Parsing Risk for the Use of Selective Serotonin Reuptake Inhibitors in Pregnancy

A number of reports have explored the fetal risks related to maternal use of antidepressant agents, particularly selective serotonin reuptake inhibitors (SSRIs). This considerable database has yielded inconsistent findings with regard to SSRIs and fetal malformations (1), leading one expert to state that SSRIs are not "major teratogens" (2). However, complications may include other neonatal and maternal outcomes. To illustrate, preterm delivery has been linked with maternal use of antidepressants, although this may shorten delivery by less than 1 week (3). One article in this issue of the *Journal* discusses higher risks of gestational hypertension and preeclampsia found among women who took SSRIs during pregnancy. Toh et al. (4) studied a cohort of women assembled from the Slone Epidemiology Center who delivered nonmalformed infants. Study nurses obtained information on birth outcomes, health habits, medication use, physical conditions, and medical complications. However, researchers interviewed subjects after delivery and did not review medical charts. Included were 199 women who used SSRIs during the 2 months prior to pregnancy and possibly during pregnancy. Ninety-two women continued medication beyond the first trimester. The nonexposed group included 5,532 pregnant women who did not take SSRIs. The analysis controlled for demographic variables, gravidity, multifetal gestation, infertility treatment, diabetes, prepregnancy weight, and hazardous substance use. The onset of hypertension after 20 weeks occurred in 9% of those who did not use a SSRI and 19% of the 199 women who used a SSRI at some point during the study interval. The rate for women who continued SSRIs throughout pregnancy was 26%. Possible preeclampsia was experienced by 2.4% and 3.7% of women who did and did not use SSRIs, respectively, but the rate was 15% if a woman continued treatment with a SSRI beyond the first trimester (relative risk=4.9; 95% confidence interval [CI]=2.7–8.8).

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It is important to disseminate new information, such as these data, since they may illustrate an important risk for mothers. However, it is also critical to provide context and understand the limitations of the report. Gestational hypertension is a relatively common heterogeneous condition and includes women who develop new onset hypertension after the 20th week of pregnancy. In contrast, preeclampsia is characterized by hypertension (systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg at least 4 to 6 hours apart [according to two measurements]) accompanied by proteinuria (>300 mg within 24 hours) (5). About 6% of women will develop preeclampsia. In one-quarter of cases, the condition will be severe and associated with marked elevations in blood pressure, delivery of a growth restricted infant, and potential involvement of other maternal organ systems, including hepatic, renal, and hematological systems. Unfortunately, without detailed medical chart reviews, it is impossible to confirm that the affected women in the Toh et al. study truly had the disease. Risk factors include pre-existing chronic medical conditions such as diabetes, thrombophilias, rheumatologic illnesses, and renal disease. Personal characteristics, clinical factors, and habits that increase risk are obesity, multifetal gestation, primiparity, primipaternity, older maternal age, alcohol abuse, other drug abuse (non-nicotine), and gamete dona-

tion (5). Although there are many proposed etiologies, the definitive cause is unknown. Candidate pathogenic agents include inflammatory, genetic, immunologic, and prothrombotic factors that contribute to impaired trophoblastic implantation, which leads to expression of factors that induce maternal endothelial dysfunction.

If an association between maternal SSRI use and preeclampsia truly exists, what is its biological plausibility? Release of serotonin may promote microthrombotic events in the utero-placental vasculature. Similarly, serotonin binding to 5-HT_2 receptors may increase systemic and feto-placental vasoconstriction. However, some argue that SSRIs and serotonin antagonists would have the opposite vascular effects (6). Moreover, it is unclear how serotonin excess would impair trophoblast invasion, the signature pathological lesion of preeclampsia.

Instead, the risk may not lie with the biological properties of SSRIs but with the known and unknown characteristics of the women who take SSRIs in pregnancy. In the Toh et al. study, women who used SSRIs were heavier, older, more likely to have used alcohol and drugs, and more likely to have received infertility treatment. While the analysis controlled for these factors, there remains the possibility of residual confounding. Perhaps of greater concern is the fact that Toh et al. provided limited information on the general medical and psychiatric illnesses experienced by the women who required SSRIs in pregnancy. Anxiety and depressive disorders, which are linked with immunological and vascular diseases, may contribute to preeclampsia (7). Indeed, women who require treatment during pregnancy are more likely to have concurrent physical problems that are associated with endothelial dysfunction, including asthma, diabetes, and migraines (8), as well as substance abuse problems. The latter are grossly underreported in pregnancy (9) and may have been underreported in this investigation.

Cohort studies can measure associations, but they are not able to determine causality. Moreover, there are several concerns about the methods used in this study. There is significant potential for recall and differential misclassification biases given the retrospective nature of data collection and absence of either chart reviews or blood pressure and urine measurements. Individuals can only report information they know about, and not all patients have knowledge of their particular medical complications. On the other hand, individuals with anxiety and mood disorders commonly express distress about their somatic state and may overstate the problems they experienced in pregnancy, making differential bias a possibility. The week in which hypertension began may be particularly difficult to recall with accuracy. Such patients may have benign labile hypertension that they misinterpret as preeclampsia. The authors report neither the percentage of women with severe preeclampsia nor the outcomes of their children. Severity of preeclampsia is a superior indicator of the disease, and if researchers confirmed it through medical record review, they would have a better estimate of the association between SSRIs and preeclampsia.

Women who require antidepressant treatment throughout pregnancy differ from women who are able to discontinue antidepressants after a confirmed pregnancy (10). The former constitute a more severely ill group who may suffer from a number of comorbid conditions and have a different risk profile, independent of SSRI use. Data about subjects' psychiatric illnesses are nearly absent in the literature on antidepressants in pregnancy, including the study conducted by Toh et al. We urgently need such information.

Accordingly, clinicians should consider the data in this study as preliminary. If a woman is planning pregnancy, clinicians should not discontinue SSRI medication unless it is the patient's preference and she and her physician agree that her risk of clinical deterioration is minimal. If a pregnant woman who is receiving treatment with a SSRI develops hypertension or preeclampsia in pregnancy, it is not likely that discontinuation of her SSRI will reverse her hypertension. An underlying propensity for hypertension has probably been unmasked, and it will require antihypertensive treatment. If the condition is preeclampsia, the pathological insult occurred much earlier in pregnancy

and cessation of the SSRI will not reverse it. As studies about the treatment of pregnant women with psychiatric illness accumulate, we look forward to additional data that will clarify optimal management strategies.

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KIMBERLY A. YONKERS, M.D.

Address correspondence and reprint requests to Dr. Yonkers, Yale University School of Medicine, Department of Psychiatry, 142 Temple Street, Suite 301, New Haven, CT 06510; kimberly.yonkers@yale.edu (e-mail). *Editorial accepted for publication November 2008 (doi: 10.1176/appi.ajp.2008.08111703).*

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