

Pregnancy, depression, antidepressants and breast-feeding

Pierre Blier, MD, PhD

University of Ottawa Institute of Mental Health Research, Ottawa, Ont.

"Pregnancy protects against depression." This is a common belief, perhaps based in part on some women experiencing a heightened feeling of emotional well-being during pregnancy. However, the evidence indicates otherwise. In particular, pregnancy is a high-risk period for a relapse of depression. A recent prospective study, conducted on 201 patients who had been euthymic for at least 3 months, examined relapse rates over the course of pregnancy.¹ Women who discontinued their medication had more frequent relapses when compared with women who maintained their medication, with a hazard ratio of 5.0. Moreover, in the women who discontinued their antidepressant, the reintroduction of medication decreased the risk of relapse, but to a much lesser extent than if medication was continued throughout pregnancy. Therefore, transient interruption of medication may still predispose pregnant women to a negative outcome. In addition, allowing major depression to occur during pregnancy may result in a negative impact on fetal conditions. Because the placental barrier is limited in its capacity to protect the fetus against the systemic perturbations that depression can produce, it appears imperative to prevent depressive relapses from occurring. The endogenous substances that can be produced in greater concentrations during depression, and could have a negative impact, include cortisol and catecholamines. The former can lead to increased corticotropin-releasing factor production, which can induce premature labour, whereas the latter can alter uterine blood flow and induce uterine irritability.^{2,3} Finally, depressed mothers may have a decreased appetite and may be more at risk of using alcohol or illicit drugs, factors that can have a negative impact on the fetus.^{4,5} Therefore, it is important to weigh the benefits of not allowing depression to occur during pregnancy against the risks of using antidepressants during this period. The use of antidepressants clearly offers a protective influence against such relapse.

"Antidepressants increase the risk of congenital malformations and perturb organ development." Again, the evidence indicates otherwise. Reviews of the literature indicate that antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), do not increase the risk of major and minor malformations.⁶⁻⁹ However, there would appear to be a small, but statistically significant, increased risk of spontaneous abortions with SSRIs. The role of depression itself cannot be eliminated as a contributing factor to this increase from 8.7% to 12.4%.¹⁰ More troublesome is a recent study reporting an increase of persistent pulmonary hypertension of the newborn (PPHN) in babies whose mothers were exposed to SSRIs after the first 20 weeks of gestation.¹¹ This study reported that 14 infants with PPHN had been exposed to an SSRI (3.7%) versus 6 control infants (0.7%). Nevertheless, it is important to mention that the crude risk of PPHN at any time in pregnancy was not increased by SSRI exposure. This seemed to result from an apparent, though not significant ($p = 0.08$), protective effect of SSRIs in the first 20 weeks. It is also possible that the finding resulted from studying a small number of subjects. As an illustration of the latter possibility, the number needed to treat to obtain 1 PPHN was 200. This study cannot establish causality, as pointed out by the authors themselves, but it is well known that serotonin has mitogenic and comitogenic effects on pulmonary smooth-muscle cells that can produce pulmonary hypertension (PH).^{12,13} It was thus postulated that elevated circulating levels of serotonin, presumably resulting from reuptake inhibition by the SSRIs, could be responsible for the proliferation of smooth-muscle cells seen in PH.¹¹ The problem with this hypothesis is that SSRIs have been shown to protect against smooth-muscle hyperplasia in the pulmonary bed.¹⁴ This is because serotonin reuptake inhibition in the periphery decreases circulating levels of serotonin, since platelets can no longer store serotonin through reuptake,¹⁵ thereby decreasing any potential release.

Correspondence to: Dr. Pierre Blier, University of Ottawa Institute of Mental Health Research, Royal Ottawa Hospital, LG 2043, 1145 Carling Ave., Ottawa ON K1Z 7K4; fax 613 761-3610; rowilson@rohcg.on.ca

Medical subject headings: abnormalities; antidepressive agents; breast feeding; depression; pregnancy.

J Psychiatry Neurosci 2006;31(4):226-8.

It should be noted, in support of this mechanism, that serotonin synthesis inhibition has the same effect as fluoxetine.¹⁶ In mice with the serotonin transporter (5-HTT) gene deleted, pulmonary hemodynamic parameters are normal, and when these mice are exposed to hypoxia, the number and medial-wall thickness of muscular pulmonary vessels are reduced.¹⁷ Finally, in patients with chronic pulmonary obstructive disease, the presence of two l alleles, which is associated with a higher level of 5-HTT expression in pulmonary artery smooth-muscle cells than the l/s or s/s genotypes, is associated with higher PH.¹⁸ Consequently, the purported role of SSRI exposure in PPHN after the first 20 weeks of pregnancy appears doubtful.

