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REVIEW *Infertility*

The risks of selective serotonin reuptake inhibitor use in infertile women: a review of the impact on fertility, pregnancy, neonatal health and beyond

A.D. Domar[1,2,*], V.A. Moragianni[1,2], D.A. Ryley[1,2], and A.C. Urato[3]

[1]Boston IVF, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, 130 Second Avenue, Waltham, MA 02451, USA [2]Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Harvard Medical School, Waltham, MA, USA [3]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Tufts University School of Medicine, Metro West Medical Center, Framingham, MA, USA

*Correspondence address. Tel: +1-781-434-6515; E-mail: domar@domarcenter.com

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STUDY QUESTION: What is the current literature on the safety and efficacy of selective serotonin reuptake inhibitor (SSRI) use in infertile women?

SUMMARY ANSWER: There is little evidence that infertile women benefit from taking an SSRI, therefore they should be counseled appropriately about the risks and be advised to consider alternate safer treatments to treat depressive symptoms.

WHAT IS KNOWN ALREADY: SSRI use is associated with possible reduced infertility treatment efficacy as well as higher rates of pregnancy loss, preterm birth, pregnancy complications, neonatal issues and long-term neurobehavioral abnormalities in offspring.

STUDY DESIGN, SIZE, DURATION: Review of existing literature.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We conducted a review of all published studies that evaluate females with depressive symptoms who are taking antidepressant medications and who are experiencing infertility.

MAIN RESULTS AND THE ROLE OF CHANCE: Antidepressant use during pregnancy is associated with increased risks of miscarriage, birth defects, preterm birth, newborn behavioral syndrome, persistent pulmonary hypertension of the newborn and possible longer term neurobehavioral effects. There is no evidence of improved pregnancy outcomes with antidepressant use. There is some evidence that psychotherapy, including cognitive-behavioral therapy as well as physical exercise, is associated with significant decreases in depressive symptoms in the general population; research indicates that some forms of counseling are effective in treating depressive symptoms in infertile women.

LIMITATIONS, REASONS FOR CAUTION: Our findings are limited by the availability of published studies in the field, which are often retrospective and of small size.

WIDER IMPLICATIONS OF THE FINDINGS: Practitioners who care for infertility patients should have a thorough understanding of the published literature so that they can adequately counsel their patients.

STUDY FUNDING/COMPETING INTEREST(S): None.

Key words: antidepressants / depression / selective serotonin reuptake inhibitors / infertility

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Introduction

Antidepressant medications are the most commonly prescribed medications taken by persons aged 18–44 years in the USA (Pratt *et al*., 2011). The rate of antidepressant use in the USA has increased 400% in the past 20 years (Pratt *et al*., 2011). It is estimated that 11% of women take an antidepressant (Barber, 2008) and estimates suggest that up to 13.4% of pregnant women take an antidepressant during all or part of their pregnancy (Cooper *et al*., 2007). In a recent study of women who took an antidepressant during pregnancy, 3.8% took a selective serotonin reuptake inhibitor (SSRI) and 0.7% took bupropion (chemically unrelated to the SSRIs) (Alwan *et al*., 2011).

A standard recommendation for women who report the need for medication to treat symptoms of depression during their pregnancy has been that the benefit of antidepressant use outweighs the risk of depression during the gestational and post-partum period. There is an assumption in the psychiatric community that the risks to a fetus are greater if the mother has untreated symptoms of depression, which may be associated with poor nutrition, alcohol and drug use and increased suicide risk. The premise is that the antidepressant, by improving maternal mood, will lead to better pregnancy outcomes. However, to date there has never been an RCT to support that theory. There *is* compelling evidence that SSRI use prior to and during pregnancy can pose significant risks to the pregnancy and to the short- and long-term health of the baby (Wenner, 2010). These risks can include miscarriage, birth defects, preterm birth, pre-eclampsia, newborn behavioral syndrome, neonatal prolonged QT syndrome, persistent pulmonary hypertension of the newborn and long-term neurobehavioral changes (Urato, 2011). There is no published study which shows an improved pregnancy outcome in women who took SSRIs compared with unexposed women.

Additionally, there is a great deal of controversy about the efficacy of SSRI medication to treat mild-to-moderate depression. Most of the published research does show that medication is somewhat more effective than a placebo in patients with severe depression. However, the majority of unpublished data do not support this hypothesis for mild or moderate forms of depression (Urato, 2011).

These issues are particularly concerning for patients with infertility, who are especially vulnerable to symptoms of depression. They are also at an increased risk for miscarriage and pregnancy complications, including stillbirth, low birthweight and prematurity (Herbert *et al*., 2012).

The interpretation of the risk/benefit ratio of treating depression with medication in this patient population is controversial. While there have been numerous studies on antidepressants and the risks of pregnancy complications, there have been very few studies on the effectiveness of antidepressants during pregnancy. It is not clear, for example, whether antidepressants are effective in treating depression during pregnancy and what the magnitude of that effectiveness is. Cohen *et al*. (2006) determined a 68% relapse rate in depression in women who discontinued medication during pregnancy versus a 25% rate in those who continued taking their medication. Yonkers *et al*. (2011) found the opposite, showing no association between antidepressant use by pregnant women with a history of depression and the risk of a major depressive episode. The potential risks of untreated depression prior to or during pregnancy should not be ignored. However, given the potential risks to mother and baby with continued SSRI use and the lack of proven benefit, it is clear that alternative safe, effective non-pharmaceutical options are needed for the treatment of infertility patients who are depressed.

Research on alternatives to SSRI treatment for individuals with symptoms of depression supports the efficacy of psychotherapy, including cognitive behavior therapy (CBT), exercise and yoga. Recent data indicate that CBT is more effective than SSRIs for treating symptoms of depression in infertile women (Faramarzi *et al*., 2008a,b). The use of certain nutritional supplements may be beneficial as well (Osher and Belmaker, 2009; Ravindran *et al*., 2009).

Health-care professionals who treat infertility patients need to be aware of the risks of antidepressant medications in order to provide adequate counseling for their patients, as well as be able to present possible alternatives to treat depressive symptoms. This literature review is designed to cover both topics. The goals of this review are to:

- review current research on the efficacy of SSRIs to treat depression;
- review the impact of SSRI treatment on fertility and infertility treatment;
- challenge the assumption that the risks of SSRIs use are lower than the risks of untreated mild and moderate depression in pregnant women;
- explore the impact of SSRI treatment on pregnancy and neonatal health;
- provide an analysis of other research-proven options for the treatment of depressive symptoms in the infertile patient population.

The prevalence of depression and SSRI use in the infertile female population

Although depressive symptoms are a barrier to seeking infertility treatment, infertile women who do seek out medical advice are more likely than fertile women to report depressive symptoms (Herbert *et al*., 2010). Women with a history of depression are twice as likely to subsequently experience infertility compared with women with no history (Lapane *et al*., 1995). The prevalence of depressive symptoms is difficult to ascertain since it is impacted by the mode of data collection (self-report versus psychiatric interview). Recent research indicates that the prevalence can range from 11% (Volgsten *et al*., 2008) to 18% (Chiaffarino *et al*., 2011), 27% (Chen *et al*., 2004) and 73% (Farzadi and Ghasemzedah, 2008). Demyttenaere *et al*. (1998) reported that 19% of patients reported moderate-to-severe depressive symptoms prior to an IVF cycle and an additional 54% reported mild symptoms. It is clear that infertile women are significantly more likely to experience symptoms of depression than fertile women, although the exact relationship between depression and infertility is unclear. Depression appears to increase the risk of infertility, although many infertile women who report depressive symptoms do not have a prior history.

The challenge of assessing the prevalence and impact of SSRI use among any cohort of infertile women relates to the inaccuracy of patient self-reporting. In a retrospective chart review of IVF patients, only 4% were identified as taking an SSRI (Klock *et al*., 2004).

