Antidepressant Treatment and Pregnancy: 
An Update

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In women, the period of vulnerability to depression overlaps the childbearing years. The high prevalence of mood disorders in women and the likelihood of antidepressant exposure at conception or during gestation have raised concerns about potential adverse effects of antidepressants on the fetus and the clinical course of pregnancy. Optimal management of a depressive disorder during pregnancy poses a difficult therapeutic dilemma for practitioners and female patients in light of the dearth of rigorous clinical studies, as discussed in a previous column.

Limited data were available until recently to guide decision making about appropriate treatment of depression during pregnancy. Guidance was based on data from toxicology screening tests for teratogenicity and mutagenicity in animal models. Clinical experience with selective serotonin reuptake inhibitor (SSRI) treatment involving mostly fluoxetine during pregnancy was limited to ~12 published trials with a total of 2,600 pregnant patients and registry data on 4,000 children born to mothers exposed to SSRIs. Several methodologically sound studies involving extensive databases now have added to our fund of knowledge about managing depression in pregnancy.

ANTIDEPRESSANT LABELING AND PREGNANCY

A decade ago, the Food and Drug Administration issued a classifying system for assigning risk during pregnancy because a better labeling guide was needed for the gravid female. Lacking adequate clinical data about antidepressants, the FDA system relied primarily on data from animal models of maternal and embryonic toxicity, fetal malformations and mortality, retarded growth and development, and functional impairment of offspring. Using the ratio of toxic dose in animals to weight-adjusted therapeutic dose in humans, the FDA adopted a classification system for drug labeling, spanning categories of A, B, C, D, and X, with A the lowest and X the highest risk category.

TERATOGENICITY OF SSRIs

The exposure rate to SSRIs immediately prior to conception or during early pregnancy is estimated to be 3% of pregnant women. In 2005, GlaxoSmithKline (GSK) reported results of a clinical trial indicating increased risk of major congenital malformations among infants exposed to paroxetine during organogenesis. Out of 527 fetuses exposed to paroxetine in the first trimester, 23 were born with major congenital defects. The adjusted odds ratio (OR) for malformation with paroxetine was 2.2 (95% confidence interval [CI], 1.3-3.6) compared with infants born to women taking other antidepressants in the first trimester. Consequently, the FDA and Canadian health authorities issued warnings, citing these data and a second unnamed trial. The FDA changed the product...
SSRIs and Neontatal Distress

Studies conducted earlier in this decade suggested that SSRIs carry increased risk of preterm birth, lower birth weight, and neurobehavioral disturbances in infants. Other reports noted respiratory distress, hypoglycemia, and irritability as more frequent in neonates of mothers receiving SSRIs.

To accurately quantify these potential risks of SSRIs, >200,000 live births between 1997 and 2002 were examined using population-based health data from British Columbia administrative databases. The study found that 14% of women had been diagnosed with depression during pregnancy, with sertraline, paroxetine, and fluoxetine as the most frequently prescribed SSRIs. During the period of the study, prenatal exposure rate to an SSRI increased from 2.3% to 5.0%. The birth weight and gestational age of infants born to SSRI-treated mothers were lower than that of infants of untreated mothers with depression. Both of these groups had lower values for these outcomes than did infants of non-depressed mothers. SSRI-exposed infants of depressed mothers also experienced more neonatal respiratory distress and feeding problems, whereas infants born to untreated depressed mothers only experienced increased frequency in feeding problems.

Many different factors may contribute to neonatal difficulty. Maternal mood influences fetal and infant development in complex ways that reflect biologic, genetic, and environmental effects extending from conception into infancy. Maternal stress may disrupt physiologic functioning and neurobehavioral development. This leads to reduced birth weight and higher prematurity rate, possibly due to elevated levels of circulating adrenal hormones. SSRIs readily cross the placenta. Animal and human studies have linked serotonergic to chronic physiologic stress during pregnancy, showing persisting dysfunction of the monoaminergic system and behavioral effects in offspring. Prenatal administration of fluoxetine to animals results in reduced uterine blood flow, low postnatal weight, transient fetal hypoxemia, and sleep disruption. It is postulated that altering serotonin levels during crucial periods of fetal development may affect maturation of the respiratory system and maladaptation to the extra-uterine environment, predisposing the fetus to neonatal respiratory distress.