"Antidepressants during pregnancy may alter neurocognitive development and predispose to mood and anxiety disorders later in life." This possibility was raised on the basis of impaired performance of rodents in some models of rat depression and anxiety.^{19,20} A persistent decrease of serotonin-dependent neuronal firing activity in adulthood has also been reported following neonatal exposure of rats to a serotonin reuptake inhibitor, but this is inconsistent with the findings of an earlier study.^{21,22} Three studies of children exposed to antidepressants and followed up to the age of 7 years showed no significant difference in intelligence quotient, language and behaviour.²³⁻²⁵ A fourth study showed subtle changes in motor movement control in children, but these children were not age-matched and were tested at varying ages.²⁶ The issue of predisposition to psychopathology thus remains an open question and will require well-controlled studies before any conclusion may be reached.

"Taking antidepressants while breast-feeding leads to harmful exposure to the baby." Antidepressants are present in breast milk generally at concentrations present in the plasma. However, when their levels are examined in the plasma of babies of mothers taking therapeutic doses, they are often undetectable or near the threshold of the method.²⁷⁻³⁰ This may appear surprising, but if one does the math, it is really what should be expected. In the case of paroxetine, for example, the plasma concentration is between 20 ng/mL and 100 ng/mL in individuals taking the minimal effective dose of 20 mg/d.³¹ This means that the baby is ingesting milk containing about this concentration of paroxetine. Assuming a 5-kg baby drinks about 1 litre per day, this would represent 100 000 ng/d or 0.1 mg/d if the mother has a plasma concentration of 100 ng/mL. This would only correspond to a daily dose of 1.5-2 mg/d for an adult of average weight. Nevertheless, it is still possible that such low exposure could lead to significant occupancy of 5-HTT in the brain. Indeed, an occupancy of about 50% of 5-HTT was recently reported in rat pups feeding from mothers receiving fluoxetine, despite the pups having very low or undetectable levels of fluoxetine/norfluoxetine.³² This degree of occupancy is still lower than that which is necessary to obtain an antidepressant effect (~80%), because there is a significant reserve of 5-HTT.³³ Finally, the low level of SSRI exposure during breast-feeding does not impair infant weight gain, whereas an exposure to maternal depression lasting 2 months or more does impair weight gain.³⁴

In summary, it seems clear that the risks of not receiving adequate antidepressant treatment thus far outweigh the risks of adverse events, not only in infants but in mothers as well. The population should therefore learn to fear the illness more than the antidepressant.

Competing interests: Dr. Blier is a consultant with Biovail, Eli Lilly, Forest Laboratories, Janssen Pharmaceuticals, Lundbeck, Organon Pharmaceuticals, Roche Pharmaceuticals, Sepracor, Wyeth Ayerst and Sanofi-Aventis and is a contract employee with Forest Laboratories, Janssen Pharmaceuticals and Steelbeach Productions. He is in the speaker's bureau for Cyberonics, Eli Lilly, Forest Laboratories, Janssen Pharmaceuticals, Lundbeck, Organon Pharmaceuticals and Wyeth Ayerst and has received grant funding from Eli Lilly, Forest Laboratories, Janssen Pharmaceuticals, Mitsubishi Pharma, Organon and Wyeth Ayerst. He is President of Medical Multimedia Inc.

References

1. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA* 2006;295:499-507.
2. Lockwood CJ. Stress-associated preterm delivery: the role of corticotropin-releasing hormone. *Am J Obstet Gynecol* 1999;180:S264-6.
3. Teixeira JM, Fisk NM, Glover V. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. *BMJ* 1999;318:153-7.
4. Lou HC, Hansen D, Nordentoft M, et al. Prenatal stressors of human life affect fetal brain development. *Dev Med Child Neurol* 1994;36:826-32.
5. Orr ST, Miller CA. Maternal depressive symptoms and the risk of poor pregnancy outcome. Review of the literature and preliminary findings. *Epidemiol Rev* 1995;17:165-71.
6. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Saf* 2005;28:137-52.
7. Sivojelezova A, Shuhaiber S, Sarkissian L, et al. Citalopram use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. *Am J Obstet Gynecol* 2005;193:2004-9.
8. Rahimi R, Nikfar S, Abdollahi M. Pregnancy outcomes following exposure to serotonin reuptake inhibitors: a meta-analysis of clinical trials. *Reprod Toxicol* 2006 May 21 [Epub ahead of print].
9. Einarson TR, Einarson A. Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. *Pharmacoepidemiol Drug Saf* 2005;14:823-7.
10. Hemels ME, Einarson A, Koren G, et al. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005;39:803-9.
11. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354:579-87.
12. Runo JR, Loyd JE. Primary pulmonary hypertension. *Lancet* 2003;361:1533-44.
13. Eddahibi S, Raffestin B, Hamon M, et al. Is the serotonin transporter involved in the pathogenesis of pulmonary hypertension? *J Lab Clin Med* 2002;139:194-201.
14. Marcos E, Adnot S, Pham MH, et al. Serotonin transporter inhibitors protect against hypoxic pulmonary hypertension. *Am J Respir Crit Care Med* 2003;168:487-93.

