The Effect of Mental Illness and Psychotropic Medication on Gametes and Fertility: A Systematic Review

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ABSTRACT

Background: Psychiatric disorders during the reproductive years and their treatment with psychotropic medications are increasingly common, and their effect on the reproductive system is an important area of research.

Objective: To review the effect of mental illness and psychotropic medication on gametes and fertility.

Data Sources: Searches of the PubMed database were conducted for English-language articles containing the keywords *gametes*, *fertility*, *psychotropic*, *oocyte*, *sperm*, *mental illness*, *depression*, and/or *anxiety*, in the title or abstract. The searches yielded 3,603 citations.

Study Selection: Studies were evaluated for relevance. Those not pertinent to the clinical question, not written in English, and focusing on invertebrates were excluded. Full texts of 50 articles were obtained for further evaluation. Additional articles were identified from reference lists. Ultimately, a total of 37 studies were deemed suitable and reviewed.

Results: Clinical studies have not demonstrated a deleterious effect of psychotropic medication on oocytes in terms of retrieval and pregnancy rates. Clinical studies demonstrate inconclusive results regarding the effect on sperm, with several studies suggesting increased sperm motility and quantity with certain psychotropics. Decreased sperm quantity and motility are described in a number of studies, including in vitro and in vivo studies. Maternal psychiatric illness is associated with decreased reproductive success, including lower rates of oocyte retrieval, lower rates of ongoing pregnancy, and dysregulation of the stress system in a majority (n = 11) but not all (n = 3) studies reviewed. Male depression did not appear to affect sperm, but anxiety did have an effect (n = 1).

Conclusions: Given the detrimental effect of untreated mental illness, current literature is not robust enough to influence the use of psychotropics in males or females who are considering reproduction.

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A quarter of Americans suffer from a mental disorder,[1,2] and the number of individuals being treated with psychotropic medication is increasing,[3] including during the reproductive lifespan. There is a growing and somewhat controversial literature regarding the effect of psychotropic medication exposure on the developing fetus. Some preclinical and clinical studies have emerged that suggest that developmental exposure to selective serotonin reuptake inhibitors (SSRIs) may indeed have an effect on the developing central nervous system, though studies are not uniform, and much research is needed.[4] What effect, if any, exposure to psychotropics has on the gametes of individuals prescribed these medications is unknown. In addition, whether mental illness itself has any effect on gametes, or fertility, is an understudied area. Mental and reproductive health share common substrates, including the hypothalamic-pituitary-adrenal axis, as well as neurotransmitter systems, including serotonin (5-HT) and dopamine. Serotonin is a neurotransmitter that is involved in mood and anxiety, as well as a host of other biological functions. Indeed, it is found in the gastrointestinal track, as well as the reproductive tract.[5–7] Similarly, gonadal steroid receptors are located throughout the central nervous system (CNS).[8] A growing literature suggests that there is an interplay between gonadal steroids and the serotonergic system, with estradiol leading to an increase in 5-HT synthesis, a decrease in 5-HT breakdown, and an overall increase in availability of 5-HT.[9] While reproductive health is frequently investigated separately, it makes sense that forces impacting the nervous system, such as disorders or psychotropics, could also affect the reproductive system. Here, we will review the current clinical literature regarding the effect of mental illness and its treatment on gametes and fertility. The consequences of potential alterations to gametes have implications not just to individuals, but to their offspring, as well. Increasing the fund of knowledge regarding the consequences of mental illness and its treatment on reproductive health will be important for both the patient and clinician when making evidence-based decisions.

METHOD

Data Sources

PRISMA guidelines (www.prisma-statement.org) were used in creating this systematic review. Searches of the PubMed database and Google Scholar were conducted for English-language articles containing the following keywords in the title or abstract: *psychotropic fertility, psychotropic gametes, SSRI gametes, SSRI fertility, depression fertility, depression infertility, psychotropic infertility, oocytes depression,* and *sperm depression*. The searches yielded 3,603 records, including duplicates.

Study Selection

A total of 3,553 records not written in English, not focusing on vertebrates, duplicate articles, or not pertinent to the topic were

excluded. An attempt was made to obtain full text of the remaining articles through the Ohio State University Interlibrary Loan system and Google Scholar, and all 50 articles were obtained. Additional articles were then found through cross-referencing these articles. After assessment, a total of 37 studies were deemed suitable and reviewed.

Clinical Points

- The current literature suggests that sperm may be negatively impacted by exposure to psychotropic medication, but this finding is not extended to oocytes, based on limited available studies.
- Psychiatric illness may also have a negative effect on fertility.
- The benefit of treatment for an individual's overall health should be weighed against any negative effect the treatment may have on fertility.

RESULTS AND DISCUSSION

Psychotropics and Males

Investigations on the effect on sperm included direct exposure of human sperm to psychotropic compounds using an in vitro system, preclinical studies, and human studies; these studies and their findings are summarized in Table 1.[10–19] Parameters examined included motility, morphology, semen volume, and sperm count.

