SOCIETY FOR REPRODUCTION AND FERTILITY: ESSAY COMPETITION 2013

"The Prozac Nation": SSRIs and fertility – mind over matter?

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Reading for BM BCh in Clinical Medicine

The first of the selective serotonin reuptake inhibitor (SSRI) drugs, the arrival of Prozac in 1987 heralded an exponential rise in use of antidepressants and spawned a cultural phenomenon, epitomised by Elizabeth Wurtzel's confessional memoir *Prozac Nation*.[1] "Prozac" became a household word and in the USA, prescription rates increased by 400% between the periods 1988-1994 and 2005-2008.[2] The side effect profile of SSRIs is generally well characterised and given that many women take antidepressants throughout pregnancy, the effects of fetal exposure to SSRIs have been extensively studied since the 1980s. But what about reproductive implications before a pregnancy even starts? This essay will explore the hypothesis that SSRIs are detrimental to fertility, analyzing the available literature, the mechanisms by which this might occur and the implications for clinical practice.

Fertility: at the mercy of pharmacology?

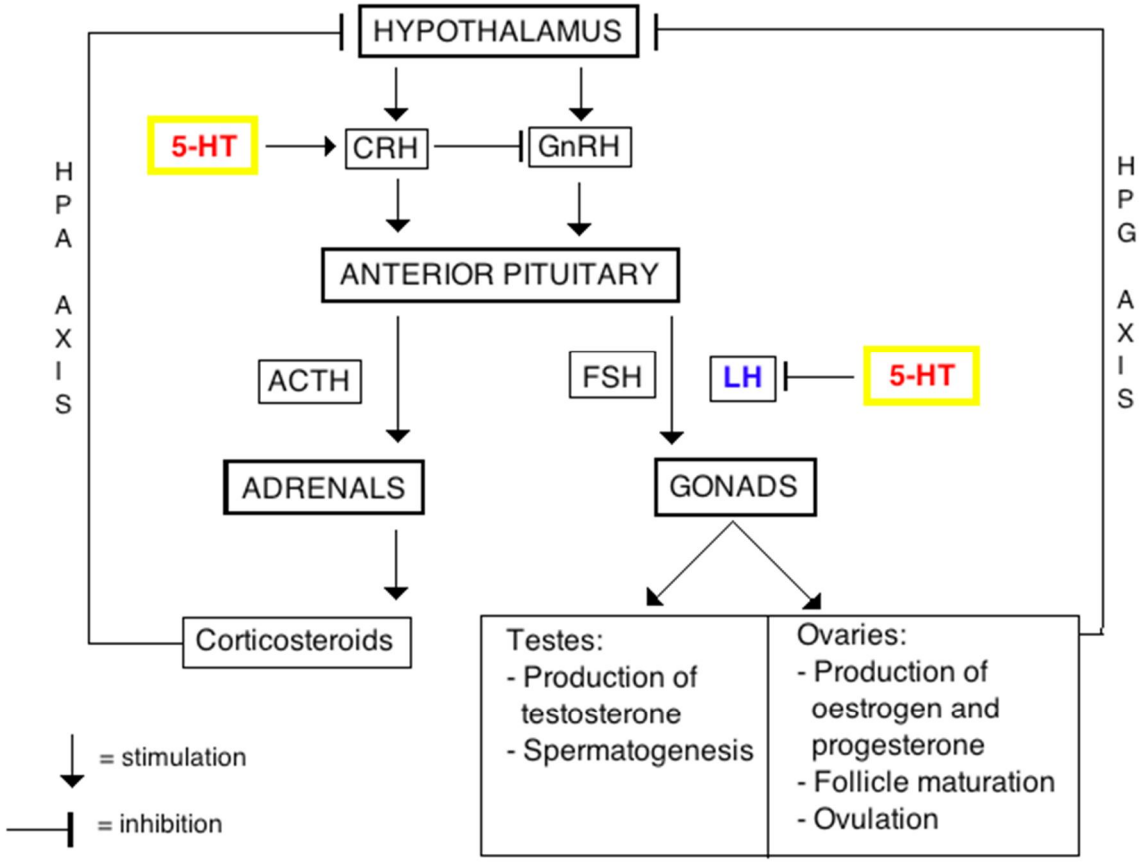
Despite its fundamental place in human biology, fertility is difficult to define. Infertility is even less straightforward: like depression, it is intangible, incompletely understood, stigmatized, widespread and challenging to investigate and manage. For practical purposes, an arbitrary time threshold must be imposed for diagnosis of infertility. NICE guidelines define it as failure to conceive after regular unprotected sexual intercourse for 2 years in the absence of known reproductive pathology, but this time cut-off varies between institutions, contributing to inconsistencies in the evidence discussed below.