Another study also determined a 4% prevalence of SSRI use (Friedman *et al.*, 2009). However, a recent review of the electronic medical records at Boston IVF, Waltham, MA, USA revealed that 11% of patients reported on the electronic medical record patient portal that they were taking an antidepressant: yet only 4% acknowledged using these medications to the anesthesiologist at the time of oocyte retrieval. Thus, it is possible that patients may feel more comfortable admitting to medication use in an electronic format compared with an oral history to a physician, thus leading to underreporting in certain circumstances.

The efficacy of antidepressants to treat symptoms of depression

The effectiveness of antidepressants for the treatment of depression has been the subject of much controversy and confusion. Three major issues contribute to the lack of clarity regarding this area. The first issue is a lack of understanding of the biologic basis of depression and how antidepressants might work. The second is the publication bias—the fact that positive studies (i.e. those showing antidepressants to be effective) tend to get published, while negative or equivocal studies do not. The third issue is the placebo effect, with numerous studies in this area showing a large benefit of placebo in the treatment of depression.

Antidepressants have been promoted as helping to restore normal brain chemistry. A prominent theory regarding the etiology of depression has been that depression represented a deficiency of serotonin, norepinephrine or other neurotransmitters. The SSRIs were then seen as helping to restore a normal level of serotonin (and other neurotransmitters) in the brain. However, evidence that depressed patients have serotonin abnormalities or deficiencies is inconclusive (Moncrieff and Cohen, 2009). Numerous studies in this area have failed to establish the serotonin deficiency hypothesis for depression (Heninger *et al.*, 1996; Roggenbach *et al.*, 2002; Lacasse and Leo, 2005). Furthermore, there is no evidence to support that antidepressant medications work to 'reverse' a neurotransmitter abnormality (Moncrieff and Cohen, 2006).

For the past few decades, the published literature has supported the theory that antidepressants were highly effective in the treatment of depressive symptoms, with >90% of published studies demonstrating positive results. In a seminal publication in the New England Journal of Medicine in 2008, Turner *et al.* (2008) obtained data directly from the US Food and Drug Administration (FDA)—some of which came through a Freedom of Information Act request. These data showed that of the 74 FDA registered studies on antidepressants, 23 of them (31%) were never published. Whether the studies were published and how they were reported were strongly related to the study outcome. The FDA found 38 out of the 74 studies to be positive, meaning that there was evidence that the antidepressant worked. Of these 38 positive studies, 37 were published. Of the remaining 36 studies, 24 were negative (i.e. showing that the antidepressant was not effective) and 12 were questionable (i.e. those studies that the FDA judged to be neither positive nor clearly negative); that is, studies that did not have significant findings on the primary outcome but may have had significant findings on several secondary outcomes. Of these 36 negative or questionable studies, only 3 were actually published as not positive. Of the remaining 33 studies, they were not published (22 of them) or were published with a positive spin (11 of them) that conflicted with the FDA's conclusion. The Turner *et al.* (2008) study demonstrated convincingly that part of the assumption of antidepressant efficacy was linked to selective publication of positive studies.

Subsequent studies have supported the idea that a thorough evaluation of the evidence on antidepressants suggests that they have limited benefit. Fournier *et al.* (2010) performed a patient-level meta-analysis on antidepressant studies. Studies were included if their authors provided the requisite original data, they comprised adult outpatients, they included a medication versus placebo comparison for at least 6 weeks, they did not exclude patients on the basis of a placebo washout period and they used the Hamilton Depression Rating Scale (HDRS). These authors found that there was a large placebo effect and that the difference between medication and placebo was a function of the initial severity of the patient's depression. The magnitude of benefit of antidepressant medication was minimal to non-existent for patients with mild-to-moderate symptoms.

The findings of Fournier *et al.* (2010) were consistent with the prior research in this area (Khan *et al.*, 2002; Kirsch *et al.*, 2008). Kirsch *et al.* (2008) obtained data on all clinical trials submitted to the US FDA for the licensing of four newer generation antidepressants (i.e. fluoxetine, venlafaxine, nefazodone and paroxetine). They then assessed the effects of initial severity on improvement scores for drug and placebo groups. They found that drug–placebo differences increased as a function of initial severity, with virtually no difference at moderate levels of depression to a small difference for patients with very severe depression. They concluded that drug–placebo differences in antidepressant effectiveness are relatively small even for severely depressed patients and no difference was found in those with moderate depression.

Much of the presumed clinical efficacy of antidepressants is due to the placebo effect of medications for the treatment of depression. A consistent finding in the antidepressant trials is that there is a very high response rate to placebo for patients with depression. Such response is typically significantly greater than 50% (Kirsch, 2009), and the response rate appears to be higher when an 'active' placebo is used compared with an 'inactive' placebo. An active placebo is a placebo that, for example, causes dry mouth. When an active placebo is compared with an inactive placebo, the result is that the patients receiving an active placebo do better; that is, they have a greater reduction in symptoms (Moncrieff *et al.*, 2004).

This phenomenon would be expected to also make antidepressants appear to be more effective than they truly are. Active placebos were compared with antidepressants in a recent Cochrane review (Moncrieff *et al*, 2004). The authors concluded the following: 'This review examined trials which compared antidepressants with 'active' placebos, that is placebos contains active substances that mimic side effects of antidepressants. Small differences were found in favor of antidepressants in terms of improvements in mood. This suggests that the effects of antidepressants may generally be overestimated and their placebo effects may be underestimated.'

Overall, the preponderance of evidence suggests that antidepressants do not provide clinically meaningful benefit for most patients with mild or moderate depression. A biochemical etiology behind

Table 1 The impact of antidepressants on fertility.

Study	Study design	Intervention	Findings
Serafini *et al*. (2009)	RCT	Fluoxetine versus folic acid	No difference in anxiety levels, IVF outcomes
Klock *et al*. (2004)	Retrospective chart review	SSRIs versus no medication[a]	Non significant decrease in pregnancy rates
Friedman *et al*. (2009)	Retrospective chart review	SSRIs versus no medication	Higher cancellation rate among SSRI users. Otherwise, no difference in IVF outcomes.
Ramezanzadeh *et al*. (2011)	RCT	Fluoxetine and CBT versus no treatment	Higher pregnancy rates with treatment

SSRI, selective serotonin reuptake inhibitor; PEDT, premature ejaculation diagnostic tool; IELT, intravaginal ejaculatory latency time; CBT, cognitive behavior therapy.
[a]Studies on SSRI use and male fertility are listed in the following: Tanrikut *et al.* (2010): prospective interventional study of paroxetine; higher mean sperm DNA fragmentation rates. No difference in semen parameters. Tanrikut and Schlegel (2007): case report ($n = 2$) of SSRIs (escitalopram and sertraline); oligoasthenoteratospermia while on treatment, return to normal parameters upon medication discontinuation. Relwani *et al.* (2011): observational study of SSRI monotherapy versus combination with oral agents (risperidol, lamictal); lower sperm motility with combination treatment. Otherwise comparable sperm parameters. Koyuncu *et al.* (2011): observational study of escitalopram; lower sperm concentration, motility, morphology, PEDT scores and IELT.

depression has not been proven and there is no evidence to support that antidepressants 'correct' a biological abnormality. Much of the presumed efficacy of antidepressants in clinical use is due to the significant placebo effect that is found with the treatment of depression. The literature appeared to support the effectiveness of antidepressants in the treatment of depression but much of this was related to selective publication of positive studies. Altogether, scientific data are lacking to provide a firm foundation for the use and efficacy of antidepressants in the treatment of most patients with depression.

The impact of antidepressants on fertility potential and infertility treatment

Limited data exist on the effect of antidepressant treatment, and specifically SSRIs, on the fertility potential of couples or on the success of infertility treatments. A Medline search was performed, using the key words 'antidepressant' or 'SSRI', and 'fertility'. After separating only pertinent publications, a total of 9 human and 10 animal studies were identified. The human studies included three on female subjects, four on male subjects and one on infertile heterosexual couples and are summarized in Table 1.

