta-catenin are highly conserved pathways which regulate proliferation, apoptosis and differentiation. While Notch system has widely been demonstrated to be involved in ovarian cancer, Wnt/ $\beta$ -catenin pathway has been poorly studied in these tumors. Besides, there is little evidence that suggests a crosstalk between them. We analyzed the effect of inhibiting these two pathways and their interaction in ovarian cancer cell lines. Two human ovarian tumor cell lines, a human granulosa-like tumor cell line (KGN) and a human ovarian adenocarcinoma cell line (IGROV-1) were incubated in the presence of a Wnt inhibitor (the tankyrase inhibitor XAV939: 1, 10, 20 and 50  $\mu$ M), a Notch inhibitor (the gamma secretase inhibitor DAPT: 15, 20  $\mu$ M) or both. We evaluated the involvement of Wnt/ $\beta$ -catenin pathway and a crosstalk with Notch system in cellular proliferation.

Our results show a significant decrease in proliferation when IGROV-1 cells were incubated in the presence of XAV939 (10, 20 and 50  $\mu$ M) or DAPT (15, 20  $\mu$ M). There was also a significant decrease in  $\beta$ -Catenin and Cyclin D1 levels and in addition a significant increase of total Axin when IGROV-1 cells were treated with XAV939. KGN cells also showed a significant decrease in proliferation after incubation with XAV939 (50 $\mu$ M). Most importantly, when IGROV-1 and KGN cells were incubated in the presence of both inhibitors, there was a synergistic decrease in proliferation suggesting a novel crosstalk between these pathways in ovarian cancer cell lines. We also tested a Wnt/ $\beta$ -catenin pathway activator: LiCl. The proliferation results using this compound suggest a biphasic effect related to the Nf- $\kappa$ B action.

In conclusion, we demonstrate a clear involvement of Wnt/ $\beta$ -catenin pathway in ovarian tumor cell proliferation and suggest an interaction between this pathway and Notch system.

### 154 Identification and regulation of Pmepa1 during early follicle development in the mouse ovary

**Sari Zara Novita; Sharum Isam; Granados-Aparici Sofia; Fenwick Mark**  
*University of Sheffield*

In the ovary, androgens are known to promote granulosa cell proliferation, leading to an increased rate of follicle development. Recent evidence indicates the effect of androgens on early follicle growth may also be augmented by local growth factors, including those that activate the TGF $\beta$ -Smad2/3 signalling pathway. In other cell types, the expression of prostate transmembrane protein, androgen induced 1 (Pmepa1) is elevated in response to androgens and TGF $\beta$  signalling, and is often associated with a proliferative phenotype. The latter is partly achieved by promotion of PI3 kinase signalling. Since the growth of small, gonadotrophin-independent follicles is regulated by the PI3 kinase pathway, and these follicles are sensitive to both TGF $\beta$  and androgen signalling, we proposed that Pmepa1 may also be important in this context. The aim of this study was to (i) examine the expression of Pmepa1 in immature mouse ovaries using quantitative PCR (qPCR) and immuno-fluorescence, and (ii), determine the effect of dihydrotestosterone (DHT; 10nM) on the regulation of Pmepa1, Smad3, and other candidates in cultured neonatal ovaries. Results showed the expression of Pmepa1 mRNA was higher in immature ovaries containing many small growing follicles relative to neonatal ovaries containing mostly primordial follicles. Pmepa1 protein was discretely localised in granulosa cells of follicles that had just initiated growth, but was absent in primordial and larger growing follicles. In culture, Pmepa1 mRNA was elevated in neonatal ovaries after 24h exposure to DHT relative to untreated controls, and this coincided with elevated Smad3, but not Smad2. This study provides initial data indicating that Pmepa1 is associated with early follicle development and can be regulated by androgens. The cross talk between androgens and TGF $\beta$  signalling may be an important pre-requisite for the initiation of follicle growth.

### 155 The involvement of transforming growth factor beta 1 in equine functional luteolysis

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<sup>1</sup>Institute of Animal Reproduction and Food Research, Poland;

<sup>2</sup>CIISA, Faculty of Veterinary Medicine, University of Lisbon, Lisbon, Portugal

The corpus luteum (CL) is a transient endocrine organ determinant for pregnancy establishment in several species. However, CL regression allows for the resumption of a new oestrous cycle. The molecular regulation of luteolysis is an intricate process, far from being fully understood. We have recently characterised the involvement of Nodal, a morphogen from transforming growth factor  $\beta$  (TGF) superfamily, on luteolysis in the mare. In the present work we have demonstrated the involvement of TGF $\beta$ 1 in equine luteolysis.



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Protein location of TGF and its receptors I (ALK5) and II (TGFRII) shown by immunohistochemistry throughout the luteal phase. An in vitro study with enzymatically isolated luteal cells (n=6/group) from mid-CL, cultured in T25 culture flasks (5.0x10<sup>6</sup>cells/mL), was performed. Cells were treated for 24h with: (i) no factor; (ii) TGF (1 to 5 ng/mL); (iii) prostaglandin (PG) F<sub>2</sub>α (10<sup>-7</sup>M); or (iv) luteinizing hormone (LH) (10ng/ml). The mRNA was evaluated by relative quantification real-time PCR (normalization with β2-microglobulin - B2MG) and protein quantified by western blotting (normalization with β-Actin).

Protein for TGF, ALK5 and TGFRII were stained in endothelial and large luteal cells. Also, TGF and ALK5 mRNA and protein expression increased from early to mid-CL (in vitro protocol, TGF treatment consistently decreased mRNA transcription and protein expression of steroidogenic enzymes StAR, CYP11A and 3βHSD (p<0.05). Regarding the in vitro protocol, TGF treatment consistently decreased mRNA transcription and protein expression of steroidogenic enzymes StAR, CYP11A and 3βHSD (p<0.05), as well as mPGES1 and cPGES (p<0.05). Conversely, TGF promoted the expression of both PGFS and PTGS2 (p<0.05). Hormonal concentration in the culture media confirmed the enzymatic profile, with a decrease in P4 and PGE2 and an increase in PGF2α (p<0.05). Our results clearly suggest the involvement of TGF signalling in functional luteolysis in mares. Thus, TGF superfamily members appear to have an important role in equine CL regression.

Work supported by MS&HE "Juventus Plus" (IP2014011373).

### 156 The role of leptin signalling in ovarian pathogenesis during obesity

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Obesity has a detrimental effect on ovarian function and fertility. Importantly, leptin (LEP), the major adipokine secreted, can affect ovarian function. We have previously demonstrated that LEP signalling is altered in the ovary of mice subjected to diet-induced obesity (DIO). Thus, in the present work we validate an in vivo model for pharmacological hyperleptinemia, to address the role of leptin on ovarian pathology in the course of obesity establishment in mice.

In the DIO protocol, C57Bl/6J (B6) mice were fed chow diet (CD) or high-fat diet (HFD) for 4 and 16 weeks (wk). In the pharmacological hyperleptinemia protocol, the daily leptin dose of 25ug (n=4), 100ug (n=10), or NaCl (n=7), have been administered intraperitoneally for 9 days. Ovaries were collected for mRNA analysis. Animal phenotype was monitored with nuclear-magnetic-resonance.

Leptin treatment at 100ug significantly decreased body weight (p<0.05), fat mass (p<0.001) and adiposity index (p<0.01). The mRNA of the ovarian functional marker Steroidogenic Acute Regulatory Protein (Star) was reduced after 16wk HFD and in both 25 and 100ug LEP, comparing to the respective controls (p<0.05). Most importantly, after 100ug LEP, Star mRNA was the lowest for all treatments, confirming LEP inhibitory effect on ovarian steroidogenesis. Regarding LEP signalling, after 16wk HFD, the mRNA level of leptin receptor b (ObRb) was decreased (p<0.05), as well as after 100ug LEP (p<0.01). The transcription of protein-tyrosine phosphatase 1B (Ptp1b)

was significantly increased after 16wk HFD and 100ug LEP (p<0.05), while the Suppressor of Cytokine Signalling 3 (Socs3) RNA was augmented after 16 wk HFD (p<0.05) and 25ug LEP (p<0.01). In conclusion, both DIO and pharmacological hyperleptinemia protocols showed impairment of LEP signalling, followed by active Ptp1b and Socs3 transcription, which might be determinant for ovarian pathogenesis during obesity progression.

Work supported by National Science Centre (2014/15/D/NZ4/01152)

### 157 Characterisation of microRNAs and zeta potential of extracellular vesicles secreted by porcine oviductal epithelial cells

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**Introduction:** The interaction of gametes and embryo with the maternal tract has an important impact on achieving a successful pregnancy. Extracellular vesicles (EVs) are known to carry microRNAs (miRNAs), which can be taken up by neighbouring and distant cells and probably modulate the function of the recipient cells. In this study we examined the presence of miRNAs in EVs derived from Porcine oviductal epithelial cells (POEC) secretions. We also measured the electrical surface properties of the POEC EVs known as zeta potential.

**Materials and Methods:** EVs were purified from conditioned medium (CM) by size exclusion chromatography (SEC) using Sepharose CL-2B SEC columns. Twenty eluted fractions each of 500ul volume were collected and analysed by Zetaview nanoparticle tracking analyser (Particle Metrix GmbH, Meerbusch, Germany) to measure EV concentration, size distribution and zeta potential. EV RNA extraction was performed using the miRCURY RNA isolation kit and quantified using a 2100 Bioanalyser. Real time-PCR was performed to quantify expression of ten miRNAs (miR-103, let-7a, miR-19a, miR203, miR126, miR19b, miR92, miR196a, miR326 and miR23a).

**Results:** Size particle analysis confirmed the presence of particles with the diameter of 50nm-350nm. The mean±standard deviation of zeta potential value was 32±0.5mV. Real time-PCR results showed that only six of the tested miRNAs (miR-103, let-7a, miR-19a, miR203, miR126, and miR19b) were detectable in EVs and had a mean threshold cycle (CT) value of 29 and higher. Bioinformatics analysis suggests that these miRNAs are involved in cell cycle, proliferation, apoptosis and migration.

**Conclusions:** The zeta potential result indicated that POEC EVs have strong anionic charges and are stable in solution therefore do not form aggregates. Furthermore our results suggest that POEC EVs contain miRNAs that can potentially serve as important signals in intercellular communications and modulate events leading to a successful pregnancy.

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### 158 Differential circulating microRNA levels as early as Day 8 of pregnancy in cattle

**Ioannidis Jason<sup>1</sup>; Donadeu Xavier<sup>2</sup>**

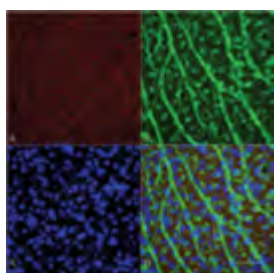
<sup>1</sup>The Roslin Institute; <sup>2</sup>Roslin Institute, Edinburgh

Low fertility is a major problem in the dairy industry, with very low calving rates that have implications for profitability and animal welfare. Early pregnancy detection could help identify non-pregnant animals within three weeks of insemination, shortening calving intervals. However, current pregnancy detection methods are limiting and cannot support such reproductive management programs. MicroRNAs (miRNAs) have been proposed as non-invasive biomarkers of pregnancy and reproductive disease in humans. The aim of this study was to determine if different profiles of circulating miRNA can be identified in early pregnancy for potential use as pregnancy biomarkers. Using miRNA sequencing, we detected 389 unique miRNAs in bovine plasma and identified 14 miRNAs with differential expression (fold-change > 2, FDR < 0.05) on Day 60 of pregnancy compared to Day 0 (non-pregnant). Results for six miRNAs were validated using RT-qPCR (let-7c, let-7f, miR-101, -143, -30c and -26a). In a follow-up experiment we profiled eight miRNA candidates during the first eight weeks of gestation and identified, for the first time, a significant increase in miR-26a levels and the miR-26/miR-205 ratio as early as Day 8 of pregnancy (2.1-fold and 7.5-fold, respectively). RT-qPCR profiling across bovine tissues showed the majority of these miRNAs are ubiquitously expressed, with the exception of miR-205 which was 8,000-fold enriched in skin compared to other tissues. Existing literature suggests that these miRNAs have roles in immunity (miR-26a, let-7f), angiogenesis (miR-101, miR-205, miR-26a) and metabolism (miR-143, miR-101, miR-30c, miR-26a). Future work could focus on identifying the specific source of the differential miRNA levels and their roles during early pregnancy. This is the first report of differential circulating miRNA expression at such an early stage of pregnancy and our findings suggest that embryo-to-maternal communication occurs prior to maternal recognition of pregnancy, which typically occurs on Day 15 in the cow.

### 159 The effects of in utero inflammation on the developing heart

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Intrauterine inflammation with or without infection induces preterm labour, causing damage to the developing foetus. This causes deleterious changes to the foetal heart seen as an accelerated maturation of the foetal heart, change in cardiomyocyte characteristics; altering the cardiac function.

We studied the effects of intrauterine lipopolysaccharide (LPS) on the foetal heart of an early gestation sheep model. The aim was to design a protocol

for staining cardiomyocytes and to determine the effects of LPS on cardiomyocyte density and proliferation rate in the right ventricle (RV) and left ventricle + Septum (LV+S).