In vitro studies. One effort demonstrated dose-dependent positive responses with imipramine, amitriptyline, phenothiazines, and lithium.[10] Diazepam had no effect on sperm motility, and haloperidol had a minimal effect and decreased spermatozoa count only at high concentrations.[10] However, further in vitro studies of semen specimens from healthy controls exposed directly to chlorpromazine, trifluoperazine, promethazine, nortriptyline, imipramine, and desipramine revealed dose-dependent inhibitory effects on sperm motility. Lithium showed no changes in sperm motility.[11] Kumar et al[12] looked at the spermicidal properties of SSRI antidepressants and found that fluoxetine, sertraline, fluvoxamine, paroxetine, and citalopram had spermicidal activity at varying concentrations when introduced directly to sperm. Pretreatment of human sperm with serotonin had no effect on the spermicidal activity of fluoxetine or fluvoxamine, suggesting that their activity was not mediated through the serotonin transporter. The spermicidal action of the SSRIs was thought to be caused by interaction with sulfhydryl groups present over the sperm membrane, or inhibition of oxidative phosphorylation of sperm mitochondria.[12] While this study reveals a detrimental direct effect of psychotropic medication on gametes in an artificial setting, where sperm and psychotropic medication interact directly, it does not address spermicidal activity in men taking these medicines orally, as metabolites of these drugs were not assessed. While these in vitro studies assessed the direct effects of psychotropic medication on gametes, they did not purport to assess the metabolic products of the psychotropic medications, or what occurs in vivo, a more practical concern.

Preclinical studies. A study that examined the effect of olanzapine on testes and spermatogenesis in rats did not find significant differences in a majority of measurements in testicular tissues.[13] However, the volume of lymphatic space was reduced in animals treated with 10 mg/kg of olanzapine in relation to the control group, and a histopathological analysis of the testes of animals treated with 5 or 10 mg/kg found changes in spermatogenesis compatible with testicular degeneration.[13] Of note, 10 mg/kg of olanzapine is approximately 2 times higher than the highest recommended dose in humans, limiting the ability to extrapolate these findings into clinically useful information.

Next, studies turned from a direct examination of the physical structure of the testes to the regulation of gonadal hormones. In an effort to examine the effect of chronic treatment with monoamine reuptake inhibitors on gonadal steroids, administration of the dopamine reuptake inhibitors benztropine and mazindol to male rats demonstrated a suppressive effect on the gonadal hormone testosterone, but found prolactin levels remained unaffected.[14] The same study also demonstrated that the serotonin reuptake inhibitors clomipramine and fluvoxamine altered neither serum testosterone levels nor prolactin levels.[14]

Clinical studies. In investigations that move into the clinical realm, subjects provide sperm samples prior to starting medication in order to establish a baseline, and then again after several weeks of exposure to a particular compound.[20] It is important to consider the control group when examining results demonstrating the potentially deleterious effects of psychotropic medications on sperm. One might argue that the appropriate control group is not healthy men, but depressed men, or that depressed untreated men should at least be included in the analysis. Depression, or other psychiatric illness, might make its own contribution to sperm function, or fertility, as discussed later in this review. Certainly depression leads to decreased libido and erectile dysfunction.[20]

Studies in men without psychiatric illness. The positive in vitro effects with amitriptyline lead to an examination of whether that medication could be used to treat asthenozoospermia, a condition where there is a reduction in sperm motility, in men without depression.[15] A significant increase in sperm count, sperm morphology, semen volume, and motility was seen after oral amitriptyline treatment. No clinical side effects were noted, though patients were not assessed for psychiatric effects of the medication.[15] This work indicated that amitriptyline may not have a deleterious effect on male fertility, and may even improve it, with improved semen analysis at the study's conclusion.

A prospective cohort study examined healthy adult men administered escalating doses of paroxetine over 5 weeks, with corresponding semen analyses performed.[16] Semen parameters were not significantly different throughout the study. However, DNA fragmentation of the semen samples was found to significantly increase during paroxetine

Table 1. The Effect of Psychotropic Medications on Males

Study	Subjects	Outcome Measured	Illness	Psychotropic Drug	Finding	Comment
Schnieden, 1974[10]	In vitro	Sperm motility	N/A	Imipramine, amitriptyline, phenothiazines, chlordiazepoxide, haloperidol, diazepam, lithium	Increased motility with: imipramine, amitriptyline, phenothiazines, lithium No effect: diazepam Reduced motility: haloperidol	Only high doses of haloperidol reduced sperm motility
Levin et al, 1981[11]	24 Psychiatric patients 31 Controls	Sperm motility	Depression	Desipramine or lithium	Reduced sperm viability following desipramine or lithium	In vivo and in vitro findings for lithium do not correlate
	In vitro	Sperm motility	N/A	Lithium, imipramine hydrochloride, desmethylimipramine, chlorpromazine, trifluoperazine, and nortriptyline hydrochloride	No effect with lithium, decreased motility with other medications	
Kumar et al, 2006[12]	In vitro	Spermicidal activity	N/A	Fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram	Spermicidal effects at varying concentrations	Spermicidal activity thought to be through interaction with sulfhydryl groups, not through 5-HT mechanisms
de Siqueira Bringel et al, 2013[13]	Rats	Testicular volume, spermatogenesis	N/A	Olanzapine	No significant effect on testicular tissues; volume of lymphatic space reduced. Changes in sperm with 10 mg/kg.	10 mg/kg is 2 times higher than highest recommended human dose
Rehavi et al, 2000[14]	CD rats	Serum gonadal steroids and prolactin	N/A	Benztropine, mazindol, clomipramine, fluvoxamine	Dopamine reuptake inhibitors lead to reduced testosterone levels. Serotonin reuptake inhibitors did not alter serum testosterone levels. No effect on prolactin levels with any medication.	
Padrón and Nodarse, 1980[15]	20 Men	Sperm motility	Asthenozoospermia	Amitriptyline	A significant increase in sperm count, sperm morphology, semen volume, and motility	
Tanrikut et al, 2010[16]	35 Men	DNA fragments and erectile function	N/A	Paroxetine	Increased abnormal DNA fragmentation (OR = 9.33, 95% CI, 2.3–37.9). 35% significant changes in ED; 47% ejaculation difficulties.	
Amsterdam et al, 1981[17]	9 Depressed men 9 Controls	Sperm viability	Depression	Desipramine or lithium	25% reduction in viability with desipramine or lithium compared to controls	
Maier and Koinig, 1994[18]	9 Depressed males 15 Controls	Sperm function	Depression	Clomipramine	Clomipramine group with decreased number of normal sperm, decreased motility, low ejaculate volume	Controls with depressive symptoms had normal spermiograms
Safarinejad, 2008[19]	74 Depressed men 44 Controls	Sperm count, motility, morphology, denatured single-stranded DNA	Depression	Escitalopram, citalopram, fluoxetine, paroxetine, sertraline	Decreased total sperm count, decreased motility, and increased denatured single-stranded DNA	

