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MGH Center for Women's Mental Health

Reproductive Psychiatry Resource and Information Center

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Dear Readers:

We are pleased to bring you this March issue of our newsletter from the MGH Center for Women's Mental Health. Previous issues of our newsletter are available on [our website](#).

The current issue addresses various safety concerns recently raised regarding the use of psychiatric medications during pregnancy. We examine the continuing debate on the reproductive safety of SSRIs, and address reports about the array of factors which appear to increase risk for persistent pulmonary hypertension in the newborn. We also discuss a new prospective study which helps to define the risks associated with discontinuing treatment for bipolar disorder during pregnancy. Finally, we share our approach to switching antidepressants during pregnancy.

Our new blog (<http://cwmh.wordpress.com>) has been very active and has been a way of sharing new findings and approaches to management of a variety of clinical situations. Since its launch this past fall, we have added over sixty posts to our blog and have responded to visitors' comments. We thank you for making this a success, and encourage you to visit our blog regularly for updates in the rapidly changing field of women's mental health.

Sincerely,

Lee S. Cohen, MD

SSRIs and Pregnancy: Evaluating New Reproductive Safety Data

Over the past 15 years, multiple studies have addressed the reproductive safety of various antidepressants. Data on the overall teratogenicity of SSRIs has come from relatively small prospective observational studies, larger international birth registries, managed health care databases, and case series; these data have cumulatively supported the reproductive safety of fluoxetine and certain other SSRIs. In a recent meta-analysis including 1774 antidepressant-exposed infants, first trimester exposure to SSRIs was not associated with an increased risk of major malformations above the baseline of 2%-3% seen in the general population ([Einarson & Einarson, 2005](#)). The bulk of the data thus far has suggested that SSRIs are not major teratogens; however, concerns about the potential teratogenicity of SSRIs were first raised in 2005 when [several preliminary studies suggested that paroxetine may be associated with a small increase in risk of congenital abnormalities](#).

More recently several other reports have raised concerns regarding the use of SSRIs during pregnancy. Using a retrospective case-control design to evaluate the risks of early exposure to SSRIs, [Alwan and colleagues](#) analyzed data from the National Birth Defects Prevention study, comparing 9622 infants with selected major birth defects to 4092 controls without defects. Their mothers were interviewed regarding exposures during pregnancy and other possible risk factors for major malformations. The investigators found an association between exposure to SSRI during the first trimester and increased risk of omphalocele (odds ratio, 2.8). The strongest effect was observed with paroxetine, which accounted for 36% of all SSRI exposures and was associated with an 8.1-fold increase in risk for omphalocele. For women who used SSRIs during the first trimester, the risk of giving birth to an infant with craniosynostosis was 2.5 times higher. The risk of anencephaly among SSRI-exposed infants was 2.4 times higher than in controls.

[Using a similar study design, researchers from the Slone Epidemiology Center at Boston University, analyzed 9849 infants](#) with identified birth defects and 5860 infants without such defects. In contrast to the previous study, they found that overall use of SSRIs was not associated with significantly increased risks of craniosynostosis, omphalocele, or heart defects. However, when they looked for associations between use of specific SSRIs and specific defects, they observed significant associations between first trimester exposure to sertraline and omphalocele (odds ratio, 5.7) and septal defects (odds ratio, 2.0) and between exposure to paroxetine and right ventricular outflow tract obstruction defects (odds ratio, 3.3).

This volley of conflicting reports has left many clinicians confused and uncertain about how to counsel their patients regarding the safety of SSRIs during pregnancy. For example, while several earlier studies suggested a link between paroxetine and septal defects, the two most recent studies show no such link. While one of these studies suggests that paroxetine may increase the risk of omphalocele, the other does not and instead indicates a link between sertraline and this defect. The differences in the results from the available studies and the diversity in the types of abnormalities reported make it difficult to definitively draw a causal link between SSRI exposure and any particular congenital abnormality.