In a prospective, randomized, double-blind, placebo-controlled trial of 152 non-depressed infertile women who were randomized to receive either fluoxetine or folic acid during their first IVF cycle (Serafini *et al*., 2009), there were no differences in the number of oocytes retrieved, number of oocytes with two pronuclei, number of embryos transferred and number of 'top-quality' embryos available for either transfer or cryopreservation.

In a retrospective chart review comparing patients who took SSRIs with matched controls (Klock *et al*., 2004), there were no significant differences in peak serum estradiol, number of oocytes retrieved, number of oocytes fertilized, percentage of zygotes reaching the 8-cell stage on Day 3, percentage achieving blastulation on Day 5, day of transfer, number of embryos transferred and frozen or post-transfer serum hCG values. The two groups did not differ significantly in terms of ongoing pregnancies (singleton or twin), miscarriage or non-pregnancy rates. However, although not significant, the SSRI group had a 46% pregnancy rate compared with a 63% rate in the non-SSRI group. The authors comment that the lack of a statistical difference between the 54% non-pregnant rate in the SSRI group and the 37% rate in the control group does not necessarily preclude clinical significance.

Friedman *et al*. (2009) compared SSRI users to non-users and demonstrated no differences in the outcome after adjusting for maternal age, ovarian stimulation protocol, parity and use of ICSI. However, there was a statistically higher cycle cancellation rate among SSRI users (26.8%) compared with non-SSRI users (10.0%).

The final study evaluated 140 infertile heterosexual couples in whom at least one of the partners was given a clinical diagnosis of depression, ranging from moderate to severe (Ramezanzadeh *et al*., 2011). The subject couples were randomized to receive psychiatric intervention before or during infertility treatment, and controls did not receive treatments. The psychiatric intervention comprised psychological treatment with CBT, individual psychotherapy and treatment with fluoxetine (20–60 mg daily depending on symptom severity). Pregnancy was achieved among 47% of the couples randomized to treatment, compared with only 7% of controls.

In summary, the data on the effects of SSRIs on fertility potential and infertility treatment success are sparse. The existing literature points to a potential negative effect of these medications on semen parameters and IVF outcomes, and meticulous investigation by large, RCTs is warranted.

The impact of antidepressants on pregnancy, neonatal health and beyond

Since the launch of the SSRI Prozac in 1987, millions of pregnancies worldwide have been exposed to antidepressants, most often the SSRIs. Numerous studies have sought to determine what effects antidepressants have on pregnancy outcomes. There are two major limitations of the studies that have been performed. The first limitation is that no RCTs have been conducted. There is controversy surrounding this issue (Coverdale *et al*., 2008) but, for the most part, the scientific consensus has been that it is not ethical to randomize a pregnant woman to receive an antidepressant drug or not.

The second limitation is that with antidepressant use during pregnancy, it is often difficult to characterize the 'exposed' group. Many women stop their antidepressants when they discover that they are pregnant (Petersen *et al.*, 2011). Most of these women have had first-trimester exposure and, in this sense, they can be considered 'exposed'. But they are not exposed to the same extent as those women who remain on the drugs throughout the entire pregnancy. In some studies the group that stops is considered exposed, while other studies consider this group to be 'not exposed'. Also, some women stop the medication for some time during the pregnancy but then resume it later. Consequently, characterizing exposure correctly can be difficult. Such misclassification is likely to bias effect estimates to the null—incorrectly establishing that a lack of association exists between antidepressants and pregnancy complications.

Despite these limitations, several findings in the literature assessing the impact of antidepressant use on pregnancy outcomes have been consistent.

Miscarriage

Several studies have assessed the association between antidepressant use during pregnancy and spontaneous abortion (miscarriage). Two meta-analyses (Hemels *et al.*, 2005; Rahimi *et al.*, 2006) have been conducted in this area and the results have been fairly consistent. Recent studies have confirmed the finding (Nakhai-Pour *et al.*, 2010). Overall, antidepressant exposure during pregnancy appears to increase rates of miscarriage.

In 2009 a joint report was published on the management of depression during pregnancy (Yonkers *et al.*, 2009). This report was from the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG). The ACOG/APA review confirmed the association between antidepressant use and miscarriage stating: 'increased risk for spontaneous abortion is associated with the use of various antidepressants in early pregnancy'.

Birth defects

The studies on the association between SSRI antidepressants and birth defects have been mixed but there has been a consistent 'signal' implicating SSRI use during pregnancy to various congenital anomalies. The most publicized and consistent of these associations has been that between paroxetine (Paxil) and cardiac defects. This association led to an FDA warning in 2005 and for the FDA to ask the manufacturer GlaxoSmithKline to change the pregnancy category from C to D, a stronger warning. Category D means that studies in pregnant women (controlled or observational) have demonstrated a risk to the fetus. Paroxetine is considered a Category D drug in pregnancy (FDA, 2005).

The miscarriage data are concerning insofar as they relate to the birth defect findings. Most agents or exposures that are consistently associated with miscarriage (e.g. diabetes, smoking, antiepileptic drugs) are also eventually shown to be associated with birth defects. It is likely that in many cases an agent that, in a worst-case scenario, can injure a pregnancy to the point at which that pregnancy is lost (miscarriage) can also cause injury to that pregnancy to a lesser extent (birth defects) if the result is not a complete pregnancy failure.

Preterm birth

Preterm birth is, perhaps, the most pressing obstetrical complication. Delivery before 37 weeks affects over 12% of pregnancies and it is associated with significant neonatal morbidity and mortality as well as financial cost to society. One estimate put the cost at 26.2 billion dollars per year (IOM, 2006).

Over 30 studies have characterized preterm birth rates in pregnancies that are exposed to antidepressants versus those that are not exposed and the results have been consistent. The overwhelming majority of these studies have found increased rates of preterm birth in the antidepressant exposed group. In most of these studies the results have been statistically significant.

The largest trial (Reis and Källén, 2010) which assessed the outcomes of 14 821 women taking antidepressants found increased rates of preterm birth across all classes of antidepressants with odds ratios (OR) ranging from 1.46 [95% confidence interval (CI): 1.31–1.63] for the SSRIs to 1.98 (CI: 1.49–2.63) for the serotonin-norepinephrine reuptake inhibitors (SNRIs) and 2.36 (CI: 1.89–2.94) for the tricyclic antidepressants.

There is also some suggestion in the literature of a dose–response effect, with patients on higher doses of antidepressants being more likely to have a preterm birth (Roca *et al.*, 2011). A similar finding has been shown for length of exposure to the antidepressant during pregnancy (Oberlander *et al.*, 2008).

Recent studies, published in 2012, in this area have confirmed the association between SSRI antidepressant use and preterm birth and have shown that a major depressive episode without SSRI use does not increase the risk of preterm birth (Hayes *et al.*, 2012; Yonkers *et al.*, 2012): again highlighting the fact that the risk of the pregnancy complication appears to be an effect of the drug (SSRI) and not the disease itself (depression) because the depressed patients who were not exposed to the SSRI did not have increased rates of preterm birth.

Newborn behavioral syndrome

It is now well established that newborns who have been exposed to antidepressants *in utero* have high rates of what has been called the newborn behavioral syndrome. This syndrome has been estimated to affect up to 30% of all exposed newborns (Levinson-Castiel *et al.*, 2006). The syndrome consists of such symptoms as persistent crying, jitteriness and difficulty feeding. While it is often mild, the syndrome can also be characterized by more severe outcomes including seizures and difficulty breathing—sometimes requiring intubation.

The FDA (FDA, 2004) and Health Canada (Health Canada, 2004) have both issued warnings regarding SSRI antidepressant use during pregnancy and newborn behavioral syndrome. It is not known whether the syndrome represents neonatal withdrawal from the medications or 'overstimulation' from the persistence of the medications in the fetal system. Long-term effects of the syndrome are also unknown.

Neonatal electrocardiograph changes

In adults the SSRI antidepressants have been shown to lead to a cardiac conduction abnormality called the prolonged QT syndrome (Zemrak and Kenna, 2008). Recently, this issue was studied in newborns to determine if exposure during pregnancy would also lead to prolonged QT syndrome (Dubnov-Raz *et al.*, 2008). The results of

this study showed that 10% of newborns exposed to the SSRI antidepressants *in utero* will have markedly prolonged QT intervals.