Abbreviations: CD = Charles River Sprague-Dawley, CI = confidence interval, DNA = deoxyribonucleic acid, ED = erectile dysfunction, OR = odds ratio, 5-HT = serotonin.

administration, and multivariate regression correcting for age and body mass index suggested that SSRI treatment was associated with DNA fragmentation. Thirty-five percent of men noted significant changes in erectile dysfunction, and 47% of men noted ejaculatory difficulties during paroxetine treatment, suggesting a negative effect on fertility.[16] This further presses the question of the potential effect of increased DNA fragmentation on future generations. Increased sperm DNA fragmentation has been correlated with reduced fertilization rates, premature delivery, and childhood illness, including cancer.[21]

Studies including men with psychiatric illness. The positive finding with amitriptyline did not necessarily extend to other psychotropics, as a significant reduction in sperm viability was found in depressed subjects treated with either desipramine or lithium, when compared to the control group.[17] However, the in vitro findings from this group[11] did not support a deleterious effect of lithium, somewhat confounding the interpretation. Another study examined the sperm of 9 depressed patients following 3 weeks of oral treatment with clomipramine.[18] The control group consisted of 15 males undergoing urological evaluation for erectile dysfunction, 7 of whom felt "depressive" though a formal evaluation of depressive symptoms was not performed. The study found that all 9 patients exposed to clomipramine had pathological sperm findings. Of note, the patients in the control group that reported depressive symptoms all had normal spermiogram results.[18] A comparison of depressed patients receiving an SSRI with healthy controls found a significant decrease in total sperm count, decreased motility, and increased denatured single-stranded DNA in the SSRI-treated patients.[19]

While some of these studies propose a negative effect of psychotropic medication on semen parameters using both in vitro and in vivo measures, these findings are not uniform. Furthermore, the mechanisms underlying potential disruption need further elucidation. And while semen parameters are important as an intermediate finding, fertility effects are really the important end goal of this research and the area for further research.

Psychotropics and Females

Studies on the effect of psychotropic medication on females are summarized in Table 2[14,22–30] and include preclinical work in animal models, as well as clinical studies in women using assisted reproductive technologies (ART) in order to conceive.

Preclinical studies. Work in rodent models has demonstrated that 5-HT plays a role in the reproductive cycle, including follicular growth, oocyte meiotic division, early embryogenesis,[31] and sexual behavior.[32] Investigators demonstrated that both oocytes and cumulus cells, which surround and support oocytes, contain both 5-HT and the 5-HT transporter (SERT) that is the putative target of SSRIs.[7] The presence of the SERT in mammalian oocytes suggests 1 potential mechanism through which SSRIs may influence fertility. Additionally, the finding that knockout mice lacking the *tph1* gene, a gene responsible for the synthesis of peripheral 5-HT, demonstrate a reduction in embryonic size supports an important role of 5-HT in early embryonic development.[33] However, murine knockout models of various 5-HT receptor types, as well as the SERT, do not demonstrate alterations in fertility,[31] leaving the role of 5-HT in oocyte development and fertility somewhat unclear. Directly examining the role of psychotropics, 1 study utilized female zebrafish to investigate the effects of fluoxetine on oocyte production.[22] It reported inhibition of oocyte production after exposure to fluoxetine and pinpointed decreased follicle-stimulating hormone (FSH), luteinizing hormone (LH), and ovarian aromatase gene expression, suggesting that a disruption in ovarian steroid synthesis and the action of gonadotropins may be the underlying mechanism of action.[22] SSRIs may influence gonadotropins through their modulation of the upstream hypothalamic-pituitary-adrenal axis (HPA-axis), a known target of SSRI action.[34]

However, further rodent work demonstrated that 1 to 3 weeks of treatment with 10 mg/kg of fluoxetine did not affect estrous cycling, as measured by vaginal smears, but did reduce receptive behaviors in females.[23] Of note, sexual motivation was not changed by fluoxetine exposure, as quantified by time spent with males versus other females.[23] Additional work in rats demonstrated that treatment with 10 mg/kg of fluoxetine initially disrupted estrous cycling; however, this effect subsided by 20 days of treatment,[24] and the effect was found to be reduced in a different rat strain.[25] Further data suggesting SSRIs influence estrogen come with the finding that fluoxetine at 1.7 mg/kg and 17 mg/kg was found to be estrogenic in Wistar rats, as reflected by increased uterine weight and induction of estrogen receptor–mediated effects in a gene reporter assay.[26] An additional study demonstrates that both serotonin and dopamine reuptake inhibitors are capable of lowering serum estradiol and progesterone levels in female rats.[14] In comparison, neither the serotonin nor the dopamine reuptake blockers altered prolactin serum levels in either male or female rats, suggesting that the effect on ovarian and testicular hormones is related to the HPA-axis, though the mechanism remains unknown.[14] Furthermore, a study conducted in ovariectomized rats administered a measured amount of estrogen demonstrated a decreased level of circulating estrogen with concomitant fluoxetine administration.[27] There was a reverse dose response curve, with the lower dose of fluoxetine causing the most suppression of estrogen. Of note, the studies were carried out in ovariectomized females, which suggests that the mechanism does not originate with reduced ovarian synthesis of estrogen. The authors speculate that fluoxetine may modify liver metabolism of estrogen.[27]