15. Blier P, Saint-André E, Hébert C, et al. Effects of different doses of venlafaxine on serotonin and norepinephrine reuptake in healthy volunteers. *Int J Neuropsychopharmacol* 2006 May [Epub ahead of print].
16. Eddahibi S, Guignabert C, Barlier-Mur AM, et al. Cross talk between endothelial and smooth muscle cells in pulmonary hypertension: critical role for serotonin-induced smooth muscle hyperplasia. *Circulation* 2006;113:1857-64.
17. Eddahibi S, Hanoun N, Lanfumey L, et al. Attenuated hypoxic pulmonary hypertension in mice lacking the 5-hydroxytryptamine transporter gene. *J Clin Invest* 2000;105:1555-62.
18. Eddahibi S, Chaouat A, Morrell N, et al. Polymorphism of the serotonin transporter gene and pulmonary hypertension in chronic obstructive pulmonary disease. *Circulation* 2003;108:1839-44.
19. Ansorge MS, Zhou M, Lira A, et al. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. *Science* 2004;306:879-81.
20. Maciag D, Simpson KL, Coppinger D, et al. Neonatal antidepressant exposure has lasting effects on behavior and serotonin circuitry. *Neuropsychopharmacology* 2006;31:47-57.
21. Maudhuit C, Hamon M, Adrien J. Electrophysiological activity of raphe dorsalis serotonergic neurones in a possible model of endogenous depression. *Neuroreport* 1995;6:681-4.
22. Vogel G, Hagler M, Hennessey A, et al. Dose-dependent decrements in adult male rat sexual behavior after neonatal clorimipramine treatment. *Pharmacol Biochem Behav* 1996;54:605-9.
23. Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; 336:258-62.
24. Nulman I, Rovet J, Stewart DE, et al. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002;159:1889-95.
25. Misri S, Reebye P, Kendrick K, et al. Internalizing behaviors in 4-year-old children exposed in utero to psychotropic medications. *Am J Psychiatry* 2006;163:1026-32.
26. Casper RC, Fleisher BE, Lee-Ancajas JC, et al. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 2003;142:402-8.
27. Suri R, Stowe ZN, Hendrick V, et al. Estimates of nursing infant daily dose of fluoxetine through breast milk. *Biol Psychiatry* 2002; 52:446-51.
28. Baab SW, Peindl KS, Piontek CM, et al. Serum bupropion levels in 2 breastfeeding mother-infant pairs. *J Clin Psychiatry* 2002;63:910-1.
29. Stowe ZN, Hostetter AL, Owens MJ, et al. The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *J Clin Psychiatry* 2003;64:73-80.
30. Berle JO, Steen VM, Aamo TO, et al. Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome p450 genotypes. *J Clin Psychiatry* 2004;65:1228-34.
31. Gilmor ML, Owens MJ, Nemeroff CB. Inhibition of norepinephrine uptake in patients with major depression treated with paroxetine. *Am J Psychiatry* 2002;159:1702-10.
32. Jones CFC, Stowe ZN, Owens MJ. Serotonin transporter occupancy in rats exposed to fluoxetine *in utero* or via breast milk [abstract]. American Psychiatric Association meeting; 2006 May 20-25; Toronto. New Research Abstracts (NR521):217.
33. Meyer JH, Wilson AA, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [¹¹C]DASB positron emission tomography study. *Am J Psychiatry* 2004;161:826-35.
34. Hendrick V, Smith LM, Hwang S, et al. Weight gain in breastfed infants of mothers taking antidepressant medications. *J Clin Psychiatry* 2003;64:410-2.

Correction

The following article should have been cited as reference 16 instead of the article that is currently cited in a recent *Journal of Psychiatry and Neuroscience* article by Sidney H. Kennedy, Henning F. Andersen and Raymond W. Lam (Efficacy of escitalopram in the treatment of major depressive disorder compared with conventional selective serotonin reuptake inhibitors and venlafaxine XR: a meta-analysis. *J Psychiatry Neurosci* 2006;31[2]:122-31).

16. Baldwin DS, Cooper JA, Huusom AKT, et al. A double-blind, randomized, parallel-group, flexible-dose study to evaluate the tolerability, efficacy and effects of treatment discontinuation with escitalopram and paroxetine in patients with major depressive disorder. *Int Clin Psychopharmacol* 2006;21:159-69.