Reverie or reality?

The search for a new male contraceptive

Since the inception of hormonal contraception in 1960, a litany of birth control methods have become accessible to women. Despite these advances, male contraceptives remain limited to condoms and vasectomies. Typical failure rates for condom use are estimated to be around 18%, comparing unfavourably to female oral hormonal contraceptives (9%) and intrauterine devices (0.2-0.8%)[1]. Similarly, whilst vasectomies are overwhelmingly safe and effective, reversal is an ineffective and often costly procedure[2]. Surveys have repeatedly established the demand for an alternative male contraceptive with 57% of American men discontinuing regular condom use after 1 year and around 25% of women abandoning a method of birth control in the same period[3]. A reversible male contraceptive with safety and efficacy comparable to that of female birth control would both reduce the incidence of unwanted pregnancies and correct the currently gender imbalanced burden of contraception.

Despite this, the development of a male contraceptive has been beset with failure. This has been variously attributed to the inherent physiological difficulties of disrupting male fertility, intolerable side effects, regulatory safety burdens and industry inertia[3]. However, progress has been made in recent years, with a variety of male contraceptives in development ranging from topical gels to pills and physical devices. This essay aims to provide a brief overview of some of the most promising in the context of male reproductive biology.

Early evidence: exogenous testosterone

A key target for male contraception is the hypothalamic-pituitary-gonadal axis (see figure 1). This relies on administration of hormones such as testosterone to supress levels of luteinising hormone (LH) and follicle stimulating hormone (FSH) released from the anterior pituitary gland. Critically, the suppression of LH reduces synthesis of testosterone from the Leydig cells of the testes. Without this high concentration of endogenous testosterone, spermatogenesis arrests. This results in a lowered sperm count (oligospermia) or a complete lack of sperm (azoospermia) in the semen.

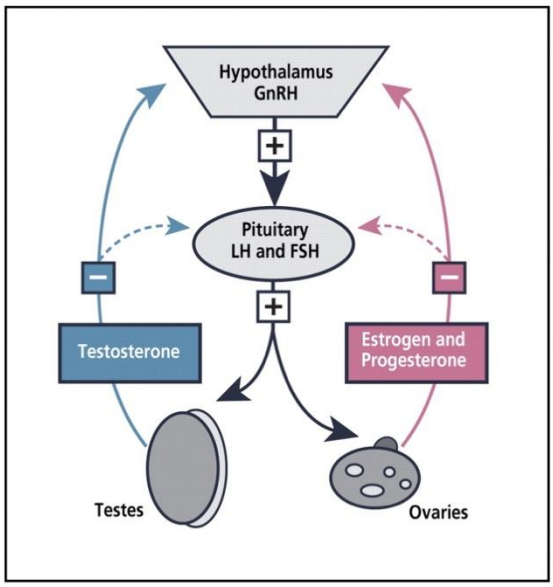

***Figure 1**: The hypothalamic-pituitary-gonadal axis. Colameco et al, 2009[4]*

The suppression of spermatogenesis using testosterone was first described in man as early as the 1930s[5]. However, it was not until two clinical trials conducted by WHO in the 1990s that it was established that the weekly administration of intramuscular (IM) testosterone enanthate could be used as an effective and reversible contraceptive method[6,7]. Failure rates observed were comparable to that of female hormonal contraceptives and no significant side effects were reported[7].

Trial and error: testosterone-progestin formulations

Yet these early studies also highlighted some key shortcomings in the use of testosterone as a contraceptive. Significant differences were observed between Asian and non-Asian populations, with Asian men more likely to reach azoospermia and take longer to recover to normal sperm concentrations[7]. This, together with frequent administration regimens led to the development of progestin/testosterone preparations. These formulations used progestins (progesterone receptor agonists) to supress LH and endogenous testosterone production whilst replacing physiological serum testosterone levels. Despite low failure rates, significant side effects were reported with a 2016 trial of 320 men receiving 8-weekly norethisterone enanthate/testosterone injections suspended due to adverse effects[8]. Common side effects included psychological disturbances, loss of libido, as well as acne in nearly half (46%) of the 320 men studied[8]. These effects were attributed to the low

testosterone levels of participants between injections. Other posited reasons included the androgenic activity of norethisterone as well as the inherent serum concentration fluctuations of IM administration[2,9].