It is known that prolonged QT interval can lead in some cases to Torsades de Points—a fatal ventricular arrhythmia. The authors of the neonatal electrocardiograph (EKG) study have called for routine screening EKGs on all newborns who have been exposed to SSRI antidepressants *in utero* (Dubnov-Raz *et al*., 2010).

Persistent pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn (PPHN) is a condition in which there are elevated pulmonary blood pressures leading to neonatal respiratory distress and hypoxemia. The condition is potentially fatal in a significant number of affected newborns (around 10%). Concerns about *in utero* exposure to SSRIs leading to PPHN were raised as early as 2006 (Chambers *et al*., 2006), in a study which showed that fetal exposure to SSRIs after 20 weeks gestation was associated with increased risks of PPHN, prompting an FDA warning regarding this association in July 2006 (FDA, 2006). Subsequent studies revealed somewhat mixed results on this issue (Kallen and Olausson, 2008; Andrade *et al*., 2009; Wilson *et al*., 2011) and the FDA released a caution in this area in 2012 (FDA, 2012).

More recent studies have shown that antidepressants do appear to be associated with PPHN. The largest study from a Nordic database has confirmed the original findings showing that SSRIs are associated with PPHN (Kieler *et al*., 2012). In this study, exposure to SSRIs in late pregnancy was associated with an increased risk of PPHN with an adjusted OR of 2.1 (95% CI: 1.5–3.0).

Pre-eclampsia

Pre-eclampsia is a common disorder during pregnancy, affecting ~5–10% of women. It is diagnosed on the basis of hypertension and proteinuria, typically developing in the third trimester of pregnancy. The pathophysiology of the disease is believed to be related to the placenta and vascular effects. As antidepressant drugs, particularly those affecting the serotonin system, are known to have vascular effects and possibly placental effects as well, an association with pre-eclampsia is plausible.

This hypothesis has been explored in recent trials. Toh *et al*. (2009a,b) analyzed data from 5731 pregnant women who were enrolled in the Sloane Epidemiology Center Birth Defects Study from 1998 to 2007. The risks of gestational hypertension and pre-eclampsia were compared between those women who did take SSRI antidepressants during pregnancy and those who did not. These investigators found that of the patients taking an SSRI during pregnancy, 19.1% developed gestational hypertension versus 9.0% of those who were not taking an SSRI. When the SSRI was taken influenced the results: of the patients taking SSRIs only during the first trimester, 13.1% developed gestational hypertension while the percentage was 26.1% in the women who continued taking SSRIs beyond the first trimester. The results for pre-eclampsia were similar, with an occurrence of 2.4% in those not taking SSRIs versus 3.7% in those exposed only during the first trimester and 15.2% among women who continued SSRIs beyond the first trimester.

The Swedish Medical Birth Register trial (Reis and Källén, 2010) is a very large trial that explored the pregnancy outcomes in 14 821 women exposed to antidepressants compared with the unexposed pregnancies in Sweden. For the association between early use of antidepressants and pre-eclampsia, this trial found an OR of 1.28 (1.19–1.37). The OR for later use of antidepressants was 1.38 (1.25–1.53). For those patients who had both early and later use, the OR was 1.50 (1.33–1.69).

Similar findings were reported by De Vera and Berard (2012). These investigators conducted a nested case–control study within the Quebec Pregnancy Registry in Canada. They found that the use of SSRIs was associated with pregnancy-induced hypertension (OR: 1.53, 95% CI: 1.01–2.33). Assessing each medication individually, they found a particularly elevated risk with the use of paroxetine (OR: 1.81, 95% CI: 1.02–3.23).

Overall, there has been relatively little published in the area of antidepressant exposure and hypertensive disorders of pregnancy. The available data suggest that there may be an association and that the association is affected by the amount and timing of exposure during the pregnancy. Given the importance of the hypertensive disorders of pregnancy in terms of maternal and newborn morbidity and mortality, and the widespread use of antidepressants during pregnancy, further investigation into this area will be essential.

Fetal growth effects

The literature on the effect of antidepressant use on fetal growth has been somewhat mixed. Several studies have addressed this area but only a few had adequate power. Trying to separate growth effects from gestational age effects can be a challenge and not all studies have addressed this. For example, a study showing that pregnancies exposed to antidepressants have more preterm births may also show a lower birthweight in the exposed group. However, it is important to separate whether the birthweight difference is simply attributable to the difference in gestational age or whether there are actual fetal growth effects. As with the study of other complications, it is also preferred to match to women with depression who are not treated with SSRIs.

Oberlander *et al*. (2006) used population health data from British Columbia, Canada, studying 119 547 births. They compared pregnancy outcomes in three groups of women: depressed mothers receiving SSRIs (SE-D), depressed mothers not treated with medication (DE) and non-exposed controls. These investigators found that birthweight (and gestational age) for SSRI-exposed infants (SE-D) was significantly less than that for depression-only exposed (DE) infants. When outcomes were compared between SE-D and propensity score-matched DE neonates, SE-D was associated with increased incidence of birthweight below the 10th percentile and rates of respiratory distress.

In another study, Oberlander *et al*. (2008) compared a 'late' gestational-exposure group with an 'early' gestational exposure group to determine whether late exposure to SSRIs is associated with increased risks of adverse neonatal outcomes compared with early exposure. They found that after controlling for maternal illness, longer prenatal exposure increased the risks of lower birthweight.

The 2009 report from the APA and ACOG (Yonkers *et al*., 2009) confirmed the association, stating the following: 'Reductions in birthweight, LBW and SGA are associated with SSRI use in pregnancy'.

Long-term neurobehavioral effects

Animal data have shown that exposure to SSRI antidepressants during development can lead to changes in brain development, including changes at the level of the individual neuron (Lee, 2009). Such brain changes have also been shown to correspond to behavioral changes in exposed animals.

Human data have shown an association between *in utero* exposure and altered motor development. Casper *et al*. (2003) studied 13 children whose mothers had depression during pregnancy and elected not to take medication, and compared this group with 31 children of depressed mothers treated with an SSRI. They found that the children who were exposed to SSRIs *in utero* scored lower on the Bayley psychomotor development indexes and the motor quality factor of the Bayley Behavioral Rating Scale than unexposed children.

Pedersen *et al*. (2010) investigated the Danish National Birth Cohort and compared developmental milestones at 6 and 19 months of age in three groups of children: 415 mothers exposed to antidepressant medication, 489 with depression and no medical treatment, and 81 042 mothers with no depression and no use of psychotropic medication. They found that children with second- or third-trimester exposure to antidepressants were able to sit 15.9 days (95% CI: 6.8–25.0) and walk 28.9 days (95% CI: 15.0–42.7) later than children of women not exposed to antidepressants. This was still within the normal range of development. Fewer children with second- or third-trimester exposure to antidepressants were able to sit without support at 6 months of age [OR: 2.1 (95% CI: 1.23–3.60)], and fewer were able to occupy themselves at 19 months of age [OR: 2.1 (95% CI: 1.09–4.02)].

A recent study (Croen *et al*., 2011) explored the association between exposure to antidepressants during pregnancy and childhood autism spectrum disorders. In this case–control study from the Kaiser Permanente Medical Care Program in Northern California, the authors found a more than 2-fold increased risk of autism spectrum disorders associated with maternal treatment with SSRI antidepressants during the pregnancy, with the strongest effect associated with treatment during the first trimester. No increase in risk was found for mothers with a history of mental health treatment in the absence of prenatal exposure to SSRIs.

Alterations in the serotonin system and autism have been explored for decades (Anderson *et al*., 1990). Animal models suggest that exposure to SSRIs during early brain development can produce abnormal emotional behaviors in adult animals, indicating an important role for serotonin in the development of the brain and behaviors (Ansorge *et al*., 2004). Given what has been described as a growing epidemic of autism spectrum disorders, further research into the association between antidepressant use during pregnancy and autism will be critical.