Finally, a decreased rate of live birth and litter size was found in mice exposed to fluoxetine when compared to control mice, suggesting an issue with implantation or placentation, though length of gestation was not affected.[28] Of note, the strain of mouse used (129/SvEvTac) has been demonstrated to have fertility issues including low fertilization rate, fewer fertilized eggs, and smaller litter size.[35] These baseline fertility issues make the findings of this study

Table 2. The Effect of Psychotropic Medications on Females

Study	Subjects	Outcome Measured	Psychotropic Drug	Finding	Comment
Preclinical studies					
Lister et al, 2009[22]	Zebrafish	Oocyte production, FSH, LH, ovarian aromatase gene expression	Fluoxetine	Decreased oocyte production, decreased FSH, LH, and ovarian aromatase gene expression	
Matuszczyk et al, 1998[23]	Rats	Estrous cycling, receptive behaviors, sexual motivation	Fluoxetine	No change in estrous cycling. Reduced receptive behaviors. No change in sexual motivation.	
Uphouse et al, 2006[24]	Fischer rats	Estrous cycling, progesterone levels, lordosis behavior, food intake	Fluoxetine	Initial disruption in estrous cycling and lordosis behavior subsided by 20 days of treatment	Changes induced by fluoxetine normalized
Maswood et al, 2008[25]	Sprague-Dawley rats	Estrous cycling, progesterone levels, lordosis behavior	Fluoxetine	6 of 15 (40%) rats showed transient altered estrous cycling and transient sexual receptivity decrease	Lack of uniformity in finding
Müller et al, 2012[26]	Wistar rats	Uterine weight, estrogen receptor function	Fluoxetine	Increased uterine weight and induction of estrogen receptor mediated effects in a gene reporter assay	
Rehavi et al, 2000[14]	CD rats	Serum gonadal steroids and prolactin	Benztropine, mazindol, clomipramine, fluvoxamine	All medications lead to reduced estradiol and progesterone levels. No effect on prolactin levels.	
Taylor et al, 2004[27]	Long-Evans rats	Serum estradiol	Fluoxetine	Decreased estrogen with fluoxetine administration; lower doses fluoxetine caused higher levels of suppression	Lower doses of fluoxetine causing increased suppression is not clearly explained
Bauer et al, 2010[28]	129/SvEvTac mice	Live birth rate, litter size, gestational length	Fluoxetine	Decreased rate of live birth and litter size. Gestational length unchanged.	Strain used has infertility issues at baseline
Clinical studies					
Klock et al, 2004[29]	25 SSRI group 50 Controls	Estradiol, oocytes retrieved and fertilized, blastocysts, hCG values, conception	Sertraline, fluoxetine, citalopram	No differences between groups. Clinical difference in rate of pregnancy: 56% of SSRI group not pregnant vs 37% of control.	No statistical difference between groups limits interpretation of finding
Serafini et al, 2009[30]	53 SSRI group 51 FA group	STAI; retrieved and fertilized oocytes; rate of embryo transfer, implantation, spontaneous abortion, and birth	Fluoxetine	No statistical difference between groups. Clinical difference: 54% of SSRI group became pregnant vs 43% of FA group. Birth rate 44% in SSRI group vs 35% in FA group. No difference in STAI.	No statistical difference between groups limits interpretation of finding

Abbreviations: CD = Charles River Sprague-Dawley, FA = folic acid, FSH = follicle-stimulating hormone, hCG = human chorionic gonadotropin, LH = luteinizing hormone, SSRI = selective serotonin reuptake inhibitor, STAI = State-Trait Anxiety Inventory.

more difficult to interpret, and future efforts should focus on replicating these findings in alternative mouse strains.

Taken together, these studies suggest that serotonin may play an important role in oocyte maturation, estrogen regulation, and the early stages of embryonic development, though the literature is hardly convergent. Studies do lend credence to the hypothesis that perturbation of the 5-HT system through mental illness or psychotropic exposure could influence fertility. Much work remains to be done to clarify the role of 5-HT and its pharmacologic counterparts on oocyte maturation, early embryonic gestation, and fertility.

Clinical studies. To date, there have been no studies that examine the impact of SSRIs on women attempting to conceive naturally, and there is a pressing need to establish this line of investigation. What exist are studies examining the impact of SSRIs on women trying to conceive with ART. Clinically, a retrospective cohort study[29] compared

women taking SSRIs for a mental health disorder with controls, women not taking SSRIs during their first *in vitro fertilization (*IVF) cycle. No statistically significant difference was seen in the number of oocytes retrieved or fertilized; however, 56% percent of the SSRI group were not pregnant after their first IVF cycle, while 37% of the control group were not pregnant.[29] While an effect of medications/mental illness on the success of IVF treatment was present, the outcomes in these groups were not statistically significant. This finding leaves the question open and leaves room for a larger study with greater sample sizes to get closer to the answer. Using an alternative study design, a prospective, randomized, controlled, double-blind trial[30] evaluated the use of fluoxetine in infertile women not engaged in psychiatric treatment, undergoing their first round of in vitro fertilization in relation to their performance on the State-Trait Anxiety Inventory (STAI). The patients started either fluoxetine or folic acid during the luteal phase of the preceding menses. In vitro fertilization outcome measures had no statistically significant differences among the 2 groups; 54% percent of the fluoxetine group became pregnant, and 43% of the folic acid group became pregnant. The STAI scores did not differ between the groups. The difference in pregnancy rates was not statistically significant, though the authors suggest that it is clinically significant.[30] With the current data, it is difficult to ascertain the effect of psychotropic medication on oocytes. These studies suggest that psychotropic medications do not have a negative impact on oocyte retrieval or fertilization, but they are inconclusive. Further evaluation of this topic is warranted. Still to be determined is whether psychiatric illness itself has an effect on gametes and fertility, and this question is addressed in the following section.