Pregnant sheep received an intra-amniotic injection of 10mg of LPS (n=5) or 2ml of phosphate buffered saline (PBS: n=4) on gestation day 89 (term = 150 days). The foetal hearts were collected 7 days later for analysis. Cardiomyocytes were stained using Troponin, Wheat germ agglutinin and Topro3. Ki-67 staining was carried out to access the percentage of proliferating cells.

The cardiomyocyte density and percentage of proliferating cells were not significantly different between groups. The cardiomyocyte density (cardiomyocyte per area counted) for the RV was 219.6±10.76 in the LPS group and 211.0±10.63 in the PBS group (p=0.59); LV+S was 263.0±1.80 in the LPS group and 251.5±1.85 in the PBS group (p=0.51). The percentage of proliferating cells in the RV was 37.20±1.80 in the LPS group and 33.50±1.85 in the PBS group (p=0.11). All results are expressed as mean ± standard error of the mean.

These indicate that intrauterine inflammation in this model does not have an effect 7 days later on the heart parameters tested. However, further research is needed since there is a known link between preterm birth and cardiovascular disease in adulthood.

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## POSTER ABSTRACTS

### 160 An investigation into the effect of IL-33 on nitric oxide production by placental endothelial cells

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Pre-eclampsia (PE) is estimated to affect ~6% of pregnancies in the UK and is considered to be due to endothelial dysfunction as a result of inappropriate placental inflammation. Previous research has shown that the systemic levels of the pro-inflammatory cytokine IL-33 and its receptor (ST2) vary throughout pregnancy, although any role this cytokine and its receptor play in the pathogenesis or protection against PE is yet to be fully determined. The aim of this project was to investigate the effect of IL-33 on the ability of placental endothelial cells to produce nitric oxide (NO). NO is a vasodilatory substance produced by the endothelium in response to stimuli. Human umbilical vein endothelial cells (HUVECs) were plated out in 96 well plates and incubated at standard conditions (37°C/5% CO<sub>2</sub>) for 24/48hrs to allow cells to adhere. Media was removed, and replaced with fresh medium, or medium supplemented with IL-33 (0.1, 1, 10 and 100ng/ml) or lipopolysaccharide (LPS) from 055:B5 or 0111B4 strains of *E. coli* (n=3/concentration). After exposure to IL-33 or LPS for 24 or 48 hours, cell supernatant was collected and Greiss assays performed to determine nitric oxide production. HUVECs were exposed to IL-33 (0, 1, 10, 100ng/ml) for 18 hours, RNA extracted and cDNA synthesized and PCR carried out for eNOS and iNOS, and the endogenous control gene TOP1. Both LPS and IL-33 did not induce nitric oxide production by HUVECs as determined by the Greiss assay. In addition, while mRNA for both eNOS and iNOS was detected, differences in expression levels in response to stimulation were not observed. These results suggest that IL-33 has no effect on nitric oxide production by HUVECs, although this does rule out a role for IL-33 in the development of PE. Studies to examine the impact of IL-33 on placental function are ongoing.

### 161 Aneuploidy rate and copy number variation profiling of equine placentas from failed early pregnancies

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<sup>1</sup>Royal Veterinary College, London; <sup>2</sup>Texas A and M University, USA

Early pregnancy loss (EPL) occurs in around 8% of equine pregnancies, with EPL rates increasing to greater than 20% in older mares. Our recent work successfully isolated and cultured placental cells from failed equine pregnancies, allowing investigations into the genetic causes of EPL in the mare. The primary aim of this work was to determine the aneuploidy rate in these lost pregnancies. Additionally, we aimed to determine if translocations or other structural genetic abnormalities play a role in EPL. Failed pregnancies identified by routine ultrasound examinations were collected by attending veterinarians using sterile uterine lavage (n=14). Conceptuses had a mean gestational age of 39 days (range 26-65) from mares with median age 13 years (range 4 – 19). These conceptuses had no known attributable cause for the

EPL. Genomic DNA (gDNA) was extracted from allantochorion isolated from conceptuses. Samples (n=12) were labelled with Cyanine 5-dUTP and male/female controls labelled with Cyanine 3-dUTP. Array Comparative Genomic Hybridisation (aCGH) was performed using a 400K whole genome tiling array and data analysed using Agilent Genomic Workbench. Additionally, trophoblast cells were isolated from the allantochorion for karyotyping using standard methods (n=2). No aneuploidies (0/14) were detected using either method of analysis. Eighty three copy number variation regions (CNVRs) were identified including 17 novel regions. The majority of the CNVs were in genic regions (77%), representing 10 gains, 70 losses and 3 complex regions. Mean size of CNVRs was 34kb (range 0.4-196). Genes involved in signal transduction, genome stability and DNA post replication repair were amongst those found in CNVRs. Karyotypes of trophoblast cells from two failed pregnancies were normal. This work suggests aneuploidies are not a significant cause of EPL in mares. Future work will quantify these identified CNVRs throughout normal placentation and determine their possible significance in contributing to EPL.

### 162 Evaluation of ET day and patient age group on clinical pregnancy rates (CPR) and multiple pregnancy rates (MPR) at Leeds Centre for Reproductive Medicine

**Smith Michael; Thompson Karen**

*Leeds Centre for Reproductive Medicine*

The HFEA demands an effective eSET strategy to limit multiple births <10%. This audit aimed to identify patient groups contributing the most to multiple pregnancies.

3769 IVF/ICSI cycles for patients ≤ 43 years with ET (2013-2016) were analysed, and patients were grouped by age.

The CPR declined with age from 46.0% in patients <35, to 28.2% in patients aged 40-43 (p<0.01). The MPR increased with age from 9.2% in patients <35 to 19.2% in patients 40-43, p<0.05).

Patients having a day 3 (vs day 5) ET had a lower CPR (34.8 % vs 49.2%, p<0.01), and a higher MPR (14.4% vs 10.0%, p<0.05). Day 3 ETs accounted for 34.1% of all multiple pregnancies, with no difference in MPR between age groups.

For Day 5 ETs, if 2 good blastocysts were available for ET (≥2Bb) and 2 transferred, there was no significant difference in MPR between age groups (overall 51.1%); however, where only 1 good blastocyst was available, the MPR was higher in DET patients <38 vs those 38-43 (42.5% vs 12.5%, p<0.05). DET in both groups accounted for 8.8% of all ETs, but yielded 37.3 % of all multiple pregnancies.

Performing more day 5ETs and restricting day 5 DET, where good blastocysts are available, has lowered the MPR to below the 11.5% average over this period.



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### 163 The influence of age and body mass index on mode of delivery, following IVF treatment

**Supramaniam Prasanna<sup>1</sup>; Mittal Monica<sup>1</sup>; Bevan Aysha<sup>2</sup>; Lim Lee Nai<sup>1</sup>; Child Tim<sup>2</sup>**

<sup>1</sup>Oxford University Hospitals NHS Foundation Trust; <sup>2</sup>Oxford Fertility Unit

Aims/Objectives:

1. To determine if the age of the woman and her body mass index (BMI) influences mode of delivery in women undergoing assisted reproductive techniques (ART).
2. To enable appropriate allocation of services for the intrapartum management of women who conceive through ART.

Content: Retrospective cohort analysis of women who underwent ART between January 2009 to March 2014 (n=7315 cycles), in a single fertility unit undertaking NHS and self-funded cycles; the population was subdivided into those with a singleton pregnancy from a fresh cycle. The overall live birth rate (LBR) during this period was 33.2% (singleton 27.6% [n=2017], multiple pregnancy rate (MPR) 5.6% [n=413]). No mode of delivery data was available for 14 cycles. Statistical significance was classified with a p value < 0.05.

Relevance/Impact: An increasing number of women are undergoing ART between the age brackets 30-40 years. This study has shown that these women have a higher risk of a caesarean section (CS) with an increasing BMI. The impact of a high BMI on CS and maternal morbidity and mortality is well documented. The subsequent impact on local obstetric units should therefore be considered.

Outcomes:

Age: 36-40 years; LBR: 24.3%

| BMI   | Vaginal Delivery | Caesarean Section | Total |
|-------|------------------|-------------------|-------|
| ≤25   | 310              | 165(34.7%)        | 475   |
| 36-30 | 109              | 102(48.3%)        | 211   |
| 31-35 | 11               | 11(50%)           | 22    |
| >35   | 2                | 0(0%)             | 2     |
| Total | 432              | 278(39.15%)       | 710   |

Age: 41-45 years; LBR: 10.7%

| BMI   | Vaginal Delivery | Caesarean Section | Total |
|-------|------------------|-------------------|-------|
| ≤25   | 29               | 27(48.2%)         | 56    |
| 36-30 | 12               | 9(42.9%)          | 21    |
| 31-35 | 0                | 2(100%)           | 2     |
| >35   | 1                | 0                 | 1     |
| Total | 42               | 38(47.5%)         | 80    |

Age: ≤30 years; LBR: 36.6%

| BMI   | Vaginal Delivery | Caesarean Section | Total |
|-------|------------------|-------------------|-------|
| ≤25   | 147              | 54(27.6%)         | 203   |
| 36-30 | 55               | 16(22.5%)         | 71    |
| 31-35 | 5                | 4(44.4%)          | 9     |
| >35   | 0                | 0(0%)             | 0     |
| Total | 207              | 76(26.9%)         | 283   |

Age: 31-35 years; LBR: 39.2%

| BMI   | Vaginal Delivery | Caesarean Section | Total |
|-------|------------------|-------------------|-------|
| ≤25   | 493              | 188(27.6%)        | 681   |
| 36-30 | 137              | 86(38.6%)         | 223   |
| 31-35 | 11               | 9(45%)            | 20    |
| >35   | 4                | 1(20%)            | 5     |
| Total | 645              | 284(30.6%)        | 929   |

Mode of delivery is not influenced by BMI category in women aged <30 or 41-45 years (p = 0.54 and p = 0.35, respectively). However, in women aged between 31-40 years a reducing rate of achieving a vaginal delivery with increasing BMI and an increasing risk of a CS is demonstrated (p < 0.05).

Discussion: Women under the age of 30 years and more than 40 years are equally likely to achieve a vaginal delivery across all BMI subgroups similar to the background population. However, women aged between 30-40 years, have a higher CS rate for increasing BMI categories compared to background population.

1. G.M. Chambers(2014), Hospital utilization, costs and mortality rates during the first 5 years of life: a population study of ART and non-ART singletonsHum. Reprod. (2014) 29 (3): 601-610 first published online December 4, 2014

2. NICE Intrapartum Care 2015

3. Sherri Jackson (2014) Pregnancy outcomes in very advanced maternal age pregnancies: the impact of assisted reproductive technology Fertility and Sterility, Vol. 103, Issue 1, p76-80

4. Herstad L(2016) Elective cesarean section or not? Maternal age and risk of adverse outcomes at term: a population-based registry study of low-risk primiparous women. BMC Pregnancy Childbirth. 2016 Aug 17;16:230. doi: 10.1186/s12884-016-1028-3.

### 164 Quantitative $\beta$ HCG concentrations at defined outcome points are predictive of likelihood of ongoing pregnancy

**Hamilton Tracey; Gaudoin Marco; Fairbairn Craig; Fleming Richard**  
GCRM, Glasgow

Aims: Serum  $\beta$ HCG concentrations rise with implantation and embryo development. The range is considerable, but lower  $\beta$ HCG levels are associated with pregnancy failure. Given that many IVF pregnancies result in developmental failure, it may be useful to determine the predictive power of serum  $\beta$ HCG concentrations regarding the likelihood of ongoing pregnancy.

Content: We examined the serum  $\beta$ HCG concentrations on the morning of day-17 after trigger in 1846 consecutive ART cases where the pregnancy test was "positive" ( $\beta$ HCG >10 IU/L). We matched categories of the  $\beta$ HCG concentration to the clinical outcomes determined at scan at 7/8 weeks. The defined outcomes were: 'biochemical' pregnancy (bleeding and failure prior to scan; N=187), non-continuing pregnancy (no bleeding but empty sac/absent fetal heartbeat at scan; N=50) and clinical pregnancy (single positive heartbeat at scan; N=521). Twin pregnancies were excluded from analyses.

Relevance: The data may be used to inform patients and providers. Further analyses are required for natural and constructed cycles, and also for days other than trigger+17.

Outcomes: When the  $\beta$ HCG concentration on trigger+17 was <30 IU/L (n=82), 93% resulted in a biochemical pregnancy, 4% in a non-continuing pregnancy and only 2% in an ongoing clinical pregnancy. With  $\beta$ HCG concentrations of 30-50 IU/L (n=68), these figures were respectively 59%, 15% and 24%. If the  $\beta$ HCG concentration was 50-70 IU/L these figures were respectively 36%, 11% and 52%. With  $\beta$ HCG concentrations >70 IU/L these figures were respectively 8%, 5% and 86%

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( $P < 0.01$ , Anova).

Discussion: These data show that  $\beta$ HCG concentrations on trigger+17 have a strong predictive power for subsequent pregnancy outcome.

When lower concentrations are identified, patients can be advised of likely outcomes with more precision and can be psychologically better prepared for the greater likelihood of a non-continuing pregnancy.

### 165 Low serum $\beta$ HCG concentration at trigger+17 is a marker of adverse perinatal outcome in ART cycles

**Gaudoin Marco; Hamilton Tracey; Ambrose Pat; Banks Claire; Mitchell Paul; Fleming Richard**  
*GCRM, Glasgow*

**Aims/Objectives:** Serum  $\beta$ HCG concentrations rise with embryo implantation and lower levels on trigger +17 are associated with increased risk of early pregnancy loss (embryo competency.) It may also be a potential marker of adverse perinatal outcome and may contribute scientifically to our understanding of pregnancy evolution. We aimed to explore relationships between the  $\beta$ HCG concentration on trigger+17 and subsequent perinatal outcome.