What the literature does not show: improved pregnancy outcomes

Since the launch of the SSRI antidepressants in the late 1980 s, it had been the hope of obstetrical and mental health providers everywhere that drug treatment of depressed pregnant women would lead to improvement in mood and avoidance of harmful behaviors, such as smoking and drug use. This would lead to better pregnancy outcomes, for example, fewer miscarriages, preterm births and newborns with problems. This was the theory but not a single study has ever shown this to be true. When pregnant women taking SSRI antidepressants are compared with a 'control' group of depressed pregnant women who are not taking such medications, the patients taking the medications only have worsened obstetrical outcomes—never better. The rates of miscarriage, preterm birth and other obstetrical complications are not lowered in the antidepressant group, in fact they are either not statistically different or higher than in women not taking antidepressants.

Depression and reproductive outcomes

Depression in women of childbearing age and pregnant women is common. While there are concerns with the risks of antidepressant use during pregnancy, these concerns should not be used as an excuse to ignore depression in these women. These women require care and supportive counseling so that they can make fully informed decisions regarding their care during pregnancy.

Several studies have specifically tried to investigate the association between maternal depression and adverse pregnancy outcomes. The most concise overview on this topic can be found in the joint report from the APA and ACOG on the Management of Depression during Pregnancy (Yonkers *et al*, 2009). In their section on Maternal Depression and Adverse Reproductive Outcomes, Yonkers *et al*. (2009) review the impact of depression on miscarriage, growth, preterm delivery and neonatal problems as well as the long-term effects on offspring. Regarding miscarriage they concluded: 'There is a paucity of information about depression and spontaneous pregnancy loss'. Regarding growth effects: 'The current state of information does not support or refute an association between MDD and LBW [low birthweight] or SGA [small for gestational age] delivery'. Concerning preterm delivery they wrote: 'The same limitations discussed above apply to the outcomes of PTD [preterm delivery] and gestational age, and thus, available data neither support nor refute a link between MDD [major depressive disorder] and these outcomes'. Conclusions regarding the neonatal effects and long-term effects on the offspring were similar.

In short, it is unclear from the available evidence whether there is an association between pregnancy complications and depression. The belief that this association has been established is prevalent, however, prompting one expert to note: 'Although this belief is strong among some investigators, the evidence to support the independent association of depression with these outcomes is weak' (Palmsten and Hernandez-Diaz, 2012).

Alternatives to SSRI use

Different complimentary modalities to treat depressive symptoms have been assessed. These include psychotherapy, exercise, relaxation training, yoga, acupuncture and various nutritional supplements.

The majority of research to date on non-pharmacological treatments for depressive symptoms has been on the efficacy of psychotherapy, specifically CBT. CBT is a short-term form of therapy in which the patient is taught to recognize and challenge distorted automatic beliefs about themselves, their environment and their future. There is overwhelming evidence that CBT is equivalent to antidepressant medication in the treatment of mild-to-moderate depression and

more recent research indicates that it is effective in the treatment of severe depression as well (Parikh *et al*., 2009). In one meta-analysis, published in a leading psychiatric journal, of CBT versus medications use in severely depressed outpatients, the authors concluded that CBT should be the treatment of choice: 'Until findings emerge from current or future comparative trials, antidepressant medication should not be considered, on the basis of empirical evidence, to be superior to cognitive behavior therapy for the acute treatment of severely depressed outpatients' (DeRubeis *et al*., 1999).

In addition, the relapse rates are lower in patients who use CBT compared with medication for the treatment of depressive symptoms (Hollon *et al*., 2005). Finally, SSRI use is the most expensive of the treatments involving medication; CBT is more cost-effective (Vos *et al*., 2005). Patient education is crucial; when depressed patients were surveyed as to their preference of CBT versus medication, the outcome was significantly positively impacted if patients received their preferred form of treatment (Mergl *et al*., 2011).

There is limited research on other treatments for depression. The strongest evidence other than psychotherapy/CBT in the general population is for physical exercise (Nahas and Sheikh, 2011). There is concern however that depressed patients might lack the motivation to change their lifestyle habits, and vigorous exercise might suppress fertility in some patients.

Relaxation training is simpler than CBT and requires less time/training; it is more effective than no treatment but not as effective as CBT (Jorm *et al*., 2008). There are also some data that yoga may be an effective treatment for depression (Shapiro *et al*., 2007; Javnbakht *et al*., 2009; Cabral *et al*., 2011; Field, 2011), although there are some limitations to the research methods (Uebelacker *et al*., 2010). However, since it is a form of treatment with no side effects, it is a treatment worth considering, especially as an alternative to medication.

There have been no RCTs to date which support the use of acupuncture for the treatment of depressive symptoms (Smith *et al*., 2010; Andreescu *et al*., 2011; Ernst *et al*., 2011; Schroer and Adamson, 2011). Past research is limited by issues with patient selection, non-standardized protocols and inadequate outcome assessment.

Nutritional supplements for the treatment of mental health disorders have received more attention recently and for two of them, omega-3 fatty acids and myo-inositol, there is some evidence to support their use. A meta-analysis concluded that there was evidence to support the use of omega-3 fatty acids in the treatment of depression but recommended it be used as an adjunctive treatment owing to the lack of 'systematic use' (Ravindran *et al*., 2009). Other research on omega-3's has supported its efficacy; one study on adult depressed patients reported 'highly significant results' when compared with a placebo (Osher and Belmaker, 2009) while other research supports its efficacy in reducing anxiety (Kiecolt-Glaser *et al*., 2011).

Finally, myo-inositol has been of interest lately due to the theory that its therapeutic action is similar to an SSRI since it is a second messenger of serotonin. A recent study on women with premenstrual dysphoric disorder indicated that two different doses of myo-inositol were more effective than placebo in the treatment of depressive symptoms and daily symptoms (Gianfranco *et al*., 2011).

Alternatives to SSRI use in the infertile population

In a review of the literature on depressive symptoms in infertile patients, the authors encourage the use of psychotherapy as a first-line treatment (Wilkins *et al*., 2010). Specifically, they recommend that practitioners '. . .take into consideration that the individual may be pregnant or soon become pregnant. Therapies which pose no risk to the fetus should be used first. . .Psychotherapy is an excellent, first-line treatment of mild-to-moderate depression with no risk to the fetus.'

There has been some good quality research on treatments other than SSRI use in infertile women with depressive symptoms. In one study, CBT was directly compared with an SSRI in a placebo-controlled trial; 89 infertile women with minimal, mild and moderate depression undergoing IVF were randomized into one of three treatment groups: (1) CBT, (2) fluoxetine (20 mg for 90 days) or (3) placebo (Faramarzi *et al*., 2008a,b). Patients were assessed using the Beck Depression Inventory (BDI) and a self-reported General Health Questionnaire (GHQ). Those subjects with a score identifying severe depression were excluded from participation. Whereas fluoxetine was associated with an improvement in three GHQ subscale scores (anxiety, social function and depression), CBT was associated with improvement in four (anxiety, social function, depression and psychosomatic signs). Although both fluoxetine and CBT significantly decreased the mean BDI scores compared with the control group, the decrease in the CBT group was significantly greater than that of the fluoxetine group; 79% of the CBT patients reported significant decreases in symptoms compared with 50% in the medication group and 10% in the control group.

Much of the research on individual and couples counseling does not show a significant impact on depressive symptoms (Hammerli *et al*, 2009). However, the research on more active forms of psychotherapy, including CBT, does indicate a significant impact on symptoms (Table 2).

Research supports the efficacy of CBT delivered in a group format to treat depressive symptoms with this patient population (Stewart *et al*, 1992; Facchinetti *et al*., 2004). Infertile women who participated in a 10-week CBT-based group treatment program experienced significant decreases in depressive symptoms and in fact the depression mean scores at the end of treatment were in the normal range (Domar *et al*., 1990, 1992, 2000). Women who were in the highest quartile of depressive symptoms at the beginning of the mind/body program had significantly higher pregnancy rates within 6 months of program completion than women who had the lowest scores, suggesting that depression suppresses fertility and a decrease in symptoms is associated with conception (Domar *et al*., 1999).