The Effect of Psychiatric Disorders and Stress on Fertility

A range of studies has attempted to determine the relationship between fertility and psychological state (Table 3[11,36–51]). The literature has turned to the population of women undergoing infertility treatment as the subjects of retrospective or prospective cohort studies in an attempt to address this issue. However, these studies carry with them a series of limitations, including selection bias, and identify associations only, not causation. Individuals coping with infertility and the associated treatments are experiencing a unique set of circumstances that can make it difficult to extrapolate findings regarding emotional state and fertility to the general population. Another question is whether depression causes infertility problems, or whether infertility causes depression; thus, causation cannot be assigned. It is important, therefore, to examine potential mechanisms generated in these studies through which mental illness and stress could alter fertility, and test whether these mechanisms play a role in the rest of the population. An additional challenge when examining this literature is the lack of uniformity in methodology in the assessment of psychiatric symptoms.

First, we examined the role of male depression and anxiety in fertility. A cohort study[11] compared men with major depressive disorder to healthy controls, all with normal semen quality. There was no difference in semen analysis between depressed and nondepressed individuals.[11] Another attempt to answer this question was made by examining healthy medical students before their examination period and 3 months after their final examinations, and assessing semen quality.[36] State anxiety scores were higher before the examination than in the nonstress period, and the concentration and rapid progressive motility of spermatozoa were higher during the nonstress condition versus the period before their examination. In the stress period, there was an increase in seminal plasma nitrous oxide levels, which was found to be related to poor semen quality and motility. Cortisol, total testosterone, prolactin, FSH, and LH were measured and found to be normal.[36] Therefore, poor sperm quality may be related to excess nitrous oxide production in stressful situations.

Next, we turned attention to psychological distress in females. Women without previous reproductive experience were administered the General Health Questionnaire to evaluate psychological distress. There was a lower rate of pregnancy in the cycles with the highest distress scores, with a probability of conception per cycle of 12.8% as compared with 16.5% in less distressed cycles (adjusted odds ratio [OR] = 0.6; 95% confidence level [CI], 0.4–1.0). Of note, women with long cycles (> 35 days) were largely accountable for this finding.[37] This outcome suggests that psychological distress may have a negative association with pregnancy, though this finding of the role of elongated cycles bears replication and clarification. In a similar vein, 1 study evaluated 13 women without a history of infertility who were attempting to become pregnant.[38] The authors found that during the month leading up to conception, women reported feeling more positive emotions, as evaluated by the Profile of Mood States and the STAI, and less hassled. Of note, there was no correlation of psychometrics with cortisol, epinephrine, or norepinephrine, leaving the biological mechanism elusive.[38] In a follow-up study with 90 women undergoing infertility treatment, a hostile mood state and high trait anxiety were associated with a lower rate of pregnancy.[39] Together, these studies suggest that distress and trait anxiety are associated with pregnancy outcome.

Finally, we branched out to look at depression and anxiety in a population with infertility; women undergoing IVF were examined in a prospective cohort study utilizing the Zung depression scale and the Westbrook coping scale.[40] The group that became pregnant demonstrated lower expressed negative emotions and higher palliative (self-soothing) coping than the nonpregnant group. The relationship between depression and pregnancy was more complex; in women who were undergoing IVF for female subfertility, a higher Zung Depression Scale score was associated with a lower pregnancy rate, but the opposite was found in women undergoing IVF for male subfertility. The authors suggest that an individual's guilt regarding fertility problems