Four factors are absolutely necessary for pregnancy: ovulation, release of adequate sperm, fertilization and implantation.[3] Textbooks generally provide comprehensive lists of medical conditions that can compromise fertility, but are prone to glossing over the potentially catastrophic effects of drugs. The alkylating agent cyclophosphamide, for example, has been shown to cause permanent azoospermia and destruction of both primordial and antral ovarian follicles.[4] Psychotropic drugs other than SSRIs have also been implicated: hyperprolactinemia, which accounts for 10% of anovulatory women, is a common consequence of antipsychotic treatment.[3] Clearly, reproductive biology is by no means immune to iatrogenic pharmacological damage.

Neuroendocrine control of reproductive cycles: a role for serotonin

The rationale for an impact of SSRIs on fertility originates from the established role of serotonin in modulating the hypothalamo-pituitary-gonadal axis, summarised in **figure 1**.[5] As early as 1969, Schneider and McCann showed that injection of serotonin into the third ventricle of anaesthetised rats produced a highly significant ($p<0.01$) decrease in plasma LH levels, which was not seen with equivalent dopamine or noradrenaline injections.[6] A few years later, Soliman and

Huston published similar work in fowls, demonstrating that subcutaneous injection of serotonin 8 hours before the expected time of ovulation resulted in failure of ovulation in 90% of treated hens.[7] This inhibitory effect of serotonin on LH release and gonadal function begs the question of whether SSRI-induced increases in circulating serotonin levels could potentiate these inhibitory effects and thus impact reproductive capacity in humans.



CRH = corticotropin-releasing hormone; GnRH = gonadotropin-releasing hormone;
ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone;
LH = luteinizing hormone; 5-HT = 5-hydroxytryptophan (serotonin).
HPA = hypothalamo-pituitary-adrenal axis; HPG = hypothalamo-pituitary-gonadal axis.

Figure 1: Serotonin-mediated inhibition of LH in the hypothalamo-pituitary-gonadal axis. Adapted from [5]

SSRIs: the missing link?

To date, studies examining a potential association between SSRIs and infertility fall into 3 categories: (1) those measuring female parameters of fertility; (2) those measuring male parameters of fertility; and (3) those investigating the effects of SSRIs on success rates of assisted conception in infertile couples.

Millions of women take antidepressants and 12% of women of reproductive age are infertile, but in up to 30% of cases, there is no identifiable cause.[3] Could SSRIs contribute? In 2006, Uphouse and colleagues examined the effect of daily treatment with fluoxetine 10mg/kg on female Fischer rats. They found that fluoxetine significantly elongated the estrous cycle and also suppressed serum progesterone levels, with corresponding failure to show sexually receptive behaviour.[8] Considering the potential implications of these findings, the paucity of subsequent research addressing the impact of SSRIs on human female fertility is both remarkable and disappointing.

In males, however, there has been a modest but promising level of research interest, no doubt reflecting the comparative ease of measuring fertility parameters in men as opposed to women. In 2007, Bataineh et al. treated adult male rats with fluoxetine 200mg/kg for 60 days and documented significant reduction in spermatogenesis, sperm motility and rate of impregnation of female rats, leading the authors to conclude that "long-term fluoxetine ingestion produces adverse effects on fertility".[9] In the same year, Tanrikut and Schlegel analyzed the semen of 2 infertile men taking SSRIs: one sertraline, the other escitalopram. Both cases revealed oligospermia, impaired motility and abnormal sperm morphology, with return to normal parameters on repeat analysis 1-2 months after SSRI discontinuation.[10] This emerging connection between SSRIs and abnormal semen parameters was reinforced by an Iranian group, who compared 74 fertile, depressed men on SSRI treatment with 44 healthy fertile controls and found a highly significant reduction in mean total sperm count: 61.2 +/-11.4 million in the SSRI group, compared to 186.2 +/- 34.1 million in the controls ($p=0.001$).[11]

The evidence discussed above lends considerable clout to the hypothesis that SSRIs have negative impact on fertility. But do these abnormalities in biological parameters actually translate into clinical infertility? Answers are scarce and often contradictory, but are beginning to accumulate from studies in the third category, analyzing IVF outcomes. Klock et al. caused a stir in 2004 when they published a retrospective chart review comparing IVF outcome-related measures in SSRI-treated women and matched controls. There were no significant differences in number of oocytes retrieved, number of oocytes fertilized or percentage of zygotes achieving blastocyst formation by day 5; nor did the two groups differ significantly in rates of miscarriage or non-pregnancy. However, the pregnancy rate in the SSRI-treated group was 46%, compared to 63% in the SSRI-free controls.[12] This failed to reach statistical significance – but does that necessarily preclude clinical significance?

