Concerns regarding antidepressant drug use during pregnancy

I have several concerns with the recent editorial by Dr. Blier regarding antidepressant drugs and pregnancy.[1] In his editorial, Dr. Blier failed to adequately discuss the association of the selective serotonin reuptake inhibitors (SSRIs) with congenital anomalies; he failed to discuss the neonatal syndrome associated with maternal SSRI use; and he failed to comment on the association of SSRIs with numerous pregnancy complications. A review of the studies he referenced reveals the absence of vital studies on this issue from some of the world's most respected journals.[2–4]

The SSRIs may be associated with congenital malformations. Paxil, for example, has been associated with cardiac defects. On September 29, 2005, GlaxoSmithKline, in discussions with Health Canada, warned health professionals about this association.[5] In December 2005, at the Food and Drug Administration's (FDA) request, GlaxoSmithKline changed paroxetine's pregnancy category from C to D.[6] Why didn't Dr. Blier mention this major issue in his editorial, and how does he justify his statement: "SSRIs do not increase the risk of major and minor malformations?" He also failed to reference a study published in the *New England Journal of Medicine* (*N Engl J Med*) showing that fluoxetine exposure was associated with increased rates of 3 or more minor malformations.[2]

SSRI use in pregnancy has been associated with low birth weight,[2,7] preterm birth[2,7] and neonatal neurobehavioural problems.[2–4] Additionally, fetal death and seizures have been shown to be increased.[7] Surely, these complications merited some mention in a discussion on antidepressant use in pregnancy. Although some people have argued that depression itself accounts for the above-mentioned associations, recent work by Oberlander and others[8] suggests that SSRI use may account for such pregnancy complications.

I found Dr. Blier's discussion of Dr. Chambers' study on the association between maternal SSRI use and persistent pulmonary hypertension of the newborn (PPHN)[9] inadequate. He spent approximately one-third of his editorial criticizing her study and concluded: "The purported role of SSRI exposure in PPHN after the first 20 weeks of pregnancy appears doubtful." The association may appear doubtful to Dr. Blier. However, the editors and reviewers at the *N Engl J Med* did not doubt the association nor did their editorialist, Dr. Mills.[10] Health Canada and the FDA have issued advisories concerning PPHN based on Chambers' study.[11,12]

In sum, in various studies, SSRI use during pregnancy has been associated with increased rates of spontaneous abortion,[13] congenital malformations,[2,5,6] preterm birth,[2,7] low birth weight,[2,7] fetal death,[7] seizures,[7] neonatal withdrawal syndrome,[2–4] PPHN[9] and a possible predisposition to psychopathology.[14] Dr. Blier inadequately covered these complications. An editorial, such as his, on antidepressant drug use and pregnancy that fails to discuss major Health Canada and FDA public health advisories and several important pregnancy complications is potentially misleading for readers, as well as for pregnant women with depression, their obstetrical providers and the public.

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Reply: Practicing medicine on the basis of the unconfirmed and omitting the established facts

I read with attention the concerns of Dr. Urato regarding my peer-reviewed

editorial on depression, the use of antidepressant medications in pregnancy and breast feeding[1] recently published in the *Journal of Psychiatry and Neuroscience*. According to Dr. Urato's analysis, I "failed" to adequately deal with 5 crucial issues. I would first like to reiterate, as in the conclusion of my editorial, that an illness during pregnancy can be far worse than the medication used to treat it. It is certainly best not to give any medication during pregnancy, but before depriving a woman and her unborn child a protection from a potential life-threatening illness, the risks and benefits must be carefully evaluated. After a thorough interview aimed at identifying the number of prior episodes of depression and duration, the degree of treatment resistance, the presence of residual symptoms and the medication(s) used, a clear recommendation must be made to the patient. Above all, the patient must not be left with a specter of a catastrophe haunting her during the pregnancy and the years to come if she uses antidepressant drugs.

Dr. Urato seemed to be very concerned about decisions taken by regulatory agencies, sometimes in concert with the pharmaceutical firms, on the basis of published manuscripts in prestigious journals. There are numerous examples of manuscripts published in first class journals that were flawed and yet made it past the peer-review process. Perhaps one of the most notorious was the paper on the "memory of water" published in *Nature* in the late 1980s.[2,3] Dr. Urato deemed lengthy and "inadequate," without stating why, my discussion of the paper on persistent pulmonary hypertension published in the *New England Journal of Medicine*.[4] The journal published the paper and, of course, they stood by it. However, I was not the only one to doubt the importance of the purported association of this severe pathology and the use of antidepressant drugs during pregnancy. Dr. David Rubinow, a world-renowned scientist in neuroendocrinology of psychiatric disorders from the National Institute of Mental Health, with 195 papers listed in the National Library of Medicine (Pubmed), also expressed concerns over this problematic publication in an editorial of the *American Journal of Psychiatry*, the official journal of the American Psychiatric Association.[5]

My editorial was not meant to be a complete and exhaustive discussion of all the possible outcomes of antidepressant medication use during pregnancy and childbirth. The main goal of my analysis was to make physicians and the public realize that abstaining from using antidepressant drugs during pregnancy and allowing depression to occur (reoccur or continue) during pregnancy can lead to long-term damages to the mothers and children that may far outweigh the potential ill effects of the medications. We are now in an era where not all medications during pregnancy are evil. Can some antidepressant drugs taken during pregnancy produce discontinuation phenomena in newborns? Certainly. Can these be lethal or produce irreversible damage? I certainly have failed to find compelling evidence supporting the latter.

There are indeed several studies suggesting that antidepressant drug use during pregnancy may have some deleterious effects, two of which were published after my editorial was in press.[6,7] Such retrospective studies on large populations with unconfirmed diagnoses are important, but not without problems. For instance, in mothers exposed to selective serotonin reuptake inhibitors versus control subjects, a statistically significant increase in seizures (0.4% v. 0.1%) and fetal deaths (1.1% v. 0.4%) was noted in the exposed population; however, also noted in this population was a 10% higher use of social assistance (marker of poverty), a 1.8% versus 0.4% frequency of drug dependence, greater maternal age, higher parity and a higher rate of multigestation.[6] In this study, in contrast to some others also mentioned by Dr. Urato, there was no increased risk of birth defects. On the other hand, there are numerous studies showing the ill effects of depression, or of allowing a relapse or recurrence to take place, when antidepressant drugs are not used or are stopped during pregnancy.[1] To the family of a woman who committed suicide or killed her baby, how could a clinician justify a recommendation to stop an antidepressant on the basis of the above-mentioned differences of less than 1%?

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