The earliest data on the potential teratogenicity of SSRIs derived from smaller cohort studies and larger pregnancy registries. These studies, when data regarding drug exposure can be ascertained prospectively before the birth outcome is known, can yield reliable data regarding teratogenic risk; however, these studies are usually limited by their small size. It is estimated that at least 500 to 600 exposures must be collected to demonstrate a two-fold increase in risk for the most common malformations, and even more exposures are required to generate adequate statistical power to detect an increase in a rarer outcome. Case-control studies, on the other hand, rely upon much larger sample sizes and have greater statistical power to detect small differences in teratogenic risk, but these studies also have limitations; for example, they are vulnerable to recall bias if drug use is self-reported. Risks may be overestimated if mothers of children with defects are more likely to recall or report drug exposures than women who gave birth to children without defects. Furthermore, one must understand that the word "association" does not necessarily mean "causation." Antidepressant exposure may be associated with other characteristics or behaviors, such as smoking or being overweight, that also modulate risk. Given these limitations, case-control studies may be more useful in identifying potential teratogens but may be less reliable in quantifying the relative risk.

While there is clearly a need for more thorough analysis of the existing data, these reports, taken together, may signal an increase in risk of malformations in children exposed to SSRIs. However, it is important to put this risk in perspective. Even if we assume the associations from these case-control studies to be true, the overall risk of malformations remains low. For example, an 8.1-fold increase in risk for omphalocele translates into an absolute risk of only 0.2% (approximately 2 out of every 1,000 births). Absolute risk is of far greater clinical value than relative risk and should be taken into consideration before patients are arbitrarily counseled to discontinue antidepressants during pregnancy.

[In an editorial accompanying these two studies](#), Michael F. Greene, MD, of the Division of Maternal and Fetal medicine at Massachusetts General Hospital in Boston, noted that these newer—and often conflicting—studies clearly have made it more difficult to make decisions regarding the treatment of depression during pregnancy. He noted further that "patients and physicians alike would prefer it if there were clear lines separating risk and no risk and if all studies gave consistent results pointing in the same direction." While these more recent reports have raised concerns, the data, taken as a whole, are reassuring and indicate that the risks associated with SSRI exposure during pregnancy are low.

Ruta Nonacs, MD PhD

[Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med.* 2007;356: 2684-2692.](#)

[Einarson TR, Einarson A. Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. *Pharmacoepidemiol Drug Saf.* 2005;14:823-827.](#)

[Greene MF. Teratogenicity of SSRIs--serious concern or much ado about little? *N Engl J Med.* 2007;356: 2732-2733.](#)

[Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med.* 2007;356:2675-2683.](#)

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PPHN and SSRIs: New Findings

Over the past few years, multiple reports have raised questions regarding the safety of selective serotonin reuptake inhibitor (SSRI) antidepressants during pregnancy. Chambers and colleagues reported that exposure to SSRIs late in pregnancy may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). In the general population, PPHN affects about 1 to 2 per 1000 live births. Infants with PPHN are typically full-term or near-term and present shortly after delivery with severe respiratory distress. In the worst cases, PPHN requires intubation and mechanical ventilation and may result in long-term morbidity. In 2006, [Chambers and colleagues published an article linking SSRI use during late pregnancy to an increased risk of persistent pulmonary hypertension in the newborn](#). Based on the results of this analysis, the authors estimated the risk of PPHN to be about 1% in infants exposed to SSRIs late in pregnancy (after 20 weeks).

This study raised significant anxiety and prompted many to question the use of SSRIs during pregnancy. However, the findings of the Chambers study have been difficult to reconcile with other studies. While earlier reports of neonatal symptoms documented cases of respiratory distress (usually tachypnea or rapid breathing), the observed symptoms were relatively mild, transient, and did not require specific medical intervention, suggesting that these cases were not PPHN, a more serious complication. Furthermore, informal surveys of sites specializing in the treatment of women during pregnancy did not reveal any cases of PPHN related to SSRI exposure.