Clinical Course of Pregnancy and SSRIs

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women receiving an SSRI. Researchers interviewed each subject after delivery about health habits, birth outcomes, medications, physical conditions, and medical complications. The data analyses controlled for demographic variables, gravidity, multi-fetal gestation, infertility treatment, diabetes, pre-pregnancy weight, and hazardous substance exposure. In this study, SSRI treatment during pregnancy was associated with greater risk of gestational hypertension, particularly preeclampsia. The risk of preeclampsia was greater among women who took SSRIs continuously beyond the first trimester (15%), compared with untreated women (2.4%) or women who discontinued SSRI treatment (3.7%). These findings may be the result of SSRI treatment or the underlying mood disorder. It is also possible that methodologic limitations of the study produced a spurious result or that a combination of all these factors yielded this outcome. Further investigation is required to determine the cause of hypertension in pregnancy associated with SSRIs.

Preeclampsia is manifested by impaired placental implantation. Although unclear how, it is possible that serotonin excess may impair trophoblastic invasion of the uterine wall (the signature pathophysiologic lesion of preeclampsia). Release of serotonin (5-HT) may promote microthrombotic events in the utero-placental vasculature. Serotonin binding to 5-HT\textsubscript{2} receptors may cause systemic and feto-placental vasoconstriction, contributing to hypertension or vascular compromise of the placenta. SSRIs are known to inhibit synthesis of the neurotransmitter nitric oxide, a vasodilator that plays a role in vascular reactivity and tone, both in utero and during natal life. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are known to elevate diastolic blood pressure, primarily due to increased noradrenergic tone that could be partly attributable to serotonin effects. However, the Harvard study\textsuperscript{10} lacked sufficient numbers of women exposed to SNRIs to assess pregnancy outcomes with this group of antidepressants.

These investigators\textsuperscript{10} stress that clinicians should not discontinue SSRI use in a patient planning pregnancy unless the patient and her physician agree that risk of clinical deterioration of the depression is minimal, or if it is the patient’s preference. If a pregnant woman receiving treatment with an SSRI develops hypertension or preeclampsia in pregnancy, it is unlikely that discontinuing the SSRI will reverse the hypertension. If preeclampsia ensues, the pathologic insult responsible for the event probably occurred early during pregnancy. Thus, cessation of SSRI therapy is unlikely to reverse it. Further studies are necessary to clarify optimal therapeutic strategies during pregnancy.

**SSRI TREATMENT AND INFANT HEALTH**

Whether or not to treat major depressive disorder (MDD) during pregnancy with medication is critical because it has implications for both the welfare of the mother and healthy development of the infant.\textsuperscript{12} Untreated depression and SSRI exposure both have effects on the neonate. A recent prospective, multicenter, observational study\textsuperscript{13} of women during pregnancy and their neonates compared pregnancy outcomes of three groups: women without depression (n=131), women with continuous or partial SSRI exposure during pregnancy (n=71), and women with untreated depression (n=36). The investigators controlled for potentially modifying influences on outcome, such as smoking, alcohol abuse, and other medications. Outcomes monitored included maternal weight gain, pregnancy duration, infant birth weight, physical anomalies of neonates, and neonatal course. Infants exposed either continuously throughout gestation to SSRIs or born to mothers with untreated MDD were more likely to be preterm (>20% rate), compared with women without depression or those intermittently exposed to SSRIs (4% to 9% rates).

Studies have consistently shown that MDD during pregnancy can impair the neurocognitive and emotional development of the child, predispose to sleep problems in infancy, alter neuroendocrine function, and increase risk of mental disorders in later life.\textsuperscript{12} Furthermore, depression during pregnancy is a risk factor for postpartum depression, which in turn may impair healthy development of the child. The risk of not treating depression in the mother must be weighed against potential long-term effects of pharmacologic treatment. A study\textsuperscript{15} of children followed up to 71 months after birth with exposure to a tricyclic antidepressant or fluoxetine throughout fetal life detected no evidence of adverse effects on intelligence quotient, language development, or behavior. On balance, most authorities believe that the risk of untreated MDD outweighs potential risk of SSRI treatment on neonatal outcome.

**CONCLUSION**

With the exception of paroxetine, SSRI exposure carries negligible risk of teratogenicity. Hypertension and preeclampsia are more frequent in women receiving continuous SSRI treatment throughout gestation. However, it is unclear whether this is a result of antidepressant treatment or the underlying depressive disorder. Further studies are needed to clarify. Low birth weight and pre-term births...
are associated with maternal SSRI treatment. Respiratory distress and feeding problems are more frequent in neonates born to SSRI-exposed mothers, while feeding problems are more frequent in infants of untreated, depressed mothers. Based on extensive investigation, it appears that the risks of untreated MDD outweigh potential adverse effects of SSRI treatment on pregnancy and neonatal course. PP

REFERENCES