**Content:** Perinatal outcomes of all singleton pregnancies following ART delivering after 24 weeks' gestation (viable) in consecutive cases from November 2006 to August 2015. Categorisation was based on a serum  $\beta$ HCG concentration below and above 80 IU/L on the morning of trigger day+17. We examined the mean birthweight, mean gestational age at delivery, rate of prematurity and controlled for maternal age and BMI.

**Relevance/Impact:** ART pregnancies are at greater risk of poorer perinatal outcome, compared to naturally conceived pregnancies, possibly due to adverse implantation conditions associated with the IVF process itself.

**Outcomes:** 55 women had a  $\beta$ HCG concentration  $< 80$  IU/L (Group1). 418 women had a  $\beta$ HCG concentration  $\geq 80$  IU/L (Group2). There were no differences in the age (36.1y vs 35.1y respectively), BMI (24.0Kg/m<sup>2</sup> vs 24.2Kg/m<sup>2</sup>) or median delivery gestation (277d vs 277d) between the groups. However, there was a higher proportion of singletons  $< 3000$ g in Group1 (36% vs 21%,  $P < 0.02$ ) and a higher rate of premature delivery (31% vs 15%,  $P < 0.007$ ).

Discussion: These data suggest that a  $\beta$ HCG concentration threshold below 80 IU/L identifies compromised implantation of embryos leading to a higher risk group of singleton ART pregnancies. It also supports other data that subsequent perinatal outcome is influenced by embryo competency at a very early stage<sup>1,2</sup>.

1. Dumoulin JC et al. Effect of in vitro culture of human embryos on birthweight of newborns. Hum Reprod. 2010; 25(3): 605-12
2. Sunde et al. Time to take human embryo culture seriously. Hum Reprod. 2016 Aug 23. pii: dew157. [Epub ahead of print]

### 166 Laboratory culture environment affects mitotic aneuploidy, not meiotic aneuploidy

**Hickman Cristina<sup>1</sup>; Wells Dagan<sup>2</sup>; Lavery Stuart<sup>3</sup>**

<sup>1</sup>Boston Place Clinic, London; <sup>2</sup>Reprogenetics UK; <sup>3</sup>The Fertility Partnership

**Aim:** Previous study presented by our group suggested that the culture of embryos in two different media at different pHs (A: KSOM supplemented with  $\alpha$  and  $\beta$  globulins at pH 7.27 vs B: Sage supplemented with HSA at pH7.14) led to a 3.5-fold difference in biochemical loss rate (23.6%vs6.7%,  $p < 0.025$ ), and two-fold difference in proportion of euploid embryos (16%,N=141 vs 29%,N=154,  $p < 0.025$ ) in favour of culturing embryos in a more acidic environment. The objective of this study was to assess the database with regards to type of aneuploidy: meiotic or mitotic.

**Content:** This study refers to the largest balanced randomised controlled blind sibling study to date assessing the effect of culture environment on ploidy rate and biochemical loss (2620 mature oocytes from 363 patients). This abstract refers to detailed genetic assessment of a subset of this study to clarify the source of the aneuploidy observed: Treatment A (N=28) and B (N=37).

**Relevance:** Several studies have demonstrated that media composition and pH may have an impact on the quality of embryos generated, implantation, live birth and perinatal outcome and weight. With a variety of media composition used in IVF, it is still unclear what is the ideal composition and pH to culture human embryos in.

**Outcomes:** There was no difference between treatments with regards to meiotic aneuploidy (Treatment A vs B: 12/28=43% vs 20/37=54%). Treatment A had a greater proportion of mosaic embryos (with or without meiotic aneuploidy: 19/28=68% vs 13/37=35%,  $p = 0.011$ ), a greater proportion of mosaic embryos in the absence of meiotic errors (12/28=43% vs 3/37=8%,  $p = 0.002$ ) and a lower proportion of euploid embryos (4/28=14% vs 14/37=38%,  $p = 0.05$ ) compared to treatment B.

**Discussion:** Culture environment may reduce the number of euploid embryos available for transfer by increasing mitotic errors leading to increased proportion of mosaic embryos.

### 167 Comparison of outcomes from two media - dual culture systems best practice for ART?

**Davidson Olivia; Snell Phil; McGrane Mollie; Oakley Rebecca; Blayney Martyn; Shaikly Valerie**

*Bourn Hall Clinic, Cambridge*

**Aims/Objectives:** To investigate the relative performance of two commercial media, A and B. By comparing differences in Key Performance Indicators (KPI) we evaluate the use of a dual culture system.

**Content:** Retrospective analysis of KPI for a dual culture system of 988 fresh ART cycles in which embryos were transferred from a single medium. Following insemination normally fertilised oocytes were split between Media A and B and cultured until day 5. Cleavage, blastocyst formation, utilisation, clinical pregnancy and miscarriage rates for each media were compared for statistical differences using Fishers Exact test.



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**Relevance/Impact:** Dual culture systems, although more labour intensive, are practiced due to improved outcomes having been reported compared to the use of a single culture media, within a patient cycle.

**Outcomes:** Differences between blastocyst formation and utilisation rates in Media A and B were not significant,  $P > 0.5$  (65.3% vs 63.4% and 35.7% vs 35.5% respectively). Similarly no significant difference was observed in CPR for patients where the embryos that were transferred had been cultured in either media A or B, (42.9% vs 45.3%)  $P > 0.5$ . However a significant difference was observed for cleavage rate in media A compared to media B  $P < 0.5$  (97.6% vs 96.7%).

**Discussion:** Evidence has shown that culture conditions are critical for IVF outcome. Commercialisation of culture media has necessitated strict quality control and standardisation. Despite this, differences in media composition have been suggested, and observed in specific cases in our clinic, to favour development of embryos in a patient specific manner. Taking this into account, alongside additional effects of media batch variation, although no significant difference in clinical outcome was observed in this investigation we believe it is best practice at our clinic to continue to operate a dual culture system.

1. Chronopoulou, Elpiniki, and Joyce C. Harper. "IVF culture media: past, present and future." Human reproduction update (2014): Vol.0, No.0 pp. 1–1

### 168 IVF laboratory environmental effects on treatment success and offspring birth weight: A national culture media questionnaire and HFEA Register data linkage study

**Castillo Catherine<sup>1</sup>; Harper Joyce<sup>2</sup>; O'Neill Helen C<sup>2</sup>; Johnstone Edward<sup>3</sup>; Roberts Stephen A<sup>4</sup>; Brison Daniel R<sup>5</sup>**

<sup>1</sup>School of Medical Sciences, Division of Developmental Biology & Medicine, University of Manchester; <sup>2</sup>Institute for Women's Health, University College London; <sup>3</sup>Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre; <sup>4</sup>Centre for Biostatistics, University of Manchester; <sup>5</sup>Dept. of Reproductive Medicine, Central Manchester University Hospitals NHS Foundation Trust

**Introduction:** The impact of culture medium and conditions on IVF treatment success rates and offspring birth weight (BW) is largely unknown. This study aimed to examine these factors in a national survey capturing the range of clinical practice.

**Methods:** Data from a survey circulated to all UK IVF clinics requesting information regarding culture media brand, incubator type and oxygen level used between January 2011 and December 2013 was merged with routinely recorded treatment and outcome data held in the Human Fertilisation and Embryology Authority (HFEA) Register. IVF success (live birth event [LBE]) and singleton gestation-adjusted BW were analysed using logistic and linear regression models adjusting for patient/treatment characteristics and clinic-specific effects.

**Results:** 46 (62%) UK clinics responded. A total of 75,287 fresh IVF/ICSI cycles were captured, including 18,708 singleton LBEs. There were statistically significant differences in LBE rates between three of the nine culture media ( $p = 0.0097$ ). None of the primary factors showed statistically significant associations with BW after controlling for treatment clinic. Additional prognostic patient and treatment

factors including: years of infertility (OR for LBE=0.98,  $p < 0.0001$ ; BW difference=-3.2g per year of infertility,  $p = 0.004$ ), days of embryo culture (OR=1.29,  $p < 0.0001$ ; BWdiff=15.89g/day,  $p < 0.0001$ ), and the transfer of two embryos vs. one (OR=1.28,  $p < 0.0001$ ; BWdiff=-25.46g,  $p < 0.0001$ ) were shown to have statistically significant associations with both IVF success and adjusted BW.

**Conclusions:** This study is the largest UK-based investigation of laboratory environmental effects in IVF on both live birth outcome and singleton BW. The impact of culture media type on IVF success is robustly shown. RCTs are needed in order to reliably determine any effects on the health of IVF conceived offspring. Confounding between treatment practice and clinic may have masked other treatment effects, and larger datasets with more intra-centre variation are needed – these factors need to be comprehensively recorded in national treatment registries.

### 169 Evaluation of a "freeze-all" strategy

**Sellers Rafael; Ten Jorge; Sellers Francisco; Rodríguez-Arnedo Adoración; Llácer Joaquín; Bernabeu Rafael**  
*Instituto Bernabeu, Spain*

**Objectives:** The aim of this study was evaluate the effectiveness of our elective vitrification program.

**Content:** Retrospective study, conducted since January 2014 to December 2015 including 249 autologous cycles, 99 cycles where elective embryo vitrification and diferred transfer were performed compared with 150 treatments with fresh embryo transfer and vitrification of the remaining embryos.

**Impact:** An effective elective vitrification strategy is key determinant in order to avoid some of the complications derived from assisted reproduction cycles as well as it has been suggested that pregnancy chances could be improved.

**Outcomes:** Baseline characteristics as maternal age, endometrial thickness, and number of embryos transferred were homogeneous in both groups. In 54.5% of cases the indication for elective vitrification was to prevent Ovarian Hyperstimulation Syndrome (OHSS), avoided in all cases. Top quality embryos (grade A and/or B according to ASEBIR criteria) showed higher positive pregnancy test in freeze-all group (58.5% vs. 42.9%,  $p = 0.082$ ), as well as clinical pregnancy rate (41.5% vs. 32.5%,  $p = 0.360$ ) and implantation rate (35.2% vs. 27%,  $p = 0.230$ ), although not significant.

**Discussion:** "Freeze-all" is mainly supported by the consistent results offered by the embryo vitrification program conducted in our IVF laboratory. In our case, especially in patients at risk of OHSS, is the first choice strategy. Moreover, the possible asynchrony between embryos and the endometrium is avoided when we apply this strategy.

### 170 Does assisted hatching of vitrified blastocysts improve clinical outcomes?

**Thomson Andrew; Turner Karen; Child Tim**  
*Oxford Fertility*

Assisted hatching (AH) has been proposed as a method to bypass zona pellucida (ZP) hardening when warming vitrified blastocysts to try and improve overall outcomes. AH is not currently recommended to be performed by NICE guidelines or the 2012 Cochrane review.



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This is a retrospective study of 747 (579 after exclusion criteria) frozen embryo replacement (FER) cycles over a 3 year period (October 2009- December 2012 inclusive) at Oxford Fertility (OF) which appears to be the largest study to date investigating AH in vitrified/warmed blastocysts. All patients undergoing FER from October 2009- June 2011 did not undergo AH (208), whereas all patients from July 2011 until December 2012 did have AH performed (371). Data analysis demonstrated that performing assisted hatching on warmed vitrified blastocysts had no significance on pregnancy (No AH vs AH, 45.2% vs 43.4%, 94/208 vs 161/371,  $P=0.68$ ), implantation (30.2% vs 29.0%, 93/308 vs 146/503,  $P=0.72$ ), miscarriage (7.7% vs 11.6%, 8/104 vs 17/146,  $P=0.30$ ) and live birth rates (38.9% vs 33.2%, 81/208 vs 123/371,  $P=0.16$ ). No ectopic pregnancies were observed. Data was also reanalysed allowing for patient age at the time of vitrification (<38 years, no AH vs AH, 182 vs 324 and  $\geq 38$  years, 43 vs 30) and again no significant difference in any of the above outcomes were observed.

**In conclusion:** This retrospective study confirms the recommendations of NICE guidelines that AH should not be performed. No significant difference on pregnancy, implantation, miscarriage, ectopic and live birth rates were observed regardless of age.

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De Vos, A. Van Steirteghem, A. (2000) Zona hardening, zona drilling and assisted hatching: new achievements in assisted reproduction. Cells Tiss. Organs, 166, p220-227.

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NICE. (2013). Fertility: Assessment and treatment for people with. NHS.

### 171 Retrospective study of first UK cases using cytokine enhanced extended culture medium (BlastGen) for clinically indicated patients

**Berrisford Kathryn<sup>1</sup>; Campbell Alison<sup>2</sup>; Jenner Lucy<sup>1</sup>**

<sup>1</sup>CARE Nottingham; <sup>2</sup>CARE Fertility Group

**Aims:** EmbryoGen culture medium (Origio) containing a naturally occurring cytokine growth factor Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) was introduced to our IVF group in March 2013 for patients based on history of miscarriage or recurrent implantation failure. A complementary medium, BlastGen (Origio) was introduced in March 2016. BlastGen contains the same GM-CSF as EmbryoGen, but, unlike EmbryoGen, the carrier medium supports extended culture. The introduction of any change into an IVF centre requires careful control which includes regular evaluation.

