Antidepressant use during pregnancy

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This issue of the Journal of Psychiatry & Neuroscience features an article by Einarson and colleagues describing adverse effects in pregnant women who abruptly withdraw from antidepressants (mainly selective serotonin reuptake inhibitors [SSRIs]), benzodiazepines or both. A high incidence of side effects on abrupt withdrawal from these drugs among pregnant women would not be surprising, given the well-documented abrupt withdrawal syndrome known to occur in nonpregnant women. Such side effects have led to the suggestion that these agents be discontinued on a tapering basis.

The issue of potential risk to the infant of antidepressant use during pregnancy remains controversial. Indications from the manufacturers concerning antidepressants during pregnancy generally read: “Safety during human pregnancy has not been established; should be used only if, in the physician’s opinion, the expected benefits outweigh (or markedly outweigh) the possible risks to the fetus.” In some cases, it is mentioned that animal studies indicate no teratogenic effects.

Sources of evidence to assess “possible risks to the fetus” come from human and animal studies. For SSRIs, 3 human studies concur that SSRI use during pregnancy confers no increased risk for miscarriage or major malformations. Looking at subtler measures, however, Chambers and colleagues reported that a sample of 73 infants exposed to fluoxetine, either throughout pregnancy or during only the last trimester, had increased rates of premature delivery and admission to special care nurseries, lower birth weight and poor neonatal adaptation, including respiratory difficulty, cyanosis on feeding and jitteriness. The incidence of 3 or more minor physical anomalies was also greater for 97 infants exposed to fluoxetine during the first trimester of pregnancy, compared with controls. With regard to more long-term effects, Nulman et al. reported no abnormalities in IQ, language or behavioural development in children (mean age 33 months) born to 55 women who took fluoxetine during pregnancy; in this study, data were combined for children exposed to fluoxetine throughout pregnancy or exposed during the first trimester only, and only 18 of the 55 children were exposed to fluoxetine throughout pregnancy. Thus, although SSRI use during pregnancy does not seem to have major teratogenic effects in humans, their use during pregnancy does appear to be associated with increased perinatal complications and minor malformations, and possible long-term effects require further study.

A limitation of human studies is the level of resolution of outcome measures that can be achieved. We know that disorders such as depression, anxiety and schizophrenia are not generally associated with gross morphological changes in brain, but likely involve subtle alterations in brain biochemistry or morphology. There is increasing evidence that early developmental insults (e.g., obstetric complications, low birth weight) may contribute to psychopathology that is expressed only later in life (e.g., schizophrenia) because of interactions with ongoing brain development, aging, or stressors. Thus, early insults may produce increased vulnerability.
for psychopathology related to subtle neurochemical imbalances at much later periods in the lifespan.

In animal studies, the evidence of “no teratogenicity” indicated by pharmaceutical manufacturers routinely consists of survival studies and gross morphological studies showing no major malformations. However, there are indications from animal studies that prenatal exposure to SSRIs or benzodiazepines does have long-term effects on specific neurotransmitter systems and behaviours. For example, administration of fluoxetine to pregnant rats during part of their pregnancy has been shown to alter brain serotonin (5-HT) uptake sites, hypothalamic 5-HT receptor levels and responses, and 5-HT-mediated phosphoinositide turnover in cortical slices in adolescent or adult offspring. Since rats are born immature relative to humans, mimicking drug administration equivalent to an entire human pregnancy would require giving drug to the rat from conception until about postnatal day 10. However, even these studies administering fluoxetine to rats during a fraction of the pregnancy show lasting effects on 5-HT systems. Recent studies by Coleman et al. report that administration of paroxetine to mice throughout gestation results in increased anxiety in infant offspring and increased aggressive behaviour in adult male offspring. In the case of the benzodiazepines, a rich history of animal studies has documented effects of prenatal and early postnatal benzodiazepines on gamma-aminobutyric acid, monoamine and opioid neurochemistry, as well as lasting behavioural effects on learning, social interactions, aggression and anxiety (reviewed in Schroeder et al.).

It is reasonable to hypothesize that SSRIs may affect fetal brain development because 5-HT is thought to be an important regulator of early brain development. For example, 5-HT promotes the differentiation of CNS target cells and autoregulates growth of 5-HT neurons in culture. Also, 5-HT systems are very plastic. After certain CNS lesions, immense hyperinnervation of various brain regions by 5-HT terminals occurs, especially in the neonate. The mechanism of 5-HT hyperinnervation involves the activation of 5-HT1a receptors by 5-HT, which causes the release of protein S-100β from astrocytes. Thus, S-100β may be viewed as a serotonergic sprouting factor whose release is mediated via 5-HT itself.

In addition to effects on 5-HT, other documented effects of chronic SSRI treatment could also affect fetal brain development. For example:

- chronic administration of the SSRI, sertraline, to adult rats increases mRNA for brain-derived neurotrophic factor (BDNF) and for its receptor, trkB, in the hippocampus. BDNF is a neurotrophin that promotes development of immature neurons and enhances the survival and function of mature neurons;
- chronic SSRI treatment also increases mRNA for the nuclear transcription factor, cAMP response element binding protein (CREB), in rat hippocampus, as well as the expression and function of the CREB protein, which can upregulate a variety of target genes;
- the human placenta possesses an active 5-HT transporter that is potently inhibited by SSRIs