Indeed, mode of delivery has been cited as significant drawback of such a drug. Testosterone undergoes extensive first pass metabolism, necessitating parenteral administration usually via IM injection[10]. A 2006 trial of a progestin/testosterone IM formulation found that though none of the participants found the regimen 'disagreeable' only 66% would choose this as their principal form of contraception[11]. Injections themselves were identified as the biggest disadvantage of the treatment regimen, ahead of lack of protection from STIs (25%) and physical side effects (7%)[11].

Squaring the circle: gels, pills and novel progestins

A solution to this problem may be transdermal gels. These gels exploit the lipophilicity of steroid hormones to deliver drugs to the systemic circulation via the skin. This has the advantage of being noninvasive and delivering steady drug concentrations to the blood. The most promising transdermal preparation in development is nestorone/testosterone gel (NES-T). A 2012 study established that daily administration of NES-T could reliably achieve contraceptive oligospermia in 89% of participants[2]. NES does not have androgenic activity, potentially reducing the frequency of side effects such as acne associated with earlier progestins[9]. The incidence of side effects in the trial was low and rates between men given testosterone only gel and those given NES-T formulations were not significant[2]. Thus, such effects may be attributable to supra-physiological doses of testosterone as opposed to NES. Despite being non-invasive, the practicality of a male contraceptive gel is uncertain with a 2006 study finding that a significant proportion of men felt daily administration of testosterone gel negatively affected their daily routine[3]. A phase II trial of NES-T is currently being conducted in the US[12].

A second candidate to square the circle of male hormonal contraception is the androgen dimethandrolone undecanoate (DMAU). An agonist of progesterone and androgen receptors, DMAU has been found to lower gonadotrophins with no significant side effects and without the need for the co-administration of testosterone[13,14]. Moreover, DMAU is not a substrate

for 5α-reductase, an enzyme necessary for the conversion of testosterone to its powerful derivative dihydrotestosterone, potentially reducing the incidence of androgenic side effects[15]. DMAU also has the advantage of high oral bioavailability[13]. This may increase compliance compared to gels or injections. The announcement of positive findings for the safety of oral DMAU were welcomed with optimism, however, the true efficacy of DMAU as a contraceptive has yet to be ascertained[14].

Drugs old and new: non-hormonal contraceptives

A number of non-hormonal male contraceptives are also under development. One approach is the targeting of ependymal protease inhibitor, or Eppin. Eppin is a protein expressed in the cell membranes of spermatozoa[16]. Upon ejaculation, the seminal vesicles secrete the protein semenogelin 1 (SEMG1)[16]. SEMG1 binds Eppin, forming a complex inhibiting sperm motility and blocking early capacitation through a decrease in intracellular pH and calcium[17]. These effects are reversed when SEMG1 is cleaved by prostate specific antigen (PSA) in the female reproductive tract[17]. A novel contraceptive would bind Eppin, however unlike SEMG1 this would not undergo proteolysis by PSA, rendering spermatozoa infertile principally through lack of motility. Moreover, with Eppin expressed in only in the testes, an 'anti-Eppin' drug may have significantly fewer systemic side effects than hormonal alternatives. The potential of such a drug was established in a small study of macaque monkeys immunised against Eppin. All monkeys developing high titres of anti-Eppin antibodies became infertile, with 5 out of 7 (71%) of these regaining fertility after cessation of treatment[18]. Despite the potential of an anti-Eppin contraceptive research remains focussed on attempting to identify a suitable candidate compound.