There were no studies found for the treatment of depression in infertile women by acupuncture, yoga, exercise or nutritional supplements.

Summary

There is evidence that the majority of infertile women will report depressive symptoms at some point during their treatment, especially

Table 2 The impact of psychological interventions on depressive symptoms in infertile women.

Study	Study design	Intervention	Impact on depression
Domar *et al.* (1990)	Non-randomized	Mind/body group	Significant decrease
Domar *et al.* (1992)	Non-randomized	Mind/body group	Significant decrease
Domar *et al.* (2000)	Randomized	Mind/body group	Significant decrease
Haemmerli *et al.* (2010)	Randomized	Web-based CBT	Significant decrease
Hughes da Silva (2011)	Non-randomized	Art therapy group	Significant decrease
Koszycki *et al.* (2012)	Randomized	Interpersonal therapy	Significant decrease
Lemmens *et al.* (2004)	Non-randomized	Body/mind-group	Description of impact, no data
Mori *et al.* (2009)	Cluster-randomized	Stress booklet	No difference
Sexton *et al.* (2010)	Randomized	Web-based CBT	Significant decrease in stress

following unsuccessful treatment cycles. The prevalence of SSRI use in this patient population is unknown but probably is in the 4–11% range. According to the CDC, >1% of the babies born in the USA each year are the result of an IVF cycle. In 2010, there were 154 417 IVF cycles performed, which resulted in the birth of 61 561 live infants. This suggests that anywhere from 6177 to 16, 985 IVF cycles were conducted while the patient was taking an antidepressant, and anywhere from 2462 to 6772 infants may have been exposed to an antidepressant, at least at the time of conception. This does not include the thousands of infants conceived following other forms of infertility treatment whose mothers were taking antidepressant medication.

There is little evidence of benefit from antidepressants prescribed for infertile women. More broadly, there is little evidence of benefit from the antidepressants prescribed for the majority of women of childbearing age—and there is ample evidence of risk. The best available evidence suggests that antidepressants do not provide clinically meaningful benefit for most women with depression. When used by pregnant women, antidepressants do not improve pregnancy outcomes. On the contrary, these agents have been shown to lead to increased pregnancy complications. Pregnant women taking antidepressants have been shown to have higher rates of miscarriage, preterm birth and neonatal health issues.

One study indicated a 68% relapse rate in pregnant women who discontinued antidepressants compared with a 26% rate in women who continued to take their medication (Cohen *et al.*, 2006). However, this was not a randomized study and it was also not placebo controlled. In addition, the pregnancy outcomes were not reported. In terms of reassurance to the infertile population, there was a trend for married women to be somewhat protected against relapse when compared with single women, and women older than 32 years had a 60% reduction in the relapse rate compared with women younger than 32 years. Yonkers *et al.* (2011) found the opposite to the Cohen *et al.* (2006) study, showing no association between antidepressant use by pregnant women with a history of depression and the risk of a major depressive episode.

When a significant number of pregnant women are being exposed to an agent, it is essential to question whether that agent is providing benefit and what the likelihood is for harm. Some of the greatest medical 'tragedies' (e.g. thalidomide and diethylstilbestrol (DES]) have been the result of widespread treatment of pregnant women with agents that were later shown to be harmful. In particular, one of the tragedies of the DES experience is that there was no proof that it was effective for what it was prescribed for, in other words DES did not decrease the risk of pregnancy loss. The risks of DES exposure are now well known. At the current time, there is minimal evidence that antidepressants provide a significant benefit to women struggling to conceive. On the contrary, there is mounting evidence that SSRIs may in fact decrease the pregnancy rates from fertility treatment, increase the risk of pregnancy loss and are associated with risks to the fetus throughout the pregnancy and beyond. Unlike the options facing physicians in the 1950 s and 1960 s, when there were no proven alternative treatments for pregnancy loss, at the current time there is evidence for other modalities which can help treat symptoms of depression in infertile women.

Physicians, nurses and other health-care professionals who care for infertile women need to become more vigilant about directly questioning patients about antidepressant use and should encourage these patients to speak to an experienced mental health professional for a full discussion regarding the risks and alternatives to these agents for women of childbearing age. Some patients, with a strong history of recurrent depression who are psychologically stable on an SSRI, may choose to continue to take medication but it is important that they understand the potential risks. All infertile patients who have a history of depression and/or are currently taking antidepressant medication, and the providers who care for them, need to have a complete understanding of what the literature shows in this area and the importance of investigating alternatives other than medication.

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Authors' roles

A.D.D. involved in study design and conception, data collection, analysis, writing, critically revising the manuscript. V.A.M. involved in study design and conception, data collection, analysis, writing, critically revising the manuscript. D.A.R. contributed to study design and conception, data collection, analysis, writing, critically revising the

manuscript. A.C.U. contributed to study design and conception, data collection, analysis, writing, critically revising the manuscript.

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References

Alwan S, Reefhuis J, Rasmussen SA, Friedman J. National Bith Defects Prevention Study. Patterns of antidepressant medication use among pregnant women in a United States population. *J Clin Pharmacol* 2011; **2**:264–270.

Anderson GM, Horne WC, Chatterjee D, Cohen DJ. The hyperserotonemia of autism. *Ann N Y Acad Sci* 1990;**600**:331–340; discussion 341-2.

Andrade SE, McPhillips H, Loren D, Raebel MA, Lane K, Livingston J *et al*. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf* 2009; **18**:246–252.

Andreescu C, Glick RM, Emeremni CA, Houck PR, Mulsant BH. Acupuncture for the treatment of major depressive disorder: a randomized controlled trial. *J Clin Psychiatr* 2011;**72**:1129–1135.

Ansorge MS, Zhou M, Lira A, Hen R, Gingrich JA. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science* 2004; **306**:879–881.

Barber C. The medicated Americans: antidepressant prescriptions on the rise. *Sci Am* 2008.

Cabral P, Meyer HB, Ames D. Effectiveness of yoga therapy as a complementary treatment for major psychiatric disorders: a meta-analysis. *Prim Care Companion CNS Disord* 2011;**13**.

Casper RC, Fleisher BE, Lee-Ancajas JC, Gilles A, Gaylor E, DeBattista A, Hoyme HE. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 2003; **142**:402–408.

Chambers CD, Hernandez-Diaz S, Van Marter LJ, Werler MM, Louik C, Jones KL, Mitchell AA. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;**354**:579–587.

Chen TH, Chang SP, Tsai CF, Juang KD. Prevalence of depressive and anxiety disorders in an assisted reproductive technique clinic. *Hum Reprod* 2004;**19**:2313–2318.

Chiaffarino F, Baldini MP, Scarduelli C, Bommarito F, Ambrosio S, D'Orsi C, Torretta R, Bonizzoni M, Ragni G. Prevalence and incidence of depressive and anxious symptoms in couples undergoing assisted reproductive treatment in an Italian infertility department. *Euro J Obstet Gyn Reprod Biol* 2011;**158**:235–241.

Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM *et al*. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA* 2006;**295**:499–507.

Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol* 2007;**196**:544.e1–e5.

Coverdale JH, McCullough LB, Chervenak FA. The ethics of randomized placebo-controlled trials of antidepressants with pregnant women: a systematic review. *Obstet Gynecol* 2008;**112**:1361–1368.

Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry* 2011;**68**:1104–1112.

De Vera MA, Bérard A. Antidepressant use during pregnancy and the risk of pregnancy induced hypertension. *Br J Clin Pharmacol* 2012; **74**:362–369.

Demyttenaere K, Bonte L, Gheldorf M, Meuleman C, Vanderschuerem D, D'Hooghe T. Coping style and depression level influence outcome in *in vitro* fertilization. *Fertil Steril* 1998;**69**:1026–1033.

DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behavior therapy for severely depressed outpatients: mega-analysis of four randomized trials. *Am J Psychiatry* 1999;**156**:1007–1013.