**Content:** Data was retrospectively analysed following the treatment of the first 11 patients using BlastGen (mean age 35.4) and compared to an unmatched concurrent control group, not indicated for EmbryoGen/BlastGen (1081 ETs; mean age 35.9) and also to the benchmark group of patients using EmbryoGen before the introduction of BlastGen (109 ETs; mean age of 37.4). These benchmark patients either had a day 3 embryo transfer or extended culture was carried out in standard culture media.

**Relevance/Impact:** Promising results for this cohort of patients were achieved. Biochemical pregnancy rate (hCG/ET) was 54.5% (6/11), clinical pregnancy rate (CPR/ET) the same and implantation rate 42.1% (8/19).

**Outcomes:** Clinical outcome for the BlastGen group was comparable to both control groups. Those without clinical indications for using EmbryoGen/BlastGen during the same time period, with hCG/ET 54% and CPR/ET 43.9% and biochemical loss rate of 18.7% and those using EmbryoGen alone, with hCG/ET 59.6% and CPR/ET 50% and biochemical loss rate of 18.5%.

**Discussion:** EmbryoGen has been established as a preferred culture media for patients with recurrent implantation failure and/or previous miscarriages, however with our successful extended culture program, BlastGen was considered an important addition, as EmbryoGen is not designed for extended culture. Although numbers remain small, clinical outcomes for this difficult group of patients is encouraging.

### 172 Serum concentrations of Ang-2 and Flt-1 are predictive of outcome in women with pregnancies of uncertain viability

**Richardson Alison<sup>1</sup>; Deb Shilpa<sup>2</sup>; Campbell Bruce<sup>3</sup>; Raine-Fenning Nick<sup>1</sup>**

<sup>1</sup>University of Nottingham/Nurture Fertility; <sup>2</sup>Nottingham University Hospitals NHS Trust; <sup>3</sup>University of Nottingham

**Introduction:** Following current UK guidelines, women with pregnancies of uncertain viability (PUV) have to wait at least 7 days before finding out whether their pregnancy is ongoing or not. This generates considerable anxiety for women and utilizes limited resources within the EPAU setting.

**Objectives:** To determine whether serum [Ang-1], [Ang-2] and/or [Flt-1] can be used to predict viability in women with a PUV.

**Methods:** We undertook a prospective study of women presenting to the EPAU at the Queen's Medical Centre, Nottingham between 17.06.14 and 01.09.15. Blood samples were taken for analysis of [Ang-1], [Ang-2] and [Flt-1] in women with a PUV. Women were followed-up according to departmental protocols until viability was determined. Biomarker concentrations were correlated with pregnancy outcome. Serum concentrations were categorized and the nature of the association between each biomarker and pregnancy outcome explored by computing relative risks for each category relative to the lowest. The chi-squared test was undertaken to determine the statistical significance of the associations.

**Results:** 61 (64.9%) of 94 participants with a PUV were subsequently diagnosed with a viable pregnancy. There were statistically significant ( $p<0.01$ ), linear ( $p\text{-valuetrend}<0.01$ ) associations between [Ang-2] and [Flt-1] and pregnancy viability such that women with [Ang-2]  $\geq 2665.86\text{pg/ml}$  were 64% less likely to have a viable pregnancy than women with [Ang-2]  $\leq 1382.45\text{pg/ml}$  ( $RR=0.36$ , 95%CI 0.21-0.64) and women with [Flt-1]  $\geq 141.85\text{pg/ml}$  were 50% less likely to have a viable pregnancy than women with [Flt-1]  $\leq 87.36\text{pg/ml}$  ( $RR=0.50$ , 95%CI 0.31-0.80). There was also a statistically significant association between [Ang-1] and pregnancy viability ( $p=0.026$ ) but it was non-linear ( $p\text{-valuetrend}=0.199$ ).

**Conclusion:** Women with PUVs and low [Ang-2] or [Flt-1] are significantly more likely to have viable pregnancies than women with high concentrations. [Ang-2] and [Flt-1] may therefore be useful in predicting viability in cases of uncertainty. Further work is required to determine appropriate threshold levels.

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### 173 The impact of in vitro fertilisation on birth weight over 23 years: A UK single centre analysis

**Castillo Catherine<sup>1</sup>; Horne Gregory<sup>2</sup>; Fitzgerald Cheryl<sup>1,2</sup>; Johnstone Edward<sup>3</sup>; Brison Daniel R<sup>2</sup>; Roberts Stephen A<sup>4</sup>**

<sup>1</sup>School of Medical Sciences, Division of Developmental Biology & Medicine, University of Manchester; <sup>2</sup>Dept. of Reproductive Medicine, Central Manchester University Hospitals NHS Foundation Trust; <sup>3</sup>Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre; <sup>4</sup>Centre for Biostatistics, University of Manchester

**Introduction:** In vitro fertilisation (IVF) conceived singleton pregnancies are associated with an increased risk of low birthweight (BW), compared to naturally conceived singletons. This is significant because of the association between BW and long-term health outcomes, via the Developmental Origins of Health and Disease (DOHaD) hypothesis. However, it is not known whether this is associated with historical practices in IVF, and in fact few causal links between specific IVF procedures and BW have been robustly established. This study aims to explore how IVF laboratory and treatment factors may affect BW over time, whilst accounting for patient-related factors, in a large retrospective cohort from a single UK clinic.

**Methods:** An anonymised dataset was collated from 23 years of routinely recorded data from St. Mary's Hospital in Manchester, UK. This captured patient, IVF treatment and offspring neonatal outcome information for all 2,780 singletons conceived from 1991-2015 from cycles with fresh embryo transfer and those involving frozen-thawed embryo transfers (FET). All available patient and treatment covariates were included in a multiple linear regression model predicting gender-, gestation-, and maternal parity-adjusted BW.

**Results:** When accounting for all available covariates in fully adjusted multiple regression analyses, average adjusted BW increased significantly ( $p=0.001$ ) by 285 grams (9%) on average over the entire study period. FET-conceived singletons consistently remained heavier at birth compared to their fresh embryo conceived counterparts. A patient's increasing duration of infertility and the occurrence of a spontaneous fetal reduction also had statistically significant negative associations with BW.

**Conclusions:** This historical increase in IVF singleton BW with time has not been shown previously. The association of FET cycles with increased BW confirms previous findings, but extends them to show a consistent yet non-linear increasing BW trend over 23 years.

### 174 Interpreting embryo transfer difficulty using a visual analogue scale and its' impact on the IVF outcome

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**Aims:** The aim of this study was to determine whether a continuous Visual Analogue Scale (VAS) is a reliable tool to grade embryo transfer (ET) difficulty when assessing IVF outcomes.

**Background & methods:** No standardised grading system exists for reporting ET 'difficulty' which is typically recorded in

descriptive terms and has been reported to affect IVF success rates (1). Nine clinicians performing 174 day-five single embryo transfers between November 2012 and May 2014 also recorded a VAS score (0/1-100) for each procedure. Initially three ET 'difficulty' groups were established using the standard operator documentation method: A) 'easy' with no resistance, B) 'Medium' - resistance overcome by manipulating catheter sheath, C) 'Difficult' - resistance overcome only by resorting to a firm malleable stylet; which were then compared to the VAS scores ascribed by the clinician. Implantation, clinical pregnancy and live birth rates were recorded as primary outcomes.

**Results:** VAS scores were categorised according to the 25th, 50th and 75th percentiles to create four incremental groupings (Groups 1-4) for further analysis. There were no significant differences in sample characteristics or blastocyst grading between the groups. Cross-tabulation was performed with chi-squared statistical tests applied. No significant relationship was seen in implantation, clinical pregnancy or live birth rates in either the standard grading groups (Groups A-C) or the VAS categories (Group 1-4) with  $p$ -values  $> 0.05$  (Table 1). Whilst the median VAS scores increased as difficulty increased across groups (Figure 1), the interquartile ranges overlapped, suggesting the VAS is not a reliable alternative to report ET difficulty.

Table 1: Implantation, clinical pregnancy and live birth rates according to standard and VAS groupings

| Difficulty | n  | Implantation % | Clinical Pregnancy % | Live Birth % |
|------------|----|----------------|----------------------|--------------|
| A          | 82 | 70             | 61                   | 52           |
| B          | 57 | 58             | 62                   | 57           |
| C          | 55 | 56             | 49                   | 44           |
| P-value    |    | 0.267          | 0.818                | 0.419        |

| VAS score | n  | Implantation % | Clinical Pregnancy % | Live Birth % |
|-----------|----|----------------|----------------------|--------------|
| 1-3       | 45 | 62             | 56                   | 47           |
| 4-10      | 43 | 74             | 65                   | 56           |
| 11-24     | 41 | 67             | 58                   | 49           |
| 25+       | 41 | 55             | 51                   | 51           |
| P-value   |    | 0.316          | 0.818                | 0.848        |

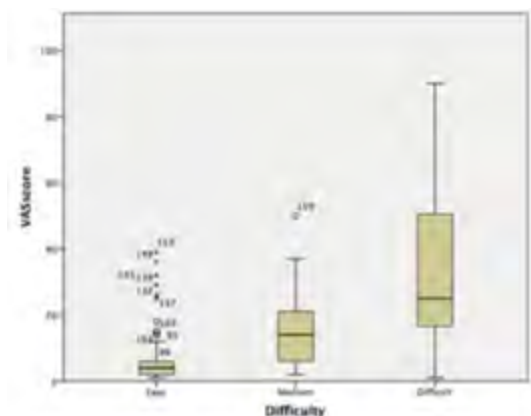


Figure 1: The VAS scores with median value (-) and interquartile range (box) displayed according to standard difficulty groupings (A-C). \* and denote outliers

**Discussion:** The VAS tool is not reliable enough to replace the standard operator documentation method for grading ET difficulty. Subjective interpretation of 'difficulty' remains problematic even in the context of a VAS tool and further work is needed to find a grading system that can be used widely by clinicians.

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## POSTER ABSTRACTS

### 175 Spontaneous pregnancy after open myomectomy: A five-year retrospective case review

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<sup>1</sup>University of Bristol; <sup>2</sup>St Michael's Hospital, Bristol

**Aim:** To determine spontaneous clinical pregnancy rates in women following open myomectomy for symptomatic uterine fibroid.

**Method:** A retrospective analysis of women with symptomatic fibroids treated by open myomectomy in a tertiary University Hospital in Southwest England over 5 years.

**Results:** 45 women underwent open myomectomy between November 2010-December 2015; infertility was main indication for open myomectomy in 51% (n=23). Of the women with infertility, 64% reported concurrent symptoms related to the presence of fibroids (menorrhagia, pelvic pain) and 48% (n=11) had distortion of the endometrial cavity by uterine fibroids. In women attempting conception (n=30), overall clinical pregnancy rate was 40% (12/30).

| Age (years) | Clinical pregnancy rate |
|-------------|-------------------------|
| 36-40       | 33% (5/15)              |
| >41         | 0% (0/1)                |

Of the 12 clinical pregnancies, there were 8 live births (mean birth weight 3.2kg), 1 ongoing pregnancy and 1 termination of pregnancy and 2 miscarriages.

**Conclusions:** Clinical pregnancy rates of 40% (95% CI 22.5-57.5) were observed, similar to published data for open myomectomy, with highest clinical pregnancy rates in women aged <35 years, as expected.

Open myomectomy using a meticulous surgical technique remains a valuable management approach for women with infertility caused by uterine fibroids. The strength of the open myomectomy technique is the multiple layer stitching and secure closure that reduces the chance of haematoma formation and uterine rupture.

Laparoscopic myomectomy is the most commonly used alternative uterine preserving approach, with pregnancy rates comparable to open myomectomy. The laparoscopic approach is associated with quicker recovery, less postoperative pain subjectively reported, less postoperative febrile morbidity and shorter hospital stay when compared to the open approach. However, use is limited by surgical expertise and complications unique to use of the power morcellator (intra-peritoneal

### 176 Comparative study of ovarian induction with biosimilar rFSH or purified urinary FSH

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**Introduction:** Traditionally recombinant gonadotropins were considered safer than urinary preparations due to their purity and homogeneity between batches. Irruption of biosimilar recombinant gonadotropins has reduced the financial burden. The objective of this study is to assess the effectiveness of Bemfola®, a novel biosimilar recombinant

gonadotropin, compared to purified urinary FSH for ovarian stimulation in oocyte donor population.

**Methods:** Retrospective study performed between January and November 2015. Study population was voluntary, healthy women under 32 years old included in an egg donation program. All donors started stimulation on day 2-4 of cycle with 225 IU/day of uFSH (Fostipur®) or rFSH (Bemfola®). GnRH agonist (Decapeptyl®, 0.4 mg) was used for final oocyte maturation. A total of 311 egg donors treated with urofollitropin (194) or alternatively with biosimilar rFSH (117) were included, as well as their matched recipients.

**Outcomes:** No differences in baseline characteristics between donors in both treatment groups were found (age, BMI, parity...). Incidence of cancelled treatments was comparable: uFSH (4.9%), rFSH (4.2%). Gonadotropin consumption with uFSH was 2126.3±383.6 IU and 2101.9±364.4 IU with rFSH. Number of retrieved eggs was 16.5±7.2 with uFSH versus 18.2±7.4 in donors with Bemfola (p=0.06). The mean number of embryos transferred in recipients of each group was similar (1.6±0.48 uFSH vs 1.5±0.51 rFSH). B-hCG, clinical pregnancy and implantation rates were also calculated: uFSH group, 65.8%, 55.3% and 38.1%; Bemfola group 66.7%, 53.9% and 39.9% respectively, non-significant.