A second target is bromodomain testes specific protein, or BRDT. Bromodomains are proteins which function as molecular switches, reading and transducing epigenetic markers[19]. Bromodomains are expressed throughout the body, though BRDT is exclusive to the testes where it is believed to modulate chromatin remodelling during spermiogenesis[19]. A 2012 study demonstrated that the treatment of mice with JQ1, a non-specific bromodomain inhibitor, results in reversible infertility (see figure 2)[20]. Though JQ1 is non-specific and therefore unsuitable as a long term contraceptive, this study validates BRDT as a therapeutic target for future research. However, the authors caution that a BRDT inhibitor may cause

epigenetic changes to the germ-line[20]. Assurances of the genetic safety of a such a contraceptive will be vital, though this may slow the development of any candidate drug.

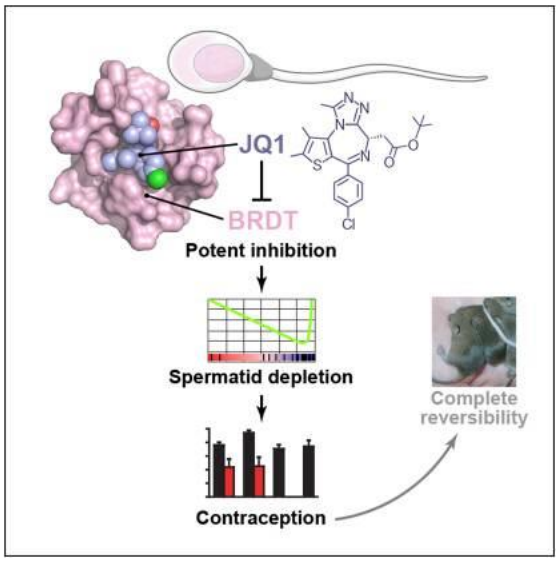

***Figure 2**: The contraceptive mechanism of JQ1. Matzuk et al, 2012* [20]

Yet the future of male contraception may lie more in older drugs than in the development of new. Alpha blockers such as tamsulosin are antagonists of the α-adrenoreceptor. This causes relaxation of smooth muscle throughout the body including in the vas deferens, resulting in anejaculation without anorgasmia. A 2012 trial of 40 men evaluated tamsulosin as a contraceptive. It found that tamsulosin produced anejaculation in all participants 4-6 hours after administration with limited side effects[21]. Similarly, the antiarrhythmic nifedipine has been observed *in vitro* to block CatSper calcium channels intrinsic to spermatic activation[22]. These examples demonstrate the role existing drugs have to play in the search for a male contraceptive.

A modern vasectomy: RISUG

Reversible inhibition of sperm under guidance (RISUG) is an exciting non-pharmacological contraceptive under development. This involves the injection of the polymer styrene maleic anhydride (SMA) into the vas deferens via a small vasectomy-like procedure[23]. SMA in solution forms a gel which partially blocks the vas deferens resulting in oligo- and

azoospermia as well as producing profound morphological changes in spermatozoa through plasma membrane disruption[23 24].

Small human trials have found that RISUG therapy results in long-term azoospermia with minimal side effects[25]. The reversibility of RISUG has been demonstrated in animals with the injection of a high pH solution into the vas[26]. However, significant spermatic morphological abnormalities persist, raising the spectre of teratogenicity post-reversal. Despite this, murine studies have shown a complete return to normal morphology within 90 days, with no apparent abnormalities in the progeny of mice treated with RISUG[26]. Phase 3 trials are currently underway in India[26].

Conclusion

Significant advances have been made in the search for a novel male contraceptive in recent years. A plethora of targets have been identified alongside the development of promising experimental technologies. Although it is likely the first licensed novel therapy will be a hormonal, non-hormonal and non-pharmacological therapies offer the prospect of enhanced specificity, lower side effect burdens and potentially safer long-term outcomes. Yet the path to a new contraceptive remains tortuous. Such a therapy will need to surmount considerable physiological challenges to prove itself a safe, effective and convenient contraceptive for the 21st century.

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