infants had no problems. Of the five follow-up studies, two a critical review of all of these studies, Ochigrossno et al. (2012) found that it is extremely difficult to differentiate the contribution of SSRIs from that of depression itself. Many of the risk factors for PPHN such as obesity, smoking, reduced length of gestation and Cesarean birth are also found more commonly in depressed women. In conclusion, evidence for an association between SSRI use in the last trimester and PPHN is very weak and must be balanced against the known risks of untreated depression.

Nulman et al. (2011) reviewed studies of the long-term cognitive effects on children whose mothers took antidepressants during pregnancy. Results on more than 1000 children in different studies found antidepressant medication did not affect the children’s global IQ, language development, behavior IQ or temperament during preschool and early school years. Maternal depression, however, resulted in less cognitive and language achievement.

Our group knows well the problem of selectively and uncritically viewing only research that supports a negative view of the use of medication during pregnancy. While cognitive therapy or IPT can be beneficial for women experiencing prenatal depression, those of us who can prescribe medication also understand that, weighing the risk/benefit of untreated depression during pregnancy versus using medication, antidepressant medication can be an important component of treating the pregnant woman and protecting the baby from harm.

References


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Reply: Risks of untreated depression outweigh any risks of SSRIs

Sir,

We appreciate Dr Robinson and Ms Einaron’s interest in our paper and their letter. We have a number of clarifications/explanations about their comments.

The section in our paper on antidepressants and pregnancy is based on fact, not opinion. We make three basic points: (i) there is evidence of risk with the use of SSRI antidepressants by pregnant women; (ii) there is no evidence of improved pregnancy outcomes with the SSRI antidepressants and (iii) pregnant women, providers and the public should be aware of this.

SSRI antidepressants have not been shown to improve pregnancy outcomes and they are increasingly associated with risk. The conventional wisdom has been that depressed pregnant women, by taking SSRI antidepressants, will treat their condition and improve their pregnancy outcomes. But there is no evidence to support this view. Robinson and Einaron cite 11 studies in their letter, but not one demonstrates better obstetrical outcomes in SSRI-treated pregnancies. No such study exists. Numerous studies are available that compare depressed pregnant women on SSRIs with those not taking medication and none of them show better pregnancy outcomes in the SSRI group. Surely, if the conventional wisdom was correct—that depression leads to pregnancy complications and treatment improves the depression—then we should see at least a few studies showing better pregnancy outcomes in the antidepressant-treated groups, but we never do. This is dramatically different to, for example, the evidence supporting the use of insulin to improve outcomes in diabetic pregnancies.

We are also concerned that Robinson and Einaron do not adequately address the scientific evidence which can lead to providing
improper counseling for patients and the public. They state that ‘aside from a possible slightly increased risk of miscarriage, SSRIs are relatively safe for use in pregnancy…’. The available scientific evidence shows that SSRI use in pregnancy is associated with increased rates of miscarriage, preterm birth and newborn behavioral syndrome.

The miscarriage data are clear and the association has been recognized by ACOG and the APA (Yonkers et al., 2009; Stewart 2011). Similarly, the association between the SSRI antidepressants and preterm birth has been assessed in over 40 studies, the overwhelming majority of which (85–95% depending on which comparisons are looked at) have confirmed that SSRIs are associated with preterm birth. Robinson and Einarson quote a study (Wisner looked at) have confirmed that SSRIs are associated with preterm birth has been assessed in over 40 studies, the overwhelming majority of which (85–95% depending on which comparisons are looked at) have confirmed that SSRIs are associated with preterm birth. Robinson and Einarson quote a study (Wisner looked at) have confirmed that SSRIs are associated with preterm birth.

That study sought to compare a ‘depressed-only’ group versus a ‘depressed on antidepressants’ group and she found preterm birth rates >20% in both. Of the 41 other available studies in this area, it is not uncommon to find high preterm birth rates (20% range) in the SSRI-treated groups but only the Wisner study found a preterm birth rate near 20% in the ‘depression-only’ group. In the Wisner study, of the 14 women in the ‘depression-only’ group, 57% were <31 years old (compared with 35% in the SSRI group), 36% were non-white (compared with 6% in the SSRI group), 0% had post-college education (compared with 33% in the SSRI group), 50% used alcohol during pregnancy (versus 26% in the SSRI group). Most importantly 33% of the ‘depression-only’ group had a history of prior preterm birth—the strongest risk factor for preterm birth. All of these risk factors were not fully accounted for. Indeed Table 4 of that paper clearly shows that when the complete analysis of the data was performed, only the SSRI group had a statistically significant increase in preterm birth. The rate ratio (RR) for the SSRI group was 5.43 with a 95% CI of 1.98–14.84 and is the only RR where the CI does not cross 1.0. The ‘depression-only’ group did not have a statistically significant increase in preterm birth.

SSRI use during pregnancy is also associated with ‘newborn behavioral syndrome’, which is often mild, but can be severe including seizures and respiratory distress requiring intubation. Health Canada and the FDA have warned the public regarding this association.

Propel counseling of patients must go beyond miscarriage, preterm birth and newborn behavioral syndrome and also include the fact that there is evidence showing an association between these agents and birth defects (Pedersen et al., 2009), pre-eclampsia (Toh et al., 2009), decreased fetal growth (Oberlander et al., 2008), neonatal EKG changes (Dubnov-Raz et al., 2008) and persistent pulmonary hypertension of the newborn (Kieler et al., 2012).