Table 3. The Effect of Psychiatric Disorders on Fertility

Study	Study Design	Subjects	Outcome Measured	Illness	Finding	Comment
Levin et al, 1981[11]	Cohort	24 Psychiatric patients 31 Controls	Sperm motility	Depression	No difference between healthy controls and depressed men	
Eskiocak et al, 2006[36]	Prospective cohort	29 Men	Sperm quantity, motility, STAI, nitrous oxide	Healthy	Increased anxiety was associated with lower sperm concentration and motility	Increased nitrous oxide levels in sperm implicated
Hjollund et al, 1999[37]	Prospective cohort	430 Couples without reproductive history	GHQ, conception	None	OR = 0.6 (95% CI 0.4–1.0) for pregnancy in highest distress cycles; probability of conception per distressed cycle of 12.8% vs 16.5% in less distressed cycles	Women with long cycles (> 35 days) accountable for finding, limiting generalizability of finding
Sanders and Bruce, 1997[38]	Prospective cohort	13 Women	Conception, STAI, POMS, epinephrine, norepinephrine, cortisol	None	Significant improvement in mood and feeling less hassled in the month conception occurred. No correlation with hormones.	Notable lack of correlation with stress hormones
Sanders and Bruce, 1999[39]	Prospective cohort	90 Women	Conception, STAI, POMS	Infertility	Hostile mood state and high trait anxiety were associated with a lower rate of pregnancy	
Demyttenaere et al, 1998[40]	Prospective cohort	40 Women	Conception, depression, coping	Infertility	High depression scores significant predictor of not getting pregnant or having ongoing pregnancy	
Smeenk et al, 2001[41]	Prospective cohort	291 Women	Depression (BDI), anxiety (STAI), number of follicles > 9 mm, number of embryos, conception status at 15 days after embryo transfer	Infertility, depression, anxiety	State anxiety ($P = .01$) and depression ($P = .03$) were associated with unsuccessful pregnancy attempt	
Smeenk et al, 2005[42]	Prospective cohort	168 Women	Depression (BDI), anxiety (STAI), epinephrine, norepinephrine, cortisol	Infertility, depression, anxiety	Higher depression score, higher levels of epinephrine at oocyte retrieval and embryo transfer and of norepinephrine at embryo transfer in unsuccessful women	
Thiering et al, 1993[43]	Prospective cohort	113 1st attempt 217 repeat cycle women (veterans)	Depression, conception	Infertility, depression	Higher level of depression in repeaters. First cycle depressed women with lower pregnancy rate than nondepressed.	Did not examine previous diagnoses of depression or specify if treated for depression
Csemiczky et al, 2000[44]	Prospective cohort	22 Infertile women 22 Fertile controls	Personality profiles, prolactin, cortisol, FSH, conception	Infertility	Infertile women had higher prolactin and cortisol levels throughout the menstrual cycle, higher hostility, guilt, and suspiciousness	Trend toward association ($P = .06$) between STAI and inability to conceive after IVF
Sbragali et al, 2008[45]	Prospective cohort	81 Infertile couples 70 Pregnant couples	SCID-1, type of infertility	Infertility	More infertile couples had adjustment disorder with mixed anxiety and depressed mood (16% vs 2%, $P = .03$), binge eating disorder (8% vs 0%, $P = .01$) than pregnant	
Demyttenaere et al, 1988[46]	Prospective cohort	116 Women	STAI, conception, spontaneous abortion	Infertility	Higher anxiety score correlated with more cycles of donor sperm treatment required to become pregnant ($F = 12.45$; $P < .0008$); also associated with a higher level of spontaneous abortion ($P < .02$)	
Aisenberg Romano et al, 2012[47]	Prospective cohort	105 Infertile women: unexplained and explained	MMPI-2, COPE, Illness Cognitions Questionnaire, STAI, CESD, LOT-R, cortisol, conception	Infertility	Statistical but not clinical significances in personality between the groups; no difference in pregnancy rate	No clinical difference between groups limits interpretation of finding

continued

Table 3 (continued). The Effect of Psychiatric Disorders on Fertility

Study	Study Design	Subjects	Outcome Measured	Illness	Finding	Comment
Ebbsen et al, 2009[48]	Prospective cohort	809 Women	Conception, LRE, BDI	Infertility	Lower number of oocytes harvested and pregnancy rates correlated with number of negative life events. No association with BDI or perceived stress.	
Gürhan et al, 2009[49]	Prospective cohort	80 Couples	Oocyte retrieval, sperm count and motility, BDI, STAI	Infertility	No effect on sperm count. Weak effect on motility. Higher depression and anxiety in females correlated with fewer oocytes retrieved. Higher depression in females correlated with lower pregnancy rates.	
Lintsen et al, 2009[50]	Prospective cohort	783 Women	Oocyte retrieval, BDI, STAI	Infertility	No relationship between baseline or procedural anxiety and pregnancy rate. No relationship to depression score.	
Zaig et al, 2012[51]	Prospective cohort	121 Women	Oocyte retrieval, oocyte fertilization, conception, healthy infant, CESD, STAI, BSI	Infertility	No relationship between pregnancy rates and depression or anxiety; trend toward increased success in individuals with psychopathology	

Abbreviations: BDI = Beck Depression Inventory, BSI = Brief Symptom Inventory, CESD = Center for Epidemiologic Studies Depression scale, COPE = coping strategy inventory, GHQ = General health questionnaire, LOT-R = Life Orientation Test–Revised, LRE = list of recent event questionnaire, MMPI-2 = Minnesota Multiphasic Personality Inventory-2, POMS = Profile of Mood States, SCID-I = Structured Clinical Interview for *DSM-IV* Axis I Disorders, STAI = State-Trait Anxiety Inventory.

increases depressive symptomatology, whereas anger about a partner's fertility problem decreases depressive symptomatology, and the depression score might reflect differences in somatic manifestation of these symptoms.[40]

The effect of depression, as rated by the Beck Depression Inventory (BDI), and anxiety, as rated by the STAI, on the probability of becoming pregnant following IVF or intracytoplasmic sperm injection (ICSI) was further examined.[41] State anxiety and depression were associated with unsuccessful pregnancy attempt. Thus, temporary or longer term negative changes in mood correlated with decreased fertility, as well. This group of researchers went on to assess stress hormones, anxiety, and depression as patients move through IVF/ICSI treatment in an attempt to examine biological correlates to mood and their relationship to fertility. The focus was on the relationship between epinephrine, norepinephrine, cortisol, anxiety, and depression, as related to successful ART treatment. There was a significant positive correlation between epinephrine levels and depression scores. Significant association was also found with cortisol concentrations at oocyte retrieval and pretreatment anxiety and depression. A comparison of the hormonal profile of unsuccessfully versus successfully treated women revealed significantly higher levels of epinephrine at the time of oocyte retrieval and embryo transfer in those who were unsuccessful in conceiving. Higher levels of norepinephrine at the time of embryo transfer were also found in unsuccessful treatment. The significant positive association of stress hormone concentration, depression, and unsuccessful treatment suggests that there may be a hormonal association between psychosocial stress and IVF/ICSI outcome.[42]

Another prospective cohort study examined the association between mood state and treatment outcome after in vitro fertilization/embryo transfer (IVF/ET) in a prospective sample, comparing first time participants (inductees) with women undergoing a repeat cycle (veterans).[43] Upon initial evaluation, there was a significantly higher level of depression among veterans and a significantly greater proportion of veterans with clinically elevated depression scores compared with inductees and community norms. The significant difference continued up to 12 months after initial assessment, when controlling for number of treatment cycles. Furthermore, depressed women demonstrated a lower rate of pregnancy for the first treatment cycle than nondepressed women.[43] Worth noting, the study did not examine whether either group had previous diagnoses of depression and did not specify whether participants received treatment for depression.