**Discussion:** A trend towards a higher number of retrieved eggs was found in group where Bemfola® was administered. According to our results the clinical efficacy of both treatments in egg donors are comparable, becoming Bemfola an affordable alternative for ovarian stimulation.

### 177 Expression of divalent cation channel in healthy and preeclamptic human placenta

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Preeclampsia is a pregnancy-specific disease characterized by hypertension, proteinuria, and oxidative stress in the placenta. During the last trimester of gestation, calcium Ca<sup>2+</sup> transport from mother to fetus increases dramatically in response to increased demand for Ca<sup>2+</sup> caused by bone mineralization in the fetus. Under preeclamptic circumstances, placental cell Ca<sup>2+</sup> transport channels (CTCs) including transient receptor potential vanilloid 6 (TRPV6), plasma membrane Ca<sup>2+</sup> ATPase (PMCA1), and Na<sup>+</sup>/Ca<sup>2+</sup> exchangers (NCKX3 or NCX1) are increased to enable successful maternal-fetal mineral transportation. Several recent studies have reported that Ca<sup>2+</sup> supplementation can significantly reduce the incidence and severity of preeclampsia or delay its onset. However, other groups have found that Ca<sup>2+</sup> supplementation did not alleviate the severity of preeclampsia. To identify the cause of these varying consequences of Ca<sup>2+</sup> supplementation, we analyzed the position, sequence and frequencies of TRPV6 variants in preeclampsia patient. 20% of these patients were found to have a TRPV6 point mutated gene sequence that resulted in a methionine to valine conversion. Moreover, patients with the mutated TRPV6 showed decreased carbamylcholine induced Ca<sup>2+</sup> influx compared to the control group. It is possible that the mutated TRPV6 could induce various calcium supplementation effects due to insufficient transport of Ca<sup>2+</sup> into components of the placenta such as decidual cells. In summary, TRPV6 mutation could be a marker for obstinate preeclampsia; therefore, identifying pregnant women with TRPV6 mutation could enable them to take efforts to prevent preeclampsia.



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### 178 Hysterosalpingogram (HSG) - Is there a role of routine antibiotics prophylaxis prior to procedure?

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Hysterosalpingogram (HSG) is a first line investigation for confirmation of tubal patency for infertility patients. Role of prophylactic antibiotics in prevention of post-procedure intrauterine infection remains controversial and unproven. There are many preventive options available to prevent such infections as a result of HSG. In literature, there are no randomized trials or any prospective studies done to prove the role of prophylactic antibiotics. Some retrospective studies have mentioned the evidence of role of prophylactic antibiotics in high risk patients.

In our trust, the HSG procedures are performed at two different sites. The prophylactic antibiotics are administered to all the patients at one site, where as antibiotics are administered to high risk patients only at the other site. We made an attempt to see the difference in outcome in these two groups of patients. The result showed that no patient with patent tubes developed any post procedure intrauterine pelvic infection, in either group. Patients who were seen to have evidence of tubal blockage on HSG, suggesting PID, were given PID prophylaxis antibiotics in both the groups.

We also discovered that one of the patients was pregnant at the time of HSG. It is therefore recommended to rule out the possibility of pregnancy at the time of HSG. It is achieved by proper pre-test advice to patients, good history taking and performing pregnancy test prior to test. Routine use of prophylactic antibiotics is not recommended.

### 179 The effect of EmbryoGlue® on clinical outcome

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**Introduction:** EmbryoGlue® is a medium rich in hyaluronan which acts as a link between glycoproteins on the uterus and embryos. This study aims to examine whether EmbryoGlue® has an impact on clinical outcome.

**Materials and Methods:** This retrospective analysis of 234 IVF/ ICSI cycles using EmbryoGlue® (EG) examined clinical pregnancy (CPR), implantation (IR), live birth (LBR) and miscarriage (MISCAR) rates against controls (C) matched for maternal age, attempt number and day of Embryo Transfer (ET) categorised in respect of age (<38 and ≥38 years) and of ET day (2/3 or 5). Statistical analysis was performed using Fisher's Exact Test.

**Results:** Mean maternal age was comparable between the EmbryoGlue® (37.38± 3.7) and Control groups (37.01±3.9). The EmbryoGlue® group had significantly higher CPR (EG:32.9% vs C:16.2%;p<0.01), IR (EG:21.8% vs C:11.2%;p<0.01) and LBR (EG:29.5% vs C: 13.7%;p<0.01). Although not statistically significant, reduced MISCAR was noted in the EmbryoGlue® group (EG: 10.3% vs C: 15%).

When examined by age, those <38 group had higher CPR (EG:45.6% vs C:17.5%; p<0.01), IR (EG:31.6% vs C:14.1%; p<0.01) and LBR (EG:38.6% vs C:16.7%; p<0.01) when EmbryoGlue® was used. Miscarriage rate was no different for the EmbryoGlue® group (EG:5.3% vs C:1.8%). In the ≥38 group the IR was higher (EG:13.8% vs C:8.64%; p<0.05) and MISCAR lower (EG:0% vs C:6.67%; p<0.01) though CPR (EG:20.8% vs C:15%) and LBR (EG:20.8% vs C:10.8%) were no different.

Stratified by ET day, patients with day 2/3 ET had CPR (EG:23.7% vs C:12.5%;p<0.05) and LBR (EG:21.7% vs C:9.2%;p<0.01) substantially higher with EmbryoGlue® while the day 5 ET group showed considerably higher CPR (EG:50% vs C:23.2%;p<0.01), IR (EG:34.8% vs C:17.2%;p<0.01) and LBR (EG:44% vs C:22%;p<0.01).

**Conclusion:** CPR, IR and LBR were significantly higher with the use of EmbryoGlue® in all age groups and at differing stages of embryo development, and miscarriage rates were significantly lower especially in patients of advanced maternal age.

### 180 The use of 3D ultrasound to assess the influence of endometrial scratch on endometrial thickness, endometrial volume, vascularity indices and implantation success

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*<sup>1</sup>Manchester IVF; <sup>2</sup>Guy's and St Thomas's; <sup>3</sup>Leuven University; <sup>4</sup>Imperial College London*

**Aim:** To assess the influence of performing an endometrial biopsy on endometrial thickness (ET), endometrial volume (EV), vascularity indices (VI, FI and VFI) and implantation success in women with recurrent miscarriage and unexplained subfertility.

**Methods:** This was a prospective longitudinal cohort study. Following ethical approval, sixty-nine women aged between 20-45 years with regular menstrual cycles and planning to conceive were recruited between July 2010 and April 2011. All women had a baseline ultrasound scan in a non-conception cycle. Subsequently, part of the study cohort had an endometrial biopsy in the luteal phase. All women had a second ultrasound scan in the luteal phase of the following cycle. Analysis of stored ultrasound volumes was done offline. The VOCALTM (Virtual Organ Computer-aided Analysis) imaging program was used to calculate endometrial volume and endometrial power Doppler flow indices: VI, FI and VFI.

**Results:** The change in ET was significantly higher in the endometrial biopsy group (mean -0.6 ± 0.9) compared to the control group (mean 2.4 ± 1.5) (P<0.001). Similarly change in EV was significantly higher in the endometrial biopsy group (mean-0.5 ± 0.6) compared to the control group (mean 1.4 ± 1.1) (P<0.001). The change in flow index was also significantly higher in the endometrial biopsy group (mean -0.2 ± 3.3) compared to the control group (mean 1.9 ± 3.6) (P=0.03).

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However, performing the biopsy had no statistically significant influence on implantation success or, in those who conceived, on the 12-week viability.

**Conclusions:** Our data provide evidence for the role of endometrial scratching in enhancing endometrial receptivity in women with recurrent miscarriages. We have shown an increase in the endometrial thickness, endometrial volume and endometrial flow index in this group after endometrial biopsy.

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**181** Caution - Not all NK cells are created equal: Uterine and peripheral blood NK cell analyses tell different stories in women undergoing ART for endometriosis associated infertility

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The merits of testing and treating presumed NK cell dysfunction is a contentious aspect of modern reproductive medicine. Implantation is critical for successful pregnancy

and the role of NK cells at this stage is unclear. We previously showed maturation of lymphoid progenitors in human endometrium and increased uterine haematopoietic precursors in women with infertility.<sup>1</sup> We also found increased proportions of uterine NK (uNK) progenitors in women with endometriosis and infertility.<sup>2</sup> The aim of this study was to examine mature NK cells and their progenitors in the endometrium and blood of women with endometriosis who underwent IVF/ICSI.

Thirty one women with endometriosis (21 stage 1-2, 10 stage 3-4) underwent ART treatment within a mean of 9.3 months of surgery. Endometrial tissue was obtained by aspiration biopsy and processed as described. 1 Matched blood samples were also collected. Mature and progenitor NK cells were investigated by flow cytometry using antibodies to CD45, CD56, CD10, CD34, CD117, CD94.

Twenty-one women (67.7%) with endometriosis had successful implantation and ten (32.3%) failed to implant. Both groups were similar with regard to age, BMI, parity, AMH levels, duration of infertility and menstrual cycle stage at endometrial biopsy. While there was considerable heterogeneity in NK phenotypes and numbers, women with successful implantation had significantly lower numbers of mature uNK cells (22.6% vs 38.2%  $P=0.07$ ) and higher levels of immature uNK cells (5.2% vs 1.0% ( $P=0.02$ )) in their endometrial tissue than women who failed implantation. In contrast, levels of peripheral blood NK cells were higher in women with successful implantation while levels of blood NK progenitors were similar in both groups. These data demonstrate significant differences in NK repertoires and developmental pathways in blood and uterine compartments. They also emphasise the limitations of focusing on blood NK cells for diagnostic or therapeutic interventions in female infertility.

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**182** Case report of a successful pregnancy following spontaneous haemoperitoneum of pregnancy due to endometriosis

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University Hospitals Coventry and Warwickshire NHS Trust

**Introduction:** To discuss the outcome of a subsequent pregnancy following the management of a rare life threatening obstetric emergency.

**Case presentation:** The patient had treatment of left endometrioma and adhesiolysis for subfertility.

In her first pregnancy she presented to labour ward triage at term with severe abdominal pain, hypotension, tachycardia and severe fetal bradycardia. The baby was delivered by forceps in theatre with severe acidosis and died 2 days later. Intra- abdominal bleed was confirmed by clinical deterioration, progressive drop in haemoglobin and FAST (Focused assessment with sonography in trauma) scan. A multi disciplinary team laparotomy identified the left uterine vein as the source of bleeding. Bilateral internal iliac artery ligation achieved haemostasis and uterine preservation. She was admitted in ITU for 12 hours due to 7-litre blood loss and was discharged home on 5th postoperative day.



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**Outcomes:** The second pregnancy progressed with no complications with an adequately grown baby. A live female baby was delivered by elective caesarean section at 38 weeks with a blood loss of 1000mls.

**Relevance:** Endometriosis is a common cause of subfertility. To expect increased frequency of occurrence due to better recognition and treatment of endometriosis for infertility.

**Discussion:** The incidence of Spontaneous haemoperitoneum of pregnancy is 1:10,000 births with 31% Perinatal mortality and 4% maternal mortality. A review by Brosens et al concluded that endometriosis was associated in 52% of women. The bleeding is from uterine vein (80%) due to progesterone withdrawal causing involution of the decidualised ectopic endometrium, angiogenesis, inflammation and invasion and narrowing of the vessels by endometriosis.

There are very few case reports of a successful outcome in a subsequent pregnancy. The risk of recurrence is not quantified for future pregnancies especially in labour. Internal iliac artery ligation is a safe alternative to embolization in preserving fertility.

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**183** 17 $\beta$  estradiol and progesterone can alter the expression of TLR4 and IL-1 $\beta$  and the release of prostaglandin E2 and prostaglandin F2 $\alpha$  in endometrial bovine cell line

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The endometrium of bovine and other mammals can express TLR4, detecting gram-negative bacteria and activating the innate immune response. The epithelial cells of endometrium activated by TLR4 can generate pro-inflammatory mediators such as IL-1 $\beta$ , Prostaglandin E2 (PGE2) and Prostaglandin F2 $\alpha$  (PGF2 $\alpha$ ), however some studies have showed that Estrogen and Progesterone can alter this response. It's important to know how these hormones, that are very important in reproduction and in the fertility treatment, can alter the immune response in the uterus. The purpose of this study is to show how 17 $\beta$  Estradiol and Progesterone can alter the immune mediators such as TLR4, IL-1 $\beta$  and prostaglandins in endometrial bovine cell line (BEND). We treated BEND cell with 17 $\beta$  Estradiol (10 $^{-7}$  – 10 $^{-8}$  M), Progesterone (10 $^{-7}$  – 10 $^{-8}$  M) and/or lipopolysaccharide (LPS) for 6 and 24 hours. We evaluated the expression of TLR4, IL-1 $\beta$  and the release of PGE2 and PGF2 $\alpha$  and we used one-way ANOVA to analyze the data. We can see that in the presence of the progesterone, the expression of TLR4 and IL-1 $\beta$  decreased. The release of PGE2 and PGF2 $\alpha$  was reduced in the presence of 17 $\beta$  Estradiol and LPS. We can suggest that those hormones could decrease the innate immune response in the uterus, predisposing it to infections. We need to keep this in mind when use those hormones in fertility treatment and when an intervention is made in different time of the estrous cycle.