Furthermore, when it comes to the issue of possible long-term effects from in utero exposure to SSRIs, animal studies in this area are very concerning (Ansorge et al., 2004; Noorlander et al., 2008; Simpson et al., 2011) showing that SSRI exposure during development leads to concerning changes in brain formation and behavior. Human studies have also shown some longer term neurobehavioral effects, including increased autism rates (Croen et al., 2011).

Depressed pregnant women need good care. Part of that good care is providing them with the proper information so that they can make their own choices about treatment; we are not making a general recommendation that all pregnant women steer clear of antidepressant medication. The goal of our paper was to provide a review of the literature on the risk/benefit ratio and a recommendation that fully informed patients and their health care team make decisions based on the available science. Our paper sought to make this information clear and we are grateful to human Reproduction for providing us with that opportunity.

References


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A dangerous bias

Sir,
In their recently published paper (Domar et al., 2013), the authors’ conclusion that ‘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’, is based on a biased reading of the literature. Rather than including a balanced analysis of the studies on the subject, they cite five articles supporting their conclusions, out of thousands. For instance, a recent meta-analysis examining six placebo-controlled studies found a significant treatment effect for patients with non-severe depression (Stewart et al., 2012). Another recent re-analysis of the Fournier article they cite concluded that Fournier’s results were based on unreliable data (Isacsson and Adler, 2012). Moreover, a number of the articles cited in the paper support the conclusion that antidepressants are an effective treatment for depression (e.g. DeRubeis et al., 1999; Faramarzi et al., 2008a,b).

Nor is this all. The authors suggest that a lack of data on antidepressants in pregnant women amounts to proof of their inefficacy. This is wrong on two counts. First, even if there were no data, it would be far more reasonable to assume that, until proven otherwise, drugs shown to work in the general population would also work in specific populations. Secondly, if there is a relative dearth of data, it is only because conducting randomized control trials of medication use in pregnancy is unethical. However, data does exist, in the form of two studies looking at rates of relapse in women who continue or discontinue their antidepressants during pregnancy (Cohen et al., 2006; Yonkers et al., 2011). While Cohen et al. found a significant increase in relapse amongst women who discontinued their medication during pregnancy, Yonkers did not find a difference amongst the two groups. In glossing over the subtleties that could account for these different results, Domar et al. miss Yonkers’ conclusion that these two studies together likely suggest that relapse is higher for some women, but not all.

Amazingly, Domar et al. also claim that ‘there is overwhelming evidence that cognitive behavioral therapy is equivalent to antidepressant medication’, citing the Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines (Parikh et al., 2009). In fact, CANMAT concludes that ‘combined [my emphasis] antidepressant and CBT or IPT are recommended as first-line treatments for acute MDD’, because evidence suggests that combined treatment is superior to either medication or therapy alone.

Possibly, Domar’s error originates with the assumption that the majority of women treated with antidepressants during pregnancy have mild depression that would respond to psychotherapy. And yet, there exists no evidence to support this assumption. Nor does this assumption takes into account the fact that many pregnant women with depression have comorbid psychiatric disorders, which often require medication management. Perhaps from Domar’s perspective, as someone who studies ‘distress’ in infertile women, it may not be clear that Major Depressive Disorder is a distinct clinical entity.

Treating depression in pregnant women is complicated; as enumerated in the APA and ACOG guidelines, a number of factors should be considered in determining the best treatment for a depressed pregnant woman (Yonkers et al., 2009). Along with the severity of the depression being treated, for instance, clinicians must also take into account a woman’s history of response to antidepressants and other treatments. For patients with clear history of decompensating off medication, and improving upon re-initiation, or for women who have already failed to improve despite psychotherapy treatment, antidepressants play an important role in treatment.

The authors minimize the risks of depression during pregnancy, and conclude that, ‘In short, it is unclear from the available evidence whether there is an association between pregnancy complications and depression’. Depressed pregnant women are more likely to receive inadequate prenatal care (Kelly et al., 1999), to use tobacco, alcohol and illicit substances during pregnancy (Horrigan et al., 2000), to not gain sufficient maternal weight (Bennett et al., 2004), and in severe cases, depression can lead to suicide. Untreated depression during pregnancy has also been associated with an elevated risk of pre-eclampsia (Kurki et al., 2000; Shamsi et al., 2010), a significant cause of morbidity and mortality. The most recent meta-analysis on outcomes associated with prenatal depression identified an increased risk of preterm delivery and low birthweight (Grote et al., 2010). Not only are women less able to care for themselves, but they are less able to emotionally prepare for the birth in their personal relationships, at work, and at home. As Domar’s own studies suggest, depression can decrease fertility, and successful treatment can improve fertility rates (Domar et al., 1999). Recent studies suggest there may be long-term developmental effects of depression in pregnancy on children, even controlling for post-partum depression (Deave et al., 2008; O’Connor et al., 2002). Finally, depression during pregnancy increases the risk of post-partum depression, which has been well documented to be associated with negative developmental outcomes.

While the number of women taking antidepressants during pregnancy is rising, there is still ample evidence that depression during pregnancy is under-recognized and under-treated. Such a one-sided paper, only adds harmful hype to an already stigmatized issue, at a time when balance is most needed.

References


Grote JS, Birobino C, Dalbert C, Fournier PM. Major Depressive Disorder in Infertile Women: A dangerous bias