Anxiety and personality characteristics were also prospectively evaluated and related to IVF outcome in another study, in which measurements also included prolactin, cortisol, and FSH.[44] A control group was found to have lower levels of prolactin and cortisol through the course of the menstrual cycle, as well as lower scores of hostility, guilt, and suspicion. Finally, there was a trend ($P = .06$) toward an association between higher STAI scores in the women who were not able to conceive after IVF.[44] Another set of data from a prospective cohort study[45] supports the relationship between mental health and fertility and goes further by specifying the type of infertility diagnosed. Infertile couples were examined with the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I) before infertility treatment and compared to pregnant couples in the third month of pregnancy. A greater number of infertile couples had adjustment disorder with mixed anxiety and depressed mood and binge eating disorder than

the pregnant couples. Infertile patients with >2 years of infertility were more likely to have adjustment disorder with depression than those with infertility <2 years.[45] This study therefore suggests that infertility is associated with worsening mental health. Corroborating this, higher levels of anxiety in subjects were found to require more cycles of donor sperm treatment in order to become pregnant; anxiety was also associated with a higher level of spontaneous abortion.[46]

Psychopathology is certainly an influential component of an individual's behavioral profile; however, personality is also an important factor. In an attempt to address potential contribution by personality, a prospective cohort study was carried out comparing women with unexplained or explained infertility, excluding those with current psychotherapeutic or psychiatric diagnosis or treatments.[47] Surveys administered during 3 time points concurrent with cortisol measurements demonstrated that the explained infertility group had a higher score on aspects of the Minnesota Multiphasic Personality Inventory-2, including a greater tendency to present oneself in a positive manner, better self-organization, increased naivety and optimism, more emotional and social support, and a more organized defense system. The group with unexplained fertility had a higher level of excitability, hyperactivity, restlessness, irritability, fear of internal disintegration or loss of control, alienation, nervousness, fearfulness, and suspicion of others. While these differences reached statistical significance, they did not reach clinical significance, as none of the scores indicated psychopathology. No other measures were statistically significant, most importantly, success rates in attaining a pregnancy. Therefore, personality differences between women with explained versus unexplained infertility are not likely to affect ability to conceive.[47]

These studies underline the concept that simply "hassle" could be enough to influence fertility. Along these lines, negative life events have the potential to impact fertility, as suggested by a prospective cohort study undertaken with women undergoing their first IVF treatment.[48] In addition to completing the BDI, participants completed the List of Recent Events (LRE) questionnaire to quantify stressful life events, as well as the Perceived Stress Scale, and a comparison was made between women who became pregnant and those who did not. The study found that women who experienced a great number of negative life events had lower number of oocytes harvested and lower pregnancy rates. However, there was no association between the BDI or perceived stress in the previous month and pregnancy outcomes. The lack of an association with the BDI may reflect that this instrument is designed to detect symptoms in depressed individuals and may not reflect mood fluctuations in a clinically stable environment.[48]

A possible effect of negative life events or mental illness on the number of oocytes being produced certainly makes sense from an evolutionary perspective, as pregnancy and child rearing take a significant amount of investment and energy from an individual perspective. One certainly cannot make that conclusion from these studies alone, but additional studies have examined oocyte harvesting, as well. A separate cohort study[49] found more oocytes were collected for women without depression compared to women with depression both at initial evaluation and on the day of oocyte pickup. In addition, women with higher ratings of State Anxiety scores and depression scores on day of oocyte pickup were more likely to have a failed IVF attempt. Males were also assessed; no effect on sperm count was found, and only a weak negative correlation between depression scores and sperm motility was found.[49] This study offers additional support to the hypothesis that mental illness or negative life events may have a detrimental effect on fertility but is not conclusive in its findings.

Certainly, the findings on the association between depression, anxiety, and pregnancy rate are not homogenous. A multicenter prospective cohort study[50] assessed the effect of anxiety and depression on cancellation and pregnancy rates in 783 women using short versions of the STAI and the BDI-primary care. Subjects were evaluated at baseline, as well as 1 day prior to procedure, in order to evaluate whether a change in anxiety during this time affected pregnancy rate. The authors found that neither baseline nor procedural anxiety affected ongoing pregnancy rates. They also did not uncover a relationship between depression, as assessed with the BDI-primary care, and pregnancy rates. Cancellation of procedure was also not predicted by depression or anxiety.[50] Furthermore, another prospective cohort study found that the group with higher levels of psychopathology did not differ from the other subjects in number of oocytes retrieved, number of fertilized oocytes, or live births.[51] Rather, a trend was seen for higher rates of pregnancy in the psychopathology group (57% vs 38%, $P=.1$). Measures of anxiety and depression did not correlate with number of oocytes retrieved, number of fertilized oocytes, or live births.[51] The authors speculate that women with chronic levels of anxiety and depression create biological reasons for infertility, such as hormonal alterations, that are bypassed by IVF treatment. While this is 1 possible explanation, clearly more investigation is needed to make conclusions.