FONDEF IDEA ID14H10050 / CONICYT-PFCHA-DOCTORADO NACIONAL-2013-21140149

**184** Endometrial-paternal dialogue: The impact of seminal fluid extracellular vesicles on stromal cell decidualisation

**Rodriguez Caro Helena; Southcombe Jen; Granne Ingrid**  
*University of Oxford*

In vitro fertilization (IVF) has enabled many infertile couples to achieve pregnancy, however even good quality blastocysts have an implantation rate of less than 60%. Endometrial factors including inadequate decidualisation are likely to account for some of these implantation failures. Recent data have shown that exposure of the female reproductive tract to seminal fluid improves clinical pregnancy rates in women undergoing IVF2. Seminal fluid contains extracellular vesicles1 that are membrane-bound complexes (<1 $\mu$ m) that facilitate cell-cell communication by delivering their cargos of proteins and nucleic acids to target cells3. Seminal fluid extracellular vesicles (SF-EVs) bind to sperm and promote motility, capacitation and the acrosome reaction1. We hypothesised that SF-EVs may also enhance endometrial decidualisation.

SF-EVs were isolated (n=11) and their average modal size was 117  $\pm$  6 nm, as determined by Nanoparticle Tracking Analysis (Malvern Instruments Ltd.); the samples contained 9x10<sup>11</sup> to 42x10<sup>11</sup> SF-EVs/ml. SF-EVs were pooled (n=11) and purified using size exclusion chromatography (Exo-SpinTM/Cell guidance Systems) to remove seminal fluid proteins. Bio-Maleimide-FITC labelled SF-EVs were incubated with primary human endometrial stromal cells. SF-EVs bound to both non-decidualised and decidualised stromal cells as observed by fluorescence microscopy and flow cytometry (n=3). Stromal cells were decidualised for 7 days and treated with SF-EVs by single or multiple exposure. SF-EVs exposure increased levels of prolactin (p<0.01) and IGFBP-1 (p<0.05) (n=5) indicating enhanced decidualisation. This evidence that paternally derived SF-EVs have a direct influence on the maternal endometrium gives rise to the possibility they could be investigated as a low-cost adjuvant to IVF to improve implantation rates.

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**185** Integrin subunit expression in porcine endometrial tissue supplying small and normal-sized fetuses throughout gestation

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Low birth weight observed in the 'runt' piglet of the litter compared to its siblings has severe consequences for neonatal and adult development that cannot be remedied post-natally. It is hypothesised that impaired foetal growth occurs due to inadequate conceptus attachment. Integrins are thought to



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regulate the attachment process by interacting with secreted phosphoprotein 1 (SPP1).

Endometrial tissue supplying small and normal-sized fetuses was collected from Large White x Landrace gilts at gestational days (GD) 30 (n=5), 60 (n=7) and 90 (n=5). Samples were collected from the smallest and a normal-sized littermate from both sexes at GD60 and 90. The mRNA expression of five integrin subunits ( $\alpha$ v,  $\beta$ 3,  $\beta$ 5,  $\beta$ 6 and  $\beta$ 8) was assessed by qPCR.

The expression of  $\alpha$ v (FPr $\leq$ 0.001),  $\beta$ 3 (FPr $\leq$ 0.001) and  $\beta$ 6 (FPr=0.002) subunits increased while  $\beta$ 5 (FPr=0.024) decreased throughout gestation. No size or sex effects were detected. The mRNA expression levels of the subunits were compared with percentage SPP1 protein staining per endometrial gland from the same samples (Stenhouse et al. 2015). Integrin  $\beta$ 5 was positively correlated with percentage staining (P=0.029). Comparison of expression between each subunit from all GD revealed that all comparisons, except for  $\beta$ 3 vs  $\beta$ 6, were significantly different. When compared within gestational day, the most striking differences occurred at GD60, with all comparisons of subunits being significant. Only the  $\beta$ 5 vs  $\beta$ 6 comparison was differentially expressed at GD30. Similarly the differences were not as pronounced at GD90, with differential expression occurring only between three comparisons ( $\beta$ 3 vs  $\beta$ 5;  $\beta$ 3 vs  $\beta$ 8;  $\beta$ 5 vs  $\beta$ 6).

This study has demonstrated that endometrial mRNA expression of integrin subunits changes throughout gestation. Integrin expression was not altered in endometrial tissue supplying small fetuses however further investigation into expression at the time of attachment and in the placenta may improve understanding of the mechanisms governing foetal growth.

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### 186 Targeting progesterone receptors for the management of heavy menstrual bleeding (HMB)

**Leow Hui Wei; Maybin Jackie; Walker Kate; Whitaker Lucy; Murray Alison; Critchley Hilary**

*MRC Centre of Reproductive Health, University of Edinburgh*

Background: Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss which interferes with the woman's physical, emotional, social and material quality of life 5. It can occur alone or with other symptoms 5. Women with fibroids have HMB 9. Current medical treatments are often ineffective. There is an unmet need for alternative treatments 2. Haemostasis, vasoconstriction and epithelial repair are required to reduce menstrual blood loss 4.

Progesterone regulates uterine function. Progesterone receptors (PR) are an attractive therapeutic target. Selective Progesterone Receptor Modulators (SPRMs) are ligands for PR. SPRM, ulipristal acetate rapidly controls HMB; it's mechanism of action is unknown 8. Fibrinolysis induces the degradation of fibrin clot. It is enhanced by u-PA and t-PA, but inhibited by PAI-1 3. Women with HMB have raised t-PA activity on the second day of menstruation 1. The levonorgestrel-releasing intrauterine system (LNG-IUS), a PR ligand, reduces HMB by inhibiting t-PA secretion and promoting PAI-1 6, 7. This project investigates

whether SPRM (ulipristal acetate) affects haemostasis by modulating components of the endometrial fibrinolytic pathway, i.e. u-PA, t-PA, PAI-1.

**Methods and results:** Use of well-characterised archival endometrial tissue from women with HMB collected from the proliferative phase (n=9), secretory phase (n=9) and post administration of SPRM (n=9). Real time quantitative polymerase chain reaction (RT-qPCR) quantified mRNA and immunohistochemistry localized protein of components of fibrinolytic pathway. The relative expression of u-PA mRNA was significantly greater in proliferative phase compared to secretory phase endometrium and endometrium post-SPRM administration.

**Summary:** SPRM administration may impact the endometrial fibrinolytic pathway and modify menstrual bleeding. SPRM administration may act on inflammatory pathways or on the endometrial vasculature to reduce HMB. The mode of action of SPRMs on human endometrium and how menstrual bleeding is reduced require further study.

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## POSTER ABSTRACTS

### 187 Characterisation of endometrial progenitor cells during post-menstrual repair

**Kirkwood Phoebe; Smith Jamie; Kelepouri Olympia; Henderson Neil; Gibson Douglas; Saunders Philippa**  
*University of Edinburgh*

**Introduction:** The endometrium is a dynamic tissue that exhibits an extensive regenerative capacity as well as cyclical episodes of scarless repair. The development of clonogenic assay systems has identified putative stromal stem/progenitor cells in human endometrium that are CD146+/PDGFRβ+ but their contribution to endometrial repair processes is unknown. We used mice in which GFP is expressed under control of the PDGFRβ promoter element (Pdgfrβ-BAC-eGFP<sup>®</sup>) in combination with a hormonal protocol that recapitulates the key phases of endometrial repair and regeneration (simulated menses). The primary aim of the experiments was to elucidate the contribution of PDGFRβ-positive cells to the process of endometrial repair.

**Methods:** Menstruation was simulated in Pdgfrβ-BAC-eGFP<sup>®</sup> mice according to the protocol of Cousins et al 2014; tissues were recovered 12 and 24h following progesterone withdrawal. Uterine tissue were analysed using immunohistochemistry and Flow cytometry. Putative pericytes were identified by immunostaining for CD146 and epithelial cells using EpCAM and detailed flow cytometry analysis was utilised to elucidate changes in progenitor cell populations during endometrial repair.

**Results & Discussion:** Immunohistochemistry analysis identified two populations of GFP+/PDGFRβ+ cells: GFPdim cells dispersed throughout the stroma and GFPbright cells in close proximity of blood vessels. GFPdim cells to be PDGFRβ+CD146-, indicative of stromal fibroblasts, while GFPbright cells were PDGFRβ+CD146+, consistent with a pericyte phenotype. Flow cytometry analysis has revealed dynamic changes in both GFPdim and GFPbright populations during endometrial repair as well as increased expression of the epithelial marker EpCAM in GFPbright CD146+ cells.

In summary, we have identified a population of endometrial pericytes that are dynamically regulated during endometrial repair and provide novel evidence that they are capable of differentiating into epithelial cells via mesenchymal to epithelial transition (MET). This unique model provides a platform for future studies on the role of pericytes in scarless tissue repair.

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### 188 Establishment of a novel culture system to investigate angiogenesis and gland formation in the porcine endometrium

**Mohammed Amal<sup>1</sup>; Woad Kathryn J<sup>2</sup>; Mann George<sup>1</sup>; Robinson Robert S<sup>2</sup>**

*<sup>1</sup>The University of Nottingham/ School of Biosciences /Animal Division; <sup>2</sup>The University of Nottingham/ School of Veterinary Medicine and Science*

**Background:** Angiogenesis is essential during implantation and placentation for the development of extensive vasculature to support embryonic and fetal growth. The aim of this study was to develop a physiologically-relevant culture system to elucidate the regulation of angiogenesis in the pre-implantation porcine endometrium.

**Methods:** Porcine endometrial strips (luteal phase) were enzymatically digested. Dispersed cells (e.g. epithelial, stromal and endothelial) were plated onto fibronectin-coated coverslips [200,000 cells; 12-well plate]. In Experiment 1, cells were grown in either specialized endothelial cell medium (Lonza) or serum-free growth-factor supplemented MDCB131 media (n=3). Cells were fixed on day 5 of culture and endothelial cells (EC) immunostained for von Willebrand Factor (VWF). In Experiment 2, in vitro EC network development was assessed over time (2h-5d). Cells were stained for VWF, smooth muscle actin (SMA; pericytes) and pan-cytokeratin (epithelial).

**Results:** Experiment 1: On day 5, EC were present as predominantly EC islands (20-30 cells) and tubule-like branched EC networks. Other cell types had extensive grown. EC network development was similar in Lonza and MDCB131 media. Experiment 2: At 2h, EC were generally present as isolated, individual cells which had formed small islands of 3-10 cells by 12h. These islands increased in size and by 72h reached 30-40 cells with EC closely apposed. Between 72-120h, EC started to sprout and branch from the EC islands and formed a capillary network-like appearance. Epithelial cells were present as small group of cells by 24h which developed into glandular-shaped islands by 48h. SMA-positive cells were present as individual cells at 2h and started to surround the epithelial and endothelial cell islands by 48h.

**Conclusions:** The present study demonstrated the development of a primary porcine endometrial culture system in which both EC networks and glandular epithelium develop under serum-free conditions. This will enable the elucidation of their regulatory control mechanisms.

### 189 Hysterosalpingogram reports: Does concordance exist between reporting by radiologists and gynaecologists?

**Bowker Jennifer<sup>1</sup>; Wilson Victoria<sup>1</sup>; Moffatt Joanne<sup>2</sup>; Jones Kevin<sup>2</sup>**

*<sup>1</sup>Swindon Academy, University of Bristol; <sup>2</sup>Great Western Hospital NHS Foundation Trust*

**Background:** National and international guidance advises that couples who have not conceived after 1 year should be offered clinical investigation including fallopian tube analysis<sup>1</sup>. Tubal analysis is commonly performed by hysterosalpingogram (HSG) in low-risk women, with laparoscopy offered to high risk women. However, questions have been raised about



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the accuracy of the HSG for predicting tubal patency. Our trust guidelines require dual reporting of the HSG by both radiologists and gynaecologists.

**Aim:** To review current HSG reporting and determine rates of concordance between reports.

**Methods:** A retrospective study of patients who had a HSG between June 2014 and January 2016 (n=91) was carried out. Notes and online radiological reports were reviewed. An overall rate of concordance and inter-observer variability (Kappa value) between reports was calculated.

**Outcomes:** Concordance between gynaecologist and radiologist reports was 61.5%. An adjusted concordance rate calculated to account for missing data (n=6) was 65.9%. Inter-observer variability was calculated as 0.3828 which is interpreted as a 'fair' level of agreement. Radiologists reported more tubal occlusion than gynaecologists. Concordance was greatest for reports of 'bilaterally patent' tubes (63.4%).

**Discussion:** Analysis of HSG reporting demonstrated a sub-optimal concordance rate. This has implications in terms of uncertainty over clinical diagnosis and consequently implications for patient management. Gynaecologist reporting has the advantage of interpreting dynamic images and it may be appropriate to change protocol so that only gynaecology reporting is required. An alternative investigation hysterosalpingo-contrast-sonography (HyCoSy) may be equally effective and reduce radiation exposure, however relies on availability of trained staff<sup>2</sup>.