Two more recent studies help to shed light on the risk of PPHN in infants exposed to SSRIs during pregnancy. [The first study, presented at the annual meeting of American Psychiatric Association](#) in 2007 did not report any association between SSRI use and PPHN. Researchers at the Mayo Clinic in Rochester, Minnesota reviewed the medical records of 25,214 deliveries, including 745 mothers who had been treated with SSRIs during their pregnancies. They found no association between SSRI use during pregnancy and the occurrence of PPHN. Of the 16 infants diagnosed with persistent

pulmonary hypertension in this cohort, none had been exposed to SSRIs. Furthermore, the study did not demonstrate any association between SSRI use and any type of cardiovascular malformation.

[The second study from the Slone Epidemiology Center](#) was a case-control study designed to identify possible predictors of PPHN. In this study, 377 mothers of infants with PPHN and 836 mothers of matched control subjects were enrolled. The maternal factors that were most strongly associated with an elevated risk for persistent pulmonary hypertension of the newborn were black or Asian race, high pre-pregnancy BMI (>27 vs. <20), diabetes and asthma. The risk for PPHN was about seven times higher for those who were born by cesarean section. The risk was also moderately elevated for male infants, for infants who were born either late preterm (born between 34 and 37 weeks) or post-term (born after 41 weeks), and for infants who were large for gestational age at birth. *While this study did not rule out SSRI use as a potential risk factor for PPHN, it does indicate that there are many other factors that are stronger predictors of risk.*

Ruta Nonacs, MD PhD

[Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *New Engl J Med* 2006; 354\(6\):579-87.](#)

[Hernández-Díaz S, Van Marter LJ, Werler MM, et al. Risk Factors for Persistent Pulmonary Hypertension of the Newborn. *Pediatrics* 2007; 120: e272 - e282.](#)

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Bipolar Disorder and Pregnancy: Should Medications Be Discontinued?

As many of the traditional mood stabilizers used to treat bipolar disorder, including lithium and valproic acid, carry some teratogenic risk and the reproductive safety of other medications, including the atypical antipsychotic agents, has not been well-characterized, many women with bipolar disorder decide to discontinue their treatment during pregnancy. [A new study from Dr. Adele Viguera and her colleagues at the Massachusetts General Hospital and the Emory University School of Medicine](#) helps to better define the risks associated with discontinuing treatment during pregnancy.

The study followed 89 women with bipolar disorder (69% type I, 31% type II) prospectively across pregnancy. Pregnant women (prior to 24 weeks gestation) were eligible for the study if they 1) were euthymic for at least 1 month prior to conception, 2) were receiving treatment with a mood stabilizer, or 3) had discontinued pharmacotherapy no more than 6 months prior to pregnancy or within the first trimester. Most subjects (>70%) were taking more than one psychotropic medication, typically a mood stabilizer in combination with an antidepressant and/or antipsychotic agent. This was a naturalistic study, and based on the recommendations of their own treaters, women elected either to maintain (n=62) or to discontinue (n=27) treatment with a mood stabilizer.

During the course of pregnancy, 70.8% of the participants experienced at least one mood episode. Most of these episodes were either depressive or mixed (74%), and 47% occurred during the first trimester. The risk of recurrence was significantly higher in women who discontinued treatment with mood stabilizers (85.5%) than those who maintained treatment (37.0%). In addition, the women who discontinued mood stabilizer spent over 40% of their pregnancy in an illness episode, versus only 8.8% among subjects who maintained treatment with a mood stabilizer.

The investigators also examined whether certain demographic or clinical variables were associated with increased risk of recurrence during pregnancy. The only pregnancy-related predictor of relapse was unplanned pregnancy. Clinical variables associated with a higher risk of recurrence included younger age at illness onset (RR=1.6), bipolar II disorder diagnosis (RR=1.5), history of rapid cycling

(RR=1.5), history of mixed episodes (RR=1.5) and shorter duration of clinical stability since last episode (RR=1.5). Treatment factors associated with increased relapse rates included polytherapy with more than two psychotropic agents (RR=2.3), use of antidepressants (RR=2.0), primary mood stabilizer other than lithium (RR=1.6), and abrupt discontinuation (less than two weeks) of mood stabilizer (RR=1.4).