The rather ominous trend uncovered by Klock et al. has not been corroborated by subsequent

research. In 2009, Serafini et al. randomized 152 non-depressed infertile women to receive either fluoxetine 20mg/day or folic acid 5mg/day during their first IVF cycle. They found no significant adverse effects on number of oocytes retrieved, implantation rate, pregnancy rate or birth rate in the fluoxetine-treated group.[13] Contradicting Klock et al. even further, Ramezanzadeh and colleagues evaluated pregnancy rates in 140 infertile couples in whom at least one partner had been diagnosed with depression. The couples were randomized to either the treatment group, who received 6-8 sessions of individual psychotherapy and daily fluoxetine (20-60mg, depending on severity of depression) prior to infertility treatment, or the control group, who received no interventions. Strikingly, psychiatric intervention enhanced the success of assisted conception: 47% of couples in the treatment group achieved pregnancy, compared to just 7% of controls.[14]

If conclusive evidence for an impact of SSRIs on fertility (either beneficial or deleterious) is to be obtained, it is paramount that investigators devote their attention not just to the apparent trends, but also to the mechanisms by which they might be occurring. A major challenge is to unravel whether SSRIs exert their effects either directly, for example by inhibiting ovulation, or indirectly, by causing sexual dysfunction. The former is supported by the data from animal models discussed above and by the studies demonstrating alterations in semen parameters with SSRI treatment. The latter is much more nebulous. Sexual dysfunction has been documented in anecdotal case reports since the introduction of SSRIs in 1988, but is only recently gathering momentum as an important adverse effect, with the commonest problems being anorgasmia in females and delayed ejaculation in men. There is a wealth of data available on potential mechanisms for SSRI-induced sexual dysfunction, ranging from anorectic effects and secondary estrous cycle disruption[8] to inhibition of vas deferens motility.[15] However, despite a recent case series reporting sexual dysfunction that persisted beyond SSRI discontinuation in 3 male patients,[16] the specific associations of sexual dysfunction with fertility remain unexplored. If they are to be demystified, it is essential that quantity and design of trials improve, despite the inherent difficulties in detecting and quantifying sexual dysfunction.

Implications for clinical practice – a case against SSRIs?

At present, there is not enough evidence to contraindicate use of SSRIs in patients of childbearing age and intention. However, emerging trends hint at a potential detrimental effect on fertility parameters and are sufficient to warrant a thorough re-evaluation of whether the benefits of SSRIs outweigh their potential risks. Although a detailed analysis of the evidence basis for SSRI therapy is beyond the scope of this essay, there is no doubt that the justification of their efficacy in treatment of depression is shrouded in controversy and confusion. Of particular relevance to this essay is the widely held assumption that the risks of untreated depression during pregnancy and

the post-partum period outweigh the potential adverse effects of SSRI use. However, there is currently no published randomised clinical trial to support this theory. Furthermore, although there is convincing evidence in favour of SSRIs for severe depression, there is almost nothing to suggest that they are superior to cognitive behavioural therapy (CBT) or even placebo for mild to moderate depression. There is therefore a convincing argument for offering alternative treatments to these patients: CBT, for example, is cheaper and at least as effective as SSRIs and may even be associated with lower depression relapse rates.[17]

Conclusion

SSRIs have acquired celebrity status in popular culture and in psychiatry, licensed for an ever-increasing range of conditions. As SSRI prescription rates continue to climb and we really do seem to be living in a "Prozac Nation", it is vital that we remain vigilant about their adverse effects and satisfy ourselves that they are truly safe. Scientists, clinicians and pharmaceutical companies need to remove the rose-tinted spectacles that are at risk of obscuring some unpleasant truths about SSRIs, and intensify their efforts to prove that they do not contribute to infertility. The question of whether SSRIs disadvantage fertility must, for the moment, remain unanswered, but lack of conclusive evidence for detriment should not be misinterpreted as proof of safety.

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Word count: 2000

Details of submission

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