Domar AD, Seibel MM, Benson H. The mind/body program for infertility: a new behavioral treatment approach for women with infertility. *Fertil Steril* 1990;**53**:246–249.

Domar AD, Zuttermeister PC, Seibel MM, Benson H. Psychological improvement in infertile women following behavioral treatment: a replication. *Fertil Steril* 1992;**58**:144–147.

Domar AD, Friedman R, Zuttermeister PC. Distress and conception in infertile women: a complementary approach. *J Am Med Womens Assoc* 1999;**54**:196–198.

Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. *Health Psychol* 2000;**19**:568–575.

Dubnov-Raz G, Juurlink DN, Fogelman R, Merlob P, Ito S, Koren G, Finkelstein Y. Antenatal use of selective serotonin-reuptake inhibitors and QT interval prolongation in newborns. *Pediatrics* 2008; **122**:e710–e715.

Dubnov-Raz G, Koren G, Finkelstein Y. Selective serotonin reuptake inhibitor exposure in pregnancy and neonatal adverse events. *Arch Pediatr Adolesc Med* 2010;**164**:394.

Ernst E, Lee MS, Choi TY. Acupuncture for depression? A systematic review of systematic reviews. *Eval Health Prof* 2011;**34**:403–412.

Facchinetti F, Tarabusi M, Volpe A. Cognitive-behavioral treatment decreases cardiovascular and neuroendocrine reaction to stress in women waiting for assisted reproduction. *Psychoneuroendocrinology* 2004;**29**:132–173.

Faramarzi M, Alipor A, Esmaelzadeh S, Kheirkhah F, Poladi K, Pash H. Treatment of depression and anxiety in infertile women: cognitive behavioral therapy versus fluoxetine. *J Affective Dis* 2008a;**108**:159–164.

Faramarzi M, Kheirkhah F, Esmaelzadeh S, Alipour A, Hijahmadi M, Rahnama J. Is psychotherapy a reliable alternative to pharmacotherapy to promote the mental health of infertile women? A randomized clinical trial. *Eur J Obstet Gyn Reprod Biol* 2008b;**141**:49–53.

Farzadi L, Ghasemzedah A. Two main independent predictors of depression among infertile women: an Asian experience. *Taiwan J Obstet Gynecol* 2008;**47**:163–167.

FDA advising of risk of birth defects with Paxil, 2005. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108527.htm.

FDA Advisory Committee Minutes, 2004. http://www.fda.gov/ohrms/dockets/ac/04/minutes/2004–4050M1.pdf?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=neonatal toxicity/withdrawal SSRI&utm_content=1.

FDA Drug Safety Communication. Selective serotonin reuptake inhibitor (SSRI) antidepressant use during pregnancy and reports of a rare heart and lung condition in newborn babies, 2012. http://www.fda.gov/Drugs/DrugSafety/ucm283375.htm.

FDA Public Health Advisory. Treatment challenges of depression in pregnancy and the possibility of persistent pulmonary hypertension in newborns, 2006. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm124348.htm.

Field T. Yoga clinical research review. *Complement Ther Clin Pract* 2011; **17**:1–8.

Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA* 2010;**303**:47–53.

Friedman BE, Rogers JL, Shahine LK, Westphal LM, Lathi RB. Effect of selective serotonin inhibitors on *in vitro* fertilization outcome. *Fertil Steril* 2009;**92**:1312–1314.

Gianfranco C, Vittorio U, Silvia B, Francesco D. Myo-inositol in the treatment of premenstrual dysphoric disorder. *Hum Psychopharmacol* 2011;**26**:526–530.

Hammerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: a meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update* 2009;**15**:279–295.

Haemmerli K, Znoj H, Beeger T. Internet-based support for infertile couples: a randomized controlled study. *J Behav Med* 2010; **33**:135–146.

Hayes RM, Wu P, Shelton RC, Cooper WO, Dupont WD, Mitchel E, Hartert TV. Maternal antidepressant use and adverse outcomes: a cohort study of 228 876 pregnancies. *Am J Obstet Gynecol* 2012;**207**; 49:e1–e9.

Health Canada. Health Canada advises of potential adverse effects of SSRIs and other anti-depressants on newborns, 2004. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2004/2004_44-eng.php.

Hemels ME, Einarson A, Koren G, Lanctôt KL, Einarson TR. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005;**39**:803–809.

Heninger G, Delgado P, Charney D. The revised monoamine theory of depression: a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. *Pharmacopsychiatry* 1996;**29**:2–11.

Herbert DL, Lucke JC, Dobson AJ. Depression: an emotional obstacle to seeking medical advice for infertility. *Fertil Steril* 2010;**94**:1817–1821.

Herbert DL, Lucke JC, Dobson AJ. Birth outcomes after spontaneous or assisted conception among infertile Australian women aged 28–36 years: a prospective, population-based study. *Fertil Steril* 2012; **97**:630–638.

Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, Lovett ML, Young PR, Haman KL, Freeman BB *et al.* Prevention of relapse following cognitive therapy versus medications in moderate to severe depression. *Arch Gen Psychiatry* 2005; **62**:417–422.

Hughes EG, da Silva AM. A pilot study assessing art therapy as a mental health intervention for subfertile women. *Hum Reprod* 2011; **26**:611–615.

Institute of Medicine. Preterm birth: causes, consequences, and prevention, 2006.

Javnbakht M, Hejazi KR, Ghasemi M. Effects of yoga on depression and anxiety of women. *Complement Ther Clin Prac* 2009;**15**:102–104.

Jorm AF, Morgan AJ, Hetrick SE. Relaxation for depression. *Cochrane Database Syst Rev* 2008;**8**:CD007142.

Kallen B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf* 2008;**17**:801–806.

Khan A, Leventhal RM, Khan SR, Brown WA. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J Clin Psychopharmacol* 2002; **22**:40–45.

Kirsch I. Antidepressants and the placebo response. *Epidemiol Psychiatri Soc* 2009;**18**:318–322.

Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med* 2008;**5**:e45.

Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, glaser R. Omega-3 supplementation lowers inflammation and anxiety in medical students: a randomized controlled trial. *Brain Behav Immun* 2011; **25**:1725–1734.

Kieler H, Artama M, Engeland A, Ericsson O, Furu K, Gissler M, Nielsen RB, Nørgaard M, Stephansson O, Valdimarsdottir U *et al.* Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *BMJ* 2012;**344**:d8012.

Klock SC, Sheinin S, Kazer R, Zhang X. A pilot study of the relationship between selective serotonin reuptake inhibitors and *in vitro* fertilization outcome. *Fertil Steril* 2004;**82**:968–969.

Koszycki D, Bisserbe JC, Blier P, Bradwejn J, Markowitz J. Interpersonal psychotherapy versus brief supportive therapy for depressed infertile women: first pilot randomized controlled trial. *Arch Womens Ment Health* 2012;**15**:193–201.

Koyuncu H, Serefoglu EC, Yencilek E, Atalay H, Akbas NB, Sarıca K. Escitalopram treatment for premature ejaculation has a negative effect on semen parameters. *Int J Impot Res* 2011;**23**:257–261.

Lacasse JR, Leo J. Serotonin and depression: a disconnect between the advertisements and the scientific literature. *PLoS Med* 2005;**2**: e392.

Lapane KL, Zierler S, Lasatar TM, Stein M, Barbour MM, Hume AL. Is a history of depressive symptoms associated with an increased risk of infertility in women? *Psychosom Med* 1995;**57**:509–513.

Lee LJ. Neonatal fluoxetine exposure affects the neuronal structure in the somatosensory cortex and somatosensory-related behaviors in adolescent rats. *Neurotox Res* 2009;**15**:212–223.

Lemmens GMD, Vervaeke M, Enzlin P, Bakelants E, Vanderschueren D, D'Hooghe T, Demyttenaere K. Coping with infertility: a body–mind group intervention programme for infertile couples. *Hum Reprod* 2004;**19**:1917–1923.

Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after *in utero* exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med* 2006; **160**:173–176.