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### 190 Cyclical histone deacetylase expression across multiple timescales in the peripheral reproductive tissues of the Siberian hamster (*phodopus sungorus*)

**Lynch Eloise; Coyle Chris; Stevenson Tyler**  
*University of Aberdeen*

Recently it has become apparent that epigenetic modifications, such as histone acetylation, are dynamic and reversible. As yet, our understanding of a role for epigenetic modifications in timing biological rhythms, such as seasonal reproduction, is limited. It has recently been found that DNA methylation in the hypothalamus plays a role in regulating the internal representation of seasonal timing (Stevenson and Prendergast, 2013), and dnmt3a levels have been shown to change seasonally in the testes and uterus of the Siberian hamster (*Phodopus sungorus*) (Lynch et al, 2016). Here we tested the hypothesis that histone modifications are also responsible for controlling reproductive rhythms across a number of timescales in peripheral reproductive tissues. Using a seasonally breeding animal model, *P. sungorus*, we examined the naturally occurring seasonal and estrous variation in, and the effect of ovarian steroids on, mRNA expression of histone deacetylase (hdac) expression

in the uterus, ovaries and testes. SD conditions significantly decreased testicular expression of hdac1, but increased hdac3 expression. SD had no significant effect on hdac expression in the ovaries, but significantly increased hdac2 and decreased hdac3 expression in the uterus. There was no variation in hdac expression across the estrous cycle. A single subcutaneous injection of Estrogen and progesterone significantly reduced uterine hdac2 expression after 12hr and maintained the effect for at least 24hr. We demonstrate that uterine hdac2 may be a seasonal reproductive timer, and may represent a component of an evolutionarily ancient clock mechanism. This work was funded by an Undergraduate Vacation Scholarship from the Society for Reproduction and Fertility.

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### 191 Reactive oxygen species assessed using the mioxsys device in density gradient prepared sperm

**Clare Mitchell; Mathew Tomlinson; Waid Maalouf**  
*University of Nottingham*

Both centrifugation and density gradient sperm preparation (DGC) have been implicated in the generation of reactive oxygen species (ROS) which may have an impact on sperm function and DNA integrity, yet there is remarkably little data on this area. The objective of this study was to measure ROS generation, semen parameters and DNA fragmentation before and after preparation with in 4 different density gradient media.

Donor samples were analysed before being divided between DGC preparations (SupraSperm, PureSperm, Origio pH 7.5 and Origio pH 8.3. Gradients were centrifuged for 20 minutes at 300g before further washing for 5 minutes (300g). Data from the ROS were measured using the MiOXSYS<sup>®</sup> system which permits reading of the total redox potential (sORP) within the media in a single chip-based assay (Agarwal et al., 2016). Semen parameters were assessed using CASA and DNA fragmentation was measured using the sperm chromatin dispersion assay (SCDA). A second experiment further examined the effect of centrifugation speed on sORP.

Each DGC media formulation performed very similarly in terms of sperm number and motility. Compared to measurements in semen, sORP increased significantly in each DGC preparation (P<0.05) and was positively correlated with progressive motility (P<0.05). There was a weak negative correlation between DNA fragmentation and sORP where two assays were used in this study and their effectiveness was compared. Further experiments showed that centrifugation speeds performed similarly in terms of sORP, however when compared to previous tests of the four DGC preparations the sORP from each speed was significantly lower (P<0.05).

The relationship between ROS and semen quality is not simple and in this cohort appeared to be associated with good quality sperm. Aitken et al. (2012) mentioned that the generation of ROS must reach a tipping point before having a negative effect.

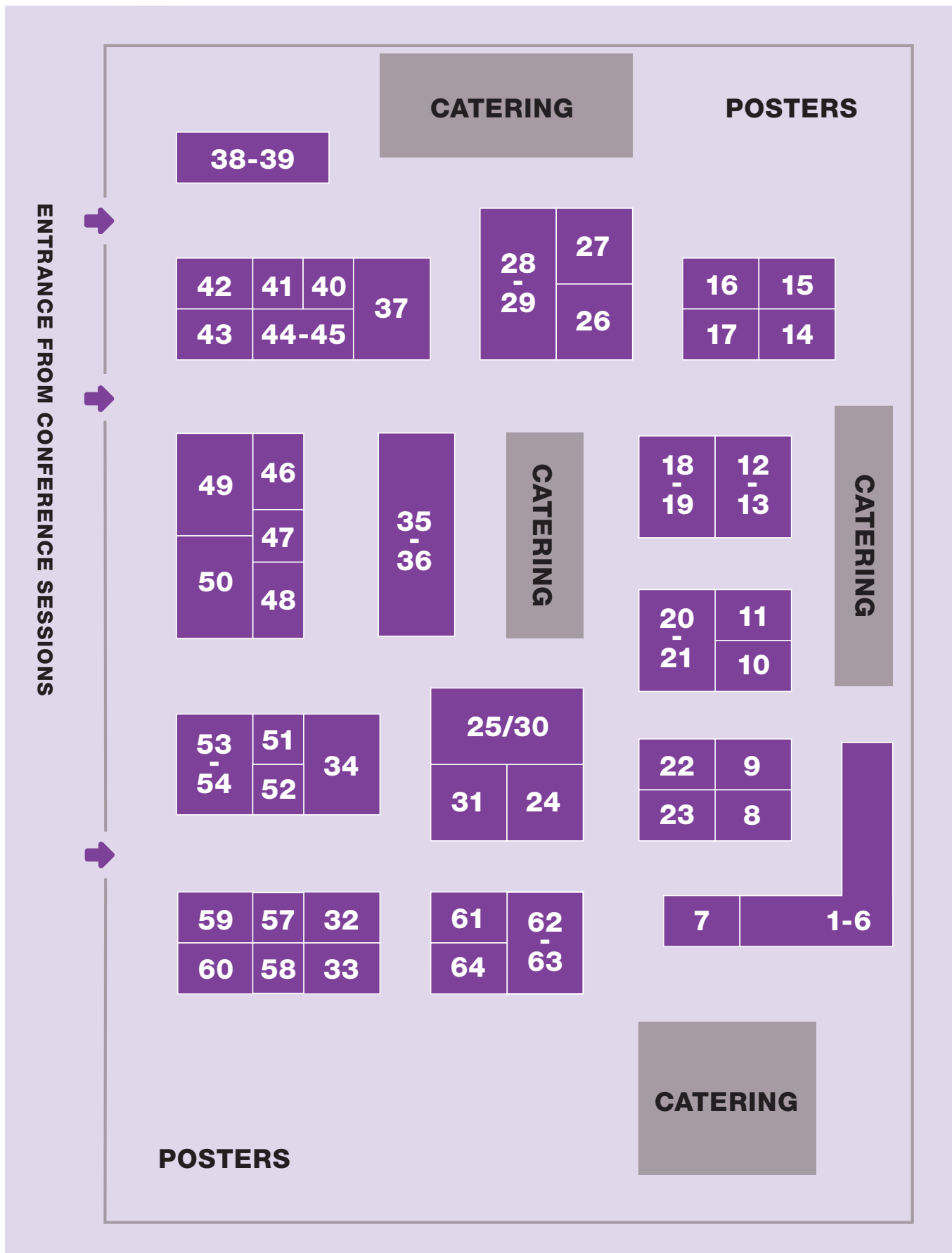


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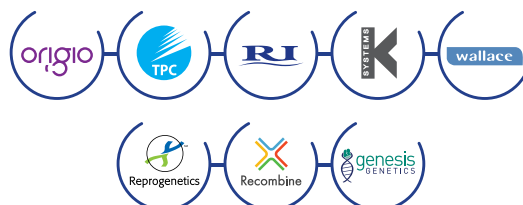
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### Fertility2u Homecare Pharmacy

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At Fertility2u we pride ourselves in providing patient focussed homecare services. We are registered with the MHRA, GPhC and have an ISO 9001 quality management system.

All our staff are trained to an expert level and our infrastructure is capable of dealing with the demanding needs of the industry, we are already in partnership with a number of clinics across the country. With our dedicated call handling staff and pharmacy team, we believe what we offer is a high standard in homecare.

To find out more please email us or give us a call, we'd love to hear from you.

### Fertility Network UK

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Fertility Network UK is the nation's leading patient-focused fertility charity providing free and

impartial support and information to anyone affected by fertility issues including those:

- considering their future fertility
- trying to become parents
- facing the challenges of involuntary childlessness
- successful after fertility issues

The patient voice in the campaign for equitable access to NHS funded fertility treatment, we co-chair the campaign group Fertility Fairness.

Our education project raises awareness of the importance of fertility education and highlights practical steps young people can take to help protect their future fertility.

No other fertility organisation offers the range of services and support we provide.

### Finox Biotech

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A Swiss company dedicated to developing and launching high quality, cost effective and easy to use fertility products. Finox Biotech is a company specialised in developing fertility drugs and innovative, patient friendly delivery devices. Bemfola rFSH is the first of Finox Biotech's fertility products.

Our focus is solely on fertility products – and as such all our expertise is directed to bringing affordable and easy-to-use medication to improve the lives of patients, nurses and IVF specialists.

Finox Biotech was founded 2007 in Switzerland and has since been working on implementing its vision.

[www.finoxbiotech.com](http://www.finoxbiotech.com)

## EXHIBITOR INFORMATION

### GYNEMED Medizinprodukte GmbH & Co. KG 41

GYNEMED offers a wide range of products for better results in assisted reproductive techniques. Come to our booth and have a look at the new members of the GM 501 Media Line Family, like "SpermMobile, Cult-Active, PVP and Bromelain in Dulbecco's PBS" and our fascinating MicroGlasPipettes.

Tel: +49-4363-903290; Email: [info@gynemed.de](mailto:info@gynemed.de)  
[www.gynemed.de](http://www.gynemed.de)

### Hunter Scientific Ltd 28,29,37



#### HUNTERSCIENTIFIC

Hunter Scientific primarily manufactures a wide range of high quality Pasteur Pipettes and Micro Tools CE Marked for IVF use as Class IIa Medical Devices. We also act as official distributors to the UK and Ireland for a wide range of IVF laboratory equipment and consumables from Thermo/NUNC, KitaZato, Nidacon, GenX, Noblegen, ReproMed and MTG. As a holder of ISO 13485:2012 and ISO 9001:2008 Quality Systems we are regularly audited both internally and externally. As a Class IIa manufacturer we are proactive in encouraging other manufacturers to supply products which meet the demands of UK licensed clinics.

### IMT International 22

IMT International provides IVF management technologies and quality management systems to fertility centres worldwide. Our innovative systems include Matcher electronic witnessing, designed to replace all human double-checking, helping to prevent errors through misidentification of patients and their gametes and embryos.

Matcher provides complete electronic traceability, recording 'who, what, where and when' at every transfer step, including photographs of all procedures, providing unbroken chain of custody evidence and comprehensive reporting for clinics.

Highly configurable, with no initial capital cost, Matcher's quality management system operates seamlessly throughout the clinic, including cryo stores, operating rooms and laboratories, offering clinics both time and money savings.

Visit us on stand 22 for your personalised demo of our NEW Matcher software.

Email: [info@imtinternational.com](mailto:info@imtinternational.com) Tel: +44 (0)1829 771 327  
Unit 1c, Canalside, Tattenhall, Chester, CH3 9BD, UK  
[www.imtinternational.com](http://www.imtinternational.com)

### IVF Couriers 17

IVF Couriers (UK) LLP specialises in cryogenic hand carry door-to-door shipment of all cell types safely and securely between laboratories in the UK and worldwide. Established in 2011 by Simon Hedley and Annare Heneghan-Bernet, both logistics professionals with over 40 years combined international experience working for well-known global airlines and express

companies. Using latest technology cryoshippers equipped with custom-designed Tinytag® temperature data loggers manufactured by joint exhibitor Gemini Data Loggers (UK) Ltd, we offer temperature-controlled bespoke premium logistics solutions for medical professionals, researchers and patients.

Please visit us on Stand 17 to discuss your specific cryo-logistics needs.

Contacts: IVF Couriers (UK) LLP - Simon Hedley / Annare Heneghan-Bernet

T +44 20 32873210 E [info@ivfcouriers.com](mailto:info@ivfcouriers.com)

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[www.gemindataloggers.com](http://www.gemindataloggers.com)

### Irvine Scientific 43



#### IrvineScientific

Irvine Scientific, a member of JX group, is a worldwide leader in the design, manufacture and distribution of cell culture products for Assisted Reproductive Technology (ART), cytogenetic, immunology, cell therapy, and biopharmaceutical development and production applications. Irvine Scientific adheres to ISO and FDA regulations and operates dual cGMP manufacturing facilities in California, USA and Tokyo, Japan. The company's consultative philosophy combined with expertise in cell culture and compliance provides customers with unique capabilities and support. For over 45 years, Irvine Scientific has remained flexible and focused on media while becoming a strategic global leader in media products and services.

### @KustodianLtd 51



New economy company, Kustodian brings the Internet of Things to ACE 2017 and launches its war on waste – Instant In Dewar statutory audits and reduced operating costs. We are the only company with technology proven to work in liquid nitrogen. Using GS1 based globally unique identification system, Kustodian tracks

samples anywhere, from Manchester to Liverpool and beyond! We are also launching the Konsumable Replacement Service (KRS). KRS tracks consumption of consumables in real time as they are used in the treatment. In so doing so we can help optimise inventory and enable costs to be assigned to a treatment. We will track your consumption and automatically replenishing inventory. Kustodian's innovative data analytics fully supports statutory reporting and helps you keep track of all the great work you are doing. We realise that confidence in Kustodian is a critical success factor and that your reputation reflects the quality of the suppliers you work with. To demonstrate our capabilities, we would be delighted to visit you and demonstrate Kustodian tracking samples in liquid nitrogen using your Dewars.