Hypothesis-driven investigations of fertility and mental illness are required to answer the larger questions of whether mental health can directly affect fertility. In an attempt to do just that, a cohort study of 2.3 million people in Sweden compared the fecundity of patients with mental illness and their unaffected siblings with the general population.[52] The main outcome measure was the fertility ratio, which reflects the average number of children compared with that of the general population, taking into account age, sex, family size, and affected status.[52] The authors explored hypotheses as to why psychiatric disorders survive in the population, defying the expectations of natural selection. For the purpose of this study, the disorders were classified based on International Classification of Diseases (ICD) codes, and a fertility ratio was calculated based on the number of children a certain group had, when compared to the general population, corrected for year of birth. Results demonstrated that across all disorders, affected men had a greater reduction

in fecundity than affected women. Siblings mirrored this finding, with sisters of those with illness having more children than brothers. However, the degree of fecundity reduction in those affected and the concomitant increase in fecundity among their siblings differed by disorder. This suggests that different types of psychiatric disorders undergo different selection pressures. The authors suggest that schizophrenia, autism, and anorexia are under strong selection pressures, and that there are de novo mutations keeping these disorders in the population. They also argue that depression and substance abuse are being maintained by genes that are beneficial under some circumstances, but not in the affected individuals, suggesting larger gene-environment interaction.[52]

CONCLUSIONS

The current literature points to the possibility that sperm may be negatively impacted by exposure to psychotropic medication, though this finding is not extended to oocytes based on the limited available studies. However, it appears that psychiatric illness may also have a deleterious effect on fertility. Therefore, it is of utmost importance that the benefit of treatment for an individual's overall health be weighed against any negative affect on fertility. Furthermore, an effect on the next generation has not been investigated or demonstrated. These studies as a whole did not pinpoint a clear mechanism through which mental illness or psychotropics could lead to changes in outcomes in the offspring via an effect on gametes. The closest study came to showing increasing rates of DNA fragmentation in sperm.[16] The majority of studies published on this topic pertain to the infertility literature, examining men and women presenting for ART. Hence, any inferences or conclusions drawn from the literature must take these important caveats into account and are a limitation of this review. Additional studies are needed that examine the effect of psychotropics on oocyte or sperm quantity and quality in the absence of infertility issues, as well as studies that examine the effect of mental illness alone on gametes, in the absence of ART.

Also needed in order to deepen our understanding of the relationship between mental health and fertility is mechanistically driven translational research into potential interactions between the 2. Brain-derived neurotrophic factor (BDNF) is a promising candidate for future study, as a role for it has been established in both the CNS and reproductive system. The role of BDNF has not been fully elucidated in the field of psychotropic medicines, psychiatric disorders, and fertility, and was not included for a full discussion in this review. Brain-derived neurotrophic factor is a growth factor that plays a role in the development and survival of brain cells and has also been implicated in the regulation of mood and in the molecular mechanism underlying antidepressant response.[53] Investigators found decreased levels of BDNF in depressed individuals, which were reversed by antidepressant treatment.[54] Emerging evidence has shown that BDNF is also produced in the ovary, where it is thought to be important in the recruitment and development of oocytes.[55,56] Its receptor, tropomyosin-related kinase B (TrkB), has been found to be required for follicular maturation and oocyte survival in mammalian ovaries, as mice lacking the TRKB receptor have a failure of follicular development.[57] Brain-derived neurotrophic factor has also been found to play a role in sperm development, as BDNF is expressed in Sertoli cells and plays a role in spermatogenesis.[58] Preclinical work in rodent models points to the possibility that decreased levels of BDNF contribute to decreased fertility in depressed individuals. Restraint stress in rodents, which could model stress in humans, was shown to impair oocyte development, including decreasing ovarian BDNF. Corticotropin-releasing hormone levels were increased, initiating an apoptotic program in cumulus cells and oocytes.[59] In additional rodent studies, chronic unpredictable stress decreased BDNF expression in ovaries and oocyte retrieval, which was rescued by endogenous BDNF treatment.[60] This research further supports a pivotal role for this important growth factor in reproductive health. Turning to clinical studies, BDNF was found to be reduced in males with oligoasthenozoospermia,[61] implying that it plays a role in male fertility. In addition, the BDNF Val66Met polymorphism, associated with vulnerability to psychiatric disorders, was associated with endometriosis and poor IVF outcome, potentially due to decreased BDNF levels in follicular fluids after controlled ovarian hyperstimulation.[62] While these findings are far from conclusive, they certainly point to a potential link and merit further examination.

Of further potential importance, and related to the topic at hand, BDNF has been demonstrated in preclinical[63] and clinical studies[64] to be a putative target of SSRIs. Therefore, the possibility exists that SSRIs may mediate an effect on BDNF in the reproductive tract, though specific studies supporting this hypothesis do not exist at this time. If SSRIs were to benefit fertility, it is unclear that this would be likely in the absence of psychiatric illness, just as SSRIs are not beneficial to mood in the absence of depression. Indeed, treatment with SSRIs has not been shown to be more efficacious than placebo in the treatment of mild–moderate depression; significant benefit emerges only with the treatment of severe depression.[65] So, while it would be tempting to prescribe antidepressants for their potentially beneficial regulation of the HPA-axis and stress response, to date, the literature would not support this recommendation.

Ideally, clinicians would have a clear understanding and knowledge of the precise mechanisms by which mental illness impacts fertility for both males and females and would be able to make informed recommendations regarding the use of psychotropics in individuals in their childbearing years. While we are far from this ideal, data are emerging that there may be an impact of psychiatric disorders on both sperm and oocytes. It is also important to keep in mind that the psychotropic medications effectively used to treat these illnesses are not without potential consequence on the reproductive system.

Drug names: benztropine (Cogentin and others), chlordiazepoxide (Librium and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), diazepam (Diastat, Valium, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lithium (Lithobid and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), promethazine (Prometh and others), sertraline (Zoloft and others).

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