While this study has some limitations, it is the largest prospective study of the course of bipolar disorder during pregnancy to date and yields important data which can help to inform the treatment of bipolar illness during pregnancy. The study indicates that the risk of recurrent illness during pregnancy is extremely high, particularly when medications were discontinued. While the authors acknowledge that these findings may not generalize to other clinical populations as the study was conducted with subjects seen in a specialty research program, the findings clearly indicate that women with more severe or recurrent illness are at greatest risk for recurrent illness.

Consistent with a similar prospective study carried out in women with unipolar depression ([Cohen et al. 2006](#)), this study demonstrates that discontinuation of ongoing maintenance treatment in women with bipolar disorder carries a very high risk of recurrent illness. In short, pregnancy does not appear to be protective against psychiatric illness. Although there may be concerns regarding the use of psychotropic medications during pregnancy, these findings challenge the common practice of abruptly discontinuing maintenance treatment for bipolar disorder during pregnancy.

Ruta Nonacs, MD PhD

[Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, et al. Risk of Recurrence in Women With Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation. Am J Psychiatry 2007; 164:1817-1824.](#)

Read more:

[Comments from Dr. Marlene Freeman](#)

[Medscape Interview With Dr. Adele Viguera](#)

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Patient Corner: Switching Antidepressants After the First Trimester

Q. I am currently taking Remeron for depression. I am about 16 weeks pregnant and doing well. I recently started working with a new psychiatrist, and my new doctor suggested that I switch to Prozac because he thought it would be safer for the baby. I am a little worried about making a change; I have never tried Prozac before and had a bad reaction (horrible anxiety and insomnia) when I tried Lexapro.

A. While it is true that we have more information regarding the reproductive safety of Prozac (fluoxetine) than [Remeron \(mirtazapine\)](#), it does not necessarily mean that switching to Prozac is the best option at this point in your pregnancy.

During the earliest stages of pregnancy, formation of the major organ systems takes place and is complete within the first 12 weeks after conception. Exposure to certain agents, including medications, may interfere with this process and result in some type of organ malformation or dysfunction. Thus, many women who are taking antidepressants for which there is less reproductive safety data elect to switch to an antidepressant that is better characterized (e.g., Prozac) to minimize the risk of any type of malformation.

This approach makes sense if it is done prior to conception or early in the first trimester, before organ formation is complete. However, later on in the pregnancy, after organogenesis is completed, there is little to suggest that one antidepressant is safer than another. The best treatment option at this stage is the one that is the most likely to keep you well. In other words, we would recommend that you remain on Remeron. Switching to another antidepressant may increase the risk of recurrent depression, and we do not know how you would tolerate or respond to the Prozac.

Ruta Nonacs, MD PhD

[Djulius J, Koren G, Einarson TR, Wilton L, et al. Exposure to Mirtazapine During Pregnancy: A Prospective, Comparative Study of Birth Outcomes. *J Clin Psychiatry* 2006; 67\(8\):1280-1284.](#)

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Current Research Studies at the Center for Women's Mental Health

NEW! Treatment of Premenstrual Worsening of Depression

If you are between 18 and 45 years old, have PMS and are currently being treated with an antidepressant for depression, you may be eligible for a research study at Massachusetts General Hospital evaluating how a birth control pill helps with premenstrual mood symptoms. The study lasts 4 months, and women who participate will receive study medication and evaluations of their mood at no cost, and will be compensated up to \$450.

For information, please call: (617) 724-6540 or email afarrell2@partners.org

Bipolar Disorder in Pregnancy

Do you have questions about bipolar disorder and anti-depressants or mood stabilizers during pregnancy? If you are pregnant, or planning pregnancy, and diagnosed with bipolar disorder (or manic depression), you may be eligible for this research study. Participants meet with research coordinators and psychiatrists who specialize in bipolar illness during pregnancy.

Contact: Rachel VanderKruik (617) 726-2912 or rvanderkruik@partners.org

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