## EXHIBITOR INFORMATION

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For more information contact our Sales Director, Steven Clarke at [Steven.Clarke@Kustodian.co.uk](mailto:Steven.Clarke@Kustodian.co.uk) or on 07795-482 770.

Follow us on Twitter @KustodianLtd and see our website [www.Kustodian.co.uk](http://www.Kustodian.co.uk)

### Life Global/Evolve

9

**global®** – Based on pure science and clinically proven for more than 15 years with more than 180 published independent studies.

**global® Family of ART media** – Leading and clinically proven 'Uninterrupted Culture Medium™'

**LifeGlobal® media products** have a proven record of consistency, quality and performance. High quality oils: LifeGuard® Oil - specially designed for uninterrupted culture; LiteOil® and LG Paraffin Oil.

**LifeGlobal® GPS® Dishware** – The future of ART dishware. Specific dish design for each culture and procedure. Universal GPS®, embryo GPS®, embryo Corral®, µDrop GPS®,

4 Well GPS® Dish and NEW: Mini GPS

**LifeGlobal® Tools:** New Precision µPipets™ for IVF

**CodaAir®:** AldaSorb® Xtra Inline® Filters, CodaAir® 800 & 900, Coda Positive Pressure Unit

Our products are manufactured in North America under strict quality control in our ISO 13485:2003 and ISO 9001:2008 Certified and FDA Registered facilities. Our products are FDA 510(k) Cleared, Health Canada Registered, and CE marked.

[www.LifeGlobalGroup.com](http://www.LifeGlobalGroup.com); [www.IVFOonline.com](http://www.IVFOonline.com).

Contact: [sales@LifeGlobal.com](mailto:sales@LifeGlobal.com) 24/7 Online Orders  
Intl: 001 519 826-5800, NA:1-800-720-6375

### LogixX Pharma

47

LogixX Pharma is a specialty pharmaceutical company with a core focus on products for the management and treatment of niche therapeutic conditions as many of these conditions are poorly treated with a high level of unmet medical need.

To meet this challenge LogixX Pharma is rapidly expanding its portfolio of products to bring new therapies to patients, new treatment approaches to healthcare professionals and better health outcomes for patients.

Our product portfolio covers the fields of respiratory (ENT and asthma), rare diseases (primary and secondary carnitine deficiency), nutraceutical supplements (fertility, sexual health, prostate health and cardiovascular supplements).

LogixX Pharma is committed and focused on acquiring, registering and marketing niche products in therapeutic areas of high unmet medical and patient need.

### MedITEX IVF - The software for life

24

MedITEX IVF - the number one fertility software used by over 300 clinics worldwide. Providing a user-friendly central information facility allowing user-specific customisation, it manages and helps coordinate procedures and workflows of any fertility unit from small private centres to group clinics. With an increasing footprint in the UK we are becoming the fertility software of choice. Our unique HFEA interface allows front-end validation ensuring compliance and accurate data submission – requirements of the HFEA Information for Quality programme.

IVF Solutions Limited, 5 Down Road, Guildford, Surrey, GU1 2PX  
Tel: +44 (0)7771 686438 Email: [andrew@ivfs.co.uk](mailto:andrew@ivfs.co.uk)

[www.meditex-ivf.com](http://www.meditex-ivf.com)

### Mellowood Medical - IDEAS

62-63

IDEAS 6: 'State of the ART' clinic management software/ electronic medical record with World Class client base. Appointments, Billing, Treatment, Prescriptions, Ultrasound,

Embryology/Andrology, Cryogenic Storage and Statistics. HL7 interfaces to blood analyzers, laboratories, scanners, CASA and Witnessing. Web-based patient portal! Registry support includes HFEA, BELRAP, SART, BORN, and NPSU. QC/QA modules ensure compliance for EU/ESHRE Directives.

Headquarters: 45 Mellowood Drive, Ste 18 Toronto ON Canada M2L 2E4/0mnibus Ctr. North Road, London N7 9DP UK.

Email: [info@mellowoodmedical.com](mailto:info@mellowoodmedical.com)

[www.mellowoodmedical.com](http://www.mellowoodmedical.com)

### Merck

35



Merck is a world leader in fertility treatments that develops and provides innovative products and devices to help infertile couples at every stage of the fertility treatment cycle. Merck combines a 60 year heritage of expertise with a visionary commitment to the future of fertility through pioneering science and technologies. Merck Serano UK is based in Feltham, Middlesex and Merck Serano Ireland is based in Dublin. Merck's global headquarters are located in Darmstadt, Germany.

UK&IE/NONF/1016/0016

### Merck Fertility Technologies, supporting your journey

36



Merck Fertility Technologies represents an evolution of our fertility business and services expanding our range of solutions to cover the main aspects of assisted reproductive technologies, contributing to our goal of improving outcomes in fertility for the benefit of patients.

## EXHIBITOR INFORMATION

Our commitment is to provide innovative science and technology based solutions to challenges in the IVF Laboratory that have the power to improve results for patients throughout the IVF process.

Innovative technological solutions in your fertility treatment

Date of Preparation: Aug 2016

EEV16-0014

### Microm UK Ltd

48

Specialists in diagnostics, consumables and media products for clinical and research units involved in human and veterinary infertility.

In 1994 Microm became the exclusive UK and Ireland distributor for FertiPro N.V. a major manufacturer of an extensive range of products for assisted reproduction techniques and semen analysis. In 2005 Microm signed an exclusive agreement with MICROPTIC S.L. to distribute the Sperm Class Analyser - SCA® in the UK & Eire.

Microm understands today's strict regulatory requirements and also the demand from our customers for quality products that are backed by the highest quality service and support.

### Mitrone Healthcare (incorporating Procreative-Diagnostics)

52

Procreative diagnostics ([www.casaexperts.com](http://www.casaexperts.com)) demonstrate their latest version of Sperminator™ with improved: sperm identification, parity with manual counting and based on a flexible Windows 10 platform (all-in-one PC, micro-compact version and touchscreen options). Mitrone's ([www.mitrone.ie](http://www.mitrone.ie)) offering is an innovative method to double the capacity in your 47/11 Dewar – ColdStash. We will also be demonstrating the Thermodata-IVF T-Plus Buttons is an affordable, Cloud based ISO17025 accredited technology for 24/7 QC monitoring. It offers accurate (0.097°C) measurement of difficult to measure locations (heated stages, incubators etc). Mitrone will also exhibit the Cell-Vision range of slides for either manual or automated sperm counting.

### Parallabs Ltd

25&30

At Fertility 2017 we will be showcasing the new EmbryoScope+ time-lapse incubator and KIDScore D5 decision support tool for embryo selection.

From Sparmed we will highlight the new Class IIa certified Oosafe Disinfectants. Popular plasticware, cryoware and air quality products will be shown.

Look out for log and alarm monitoring systems, vitrification, and our growing portfolio of andrology consumables.

Capital products from Hamilton Thorne and Labotect will also feature.

### Pharmasure

20-21

Doubling live birth rates in ART resistant male subfertility<sup>1</sup> - official launch of Condensyl®; the only male supplement improving both DNA fragmentation (DFI), sperm decondensation (SDI).

Visit the Pharmasure stand for our gonadotrophins with the highly acidic FSH isoform profile necessary in the early-mid follicular phase.

Inofolic supplementation for improved egg quality, improved response in ART and for PCOS.

1. Amar et al. Austin Journal of Reproductive Medicine & Infertility, 2nd April 2015

### Planer Plc

26

Planer are dedicated to using our years of expertise and experience in environmental temperature control and the management of human cells to develop and manufacture pioneering, high quality, innovative laboratory equipment to assist embryologists, andrologists, scientists and biologists to preserve, protect and nurture sperm and embryo's for use by fertility clinics and laboratories throughout the world.

Our product range currently includes controlled rate freezers, benchtop incubators, laboratory alarm & monitoring systems, sample tracking software and cryostorage vessels. Come and see the new state of art Planer 'PetriSense' CO2 alarm and monitoring system which will be on display at Fertility UK for the first time this year.

110 Windmill Road, Sunbury on Thames, Middlesex, TW16 7HD, United Kingdom

Tel: 01932 755000; Fax: 01932 755001;  
Email: [enquiries@planer.com](mailto:enquiries@planer.com); website:

[www.planer.com](http://www.planer.com)

### Progress Educational Trust

58

Progress Educational Trust is a charity whose mission is to educate and to debate the responsible application of reproductive and genetic science. For more than 20 years we've been trusted as an independent voice by patients who are affected by infertility or genetic conditions, and we've been trusted by professionals to help the sector thrive by advocating the responsible application of science. Every week we keep patients and professionals alike informed on scientific, legal and policy developments through our FREE publication BioNews [www.bionews.org.uk](http://www.bionews.org.uk)

Our events are a forum for debate, identifying the most challenging issues and encouraging meaningful public discussion.

## EXHIBITOR INFORMATION

### Society for Reproduction and Fertility

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Society for  
Reproduction  
and Fertility

The Society for Reproduction and Fertility (SRF) aims to enhance the knowledge of reproductive processes and fertility in humans and animals.

The SRF, a friendly and supportive Society, offers membership to scientists and students from around the world who work on any aspect of reproductive biology or fertility. As well as co-hosting the Joint Fertility Conference and organising the Sex in Three Cities public lecture series, we award generous grants and scholarships and sponsor scientific workshops. Our journal, *Reproduction*, publishes original research articles, debates and topical reviews on reproductive and developmental biology and reproductive medicine.

To find out more about the SRF and our journal, visit our exhibition stand, our website [www.srf-reproduction.org](http://www.srf-reproduction.org) or email [srf@conferencecollective.co.uk](mailto:srf@conferencecollective.co.uk).

### Teva UK

12-13

We're Teva UK Limited, a leader in healthcare, supplying a wide range of medicines to the UK health service in a wide range of disease areas. We've been around for 80 years and supply more packs of medicines to the National Health Service than anyone else – around 1 in 8 packs supplied to the UK market is a Teva pack.1

We specialise in both generic and branded medicines, with specialty products in therapy areas as diverse as treat multiple sclerosis, cancer, pain, women's health and respiratory disorders like asthma.

We're part of Teva Pharmaceutical Industries Ltd, one of the world's leading pharmaceutical companies.

Teva UK Limited, Ridings Point, Whistler Drive, Castleford WF10 5HX

Tel: 01977 628500 Email: [general.enquiries@tevauk.com](mailto:general.enquiries@tevauk.com)

For Medical queries, e-mail [medinfo@tevauk.com](mailto:medinfo@tevauk.com) or call 020 7540 7117

[www.tevauk.com](http://www.tevauk.com)

Reference: 1) Data on File

### UK NEQAS Reproductive Science

57

"Helping to ensure clinical laboratory test results are accurate, reliable and comparable wherever they are produced".

We are currently working towards ISO17043 accreditation in both schemes:

Embryology scheme:

- Embryo morphology assessment which includes video clips of 'rolling' embryos and also 'Embryoscope TM' time lapsed photography videos.
- Four distributions per year.

Andrology scheme:

- Semen analysis which includes concentration, motility and practical and online morphology.
- Four distributions per year
- CPA accredited

UK NEQAS Reproductive Science scheme, Department of Reproductive Medicine, St Mary's Hospital, Oxford Road, Manchester. M13 9WL

Email: [repscience@ukneqas.org.uk](mailto:repscience@ukneqas.org.uk)

Tel: +44 (0)161 276 6437

[www.cmft.nhs.uk/ukneqasrepsci.aspx](http://www.cmft.nhs.uk/ukneqasrepsci.aspx)

### Validair Ltd

32

Validair Monitoring Solutions - monitoring and critical alarm systems.

Monitoring the storage and security of precious and vulnerable samples is an essential part of good laboratory practice. Parameters such as temperature, CO2 and oxygen concentration, pressure and humidity may all need to be monitored and alarmed.

Validair Monitoring Solutions ensure you can sleep soundly knowing your production process, stored product and precious samples are safe, watched over by a sophisticated monitoring and critical alarm system which is capable of multiple parameters in multiple locations, measured, logged and just in case alarmed.

Contact: David Roberts on 07710 709703 and email [david-roberts@validair.com](mailto:david-roberts@validair.com) or check [www.validair.com](http://www.validair.com) to find out how we can help.

### Vitrolife

38-39

Vitrolife's vision is to fulfil the dream of having a baby. We support our customers to achieve successful treatment outcomes by providing valued solutions and services for assisted reproduction.

Vitrolife is a global company contributing products within the IVF field. Our mission is to support customers to achieve successful treatment outcomes by providing valued solutions and services for assisted reproduction.

### Xytex

59

Since 1975, families have relied on Xytex for expert assistance in accomplishing dreams of growing a family. Xytex is an industry leader in cryoservices with a commitment to unsurpassed quality and a promise to provide its clients with an experience that will last a lifetime. Xytex utilizes the latest technology and recommended procedures to cryopreserve cells and tissue – making them readily available for use when needed.

Xytex is guided by an international medical advisory board with locations in Augusta, Georgia, Atlanta, Georgia and New Brunswick, New Jersey. For more information, visit [xytex.com](http://xytex.com).





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# Fertility 2018



Join us in Liverpool for the  
next joint conference on  
4-6 January 2018.



Visit [www.fertilityconference.org](http://www.fertilityconference.org)  
for the latest information.