Mergl R, Henkel V, Allgaier AK, Kramer D, Hautzinger M, Kohnen R, Coyne J, Hegerl U. Are treatment preferences relevant in response to serotonergic antidepressants and cognitive-behavioral therapy in depressed primary care patients? Results from a randomized controlled trial including a patients' choice arm. *Psychother Psychosom* 2011;**80**:39–47.

Moncrieff J, Cohen D. Do antidepressants cure or create abnormal brain states? *PLoS Med* 2006;**3**:e240.

Moncrieff J, Cohen D. How do psychiatric drugs work? *BMJ* 2009; **338**:1535–1537.

Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. *Cochrane Database Syst Rev* 2004;CD003012.

Mori A. Supporting stress management for women undergoing the early stages of fertility treatment: a cluster-randomized controlled trial. *Jpn J Nurs Sci* 2009;**6**:37–49.

Nahas R, Sheikh O. Complementary and alternative medicine for the treatment of major depressive disorders. *Can Fam Physician* 2011; **57**:659–663.

Nakhai-Pour HR, Broy P, Bérard A. Use of antidepressants during pregnancy and the risk of spontaneous abortion. *CMAJ* 2010; **182**:1031–1037.

Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using

population-based linked health data. *Arch Gen Psychiatry* 2006; **63**:898–906.

Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: population-based study. *Br J Psychiatry* 2008; **192**:338–343.

Osher Y, Belmaker RH. Omega-3 fatty acids in depression: a review of three studies. *CNS Neurosci Ther* 2009;**15**:128–133.

Palmsten K, Hernández-Díaz S. Can nonrandomized studies on the safety of antidepressants during pregnancy convincingly beat confounding, chance, and prior beliefs? *Epidemiology* 2012;**23**:686–688.

Parikh SV, Segal ZV, Grigoriadis S, Ravindran AV, Kennedy SH, Lam RW, Patten SB. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. *J Affect Disord* 2009;**117**:S15–S25.

Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics* 2010;**125**:e600–e608.

Petersen I, Gilbert RE, Evans SJ, Man SL, Nazareth I. Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from the Health Improvement Network. *J Clin Psychiatry* 2011; **72**:979–985.

Pratt LA, Brody DL, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008, **vol 76**. US Department of Health and Human Services, Centers for Disease Control, NCHS Data Brief, 2011.

Rahimi R, Nikfar S, Abdollahi M. Pregnancy outcomes following exposure to serotonin reuptake inhibitors: a meta-analysis of clinical trials. *Reprod Toxicol* 2006;**22**:571–575.

Ramezanzadeh F, Noorbala AA, Abedinia N, Rahimi Forooshani A, Naghizadeh MM. Psychiatric intervention improved pregnancy rates in infertile couples. *Malays J Med Sci* 2011;**18**:16–24.

Ravindran AV, Lam RW, Filteau MJ, Lesperance F, Kennedy SH, Parikh SV, Patten SB., Canadian Network for Mood and Anxiety Treatments (CANMAT). Clinical guidelines for the management of major depressive disorder in adults: V. Complementary and alternative medicine treatments. *J Affect Disord* 2009;**117**:S54–S64.

Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med* 2010; **40**:1723–1733.

Relwani R, Berger D, Santoro N, Hickmon C, Nihsen M, Zapantis A, Werner M, Polotsky AJ, Jindal S. Semen parameters are unrelated to BMI but vary with SSRI use and prior urological surgery. *Reprod Sci* 2011;**18**:391–397.

Roca A, Garcia-Esteve L, Imaz ML, Torres A, Hernández S, Botet F, Gelabert E, Subirà S, Plaza A, Valdés M *et al.* Obstetrical and neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitors: the relevance of dose. *J Affect Disord* 2011;**135**:208–215.

Roggenbach J, Müller-Oerlinghausen B, Franke L. Suicidality, impulsivity, and aggression—is there a link to 5HIAA concentration in the cerebrospinal fluid? *Psychiatry Res* 2002;**113**:193–206.

Schroer S, Adamson J. Acupuncture for depression: a critique of the evidence base. *CNS Neuro Ther* 2011;**17**:398–410.

Serafini P, Lobo DS, Grosman A, Seibel D, Rocha AM, Motta ELA. Floutetine treatment for anxiety in women undergoing *in vitro* fertilization. *Int J Gynceol Obstet* 2009;**105**:136–139.

Sexton MB, Byrd MR, O'Donohue WT, Jacobs NN. Web-based treatment for infertility-related psychological distress. *Arch Womens Ment Health* 2010;**13**:347–358.

Shapiro D, Cook IA, Davydov DM, Ottaviani C, Leuchter AF, Abrams M. Yoga as a complementary treatment of depression: effects of traits and moods on treatment outcome. *Evid Based Complement Alternat Med* 2007;**4**:493–502.

Smith CA, Hay PP, Macpherson H. Acupuncture for depression. *Cochrane Database Syst Rev* 2010;CD004046.

Stewart DE, Boydell KM, McCarthy K, Swerdlyk S, Redmond C, Cohrs W. A prospective study of the effectiveness of brief professionally-led support groups for infertility patients. *Int J Psychiatry Med* 1992; **22**:173–182.

Tanrikut C, Schlegel PN. Antidepressant-associated changes in semen parameters. *Urology* 2007;**69**:185.e5–e7.

Tanrikut C, Feldman AS, Altemus M, Paduch DA, Schlegel PN. Adverse effect of paroxetine on sperm. *Fertil Steril* 2010;**94**:1021–1026.

Toh S, Mitchell AA, Louik C, Werler MM, Chambers CD, Hernández-Díaz S. Antidepressant use during pregnancy and the risk of preterm delivery and fetal growth restriction. *J Clin Psychopharmacol* 2009a;**29**:555–560.

Toh S, Mitchell AA, Louik C, Werler MM, Chambers CD, Hernandez-Diaz S. Selective serotonin reuptake inhibitor use and risk of gestational hypertension. *Am J Psychiatry* 2009b;**166**:320–328.

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;**358**:252–260.

Uebelacker LA, Epstein-Lubow G, Gaudiano BA, Tremont G, Battle CL, Miller IW. Hatha yoga for depression: critical review of the evidence for efficacy, plausible mechanisms of action, and directions for future research. *J Psychiatr Prac* 2010;**16**:22–33.

Urato AC. Antidepressants and pregnancy: continued evidence of harm-still no evidence of benefit. *Ethical Hum Psychol Psychiat* 2011; **13**:190–193.

Volgsten H, skoog SA, Ekselius L, Lundkvist O, Sundstrom PI. Prevalence of psychiatric disorders in infertile women undergoing *in vitro* fertilization treatment. *Hum Reprod* 2008;**23**:2056–2063.

Vos T, Corry J, Haby MM, Carter R, Andrews G. Cost-effectiveness of cognitive-behavioural therapy and drug interventions for major depression. *Aust N Z J Psychiatry* 2005;**39**:683–692.

Wenner M. Are antidepressants safe for pregnant women? *Sci Am* 2010.

Wilkins KM, Warnock JK, Serrano E. Depressive symptoms related to infertility and infertility treatment. *Psych Clin N Amer* 2010;**33**:309–321.

Wilson KL, Zelig CM, Harvey JP, Cunningham BS, Dolinsky BM, Napolitano PG. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. *Am J Perinatol* 2011;**28**:19–24.

Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, Ramin S, Chaudron L, Lockwood C. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2009;**114**:703–713.

Yonkers KA, Gotman N, Smith MV, Forray A, Belanger K, Brunetto WL, Lin H, Burkman RT, Zelop CM, Lockwood CJ. Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? *Epidemiology* 2011;**22**:848–854.

Yonkers KA, Norwitz ER, Smith MV, Lockwood CJ, Gotman N, Luchansky E, Lin H, Belanger K. Depression and serotonin reuptake inhibitor treatment as risk factors for preterm birth. *Epidemiology* 2012;**23**:677–685.

Zemrak WR, Kenna GA. Association of antipsychotic and antidepressant drugs with Q-T interval prolongation. *Am J Health Syst Pharm* 2008; **65**:1029–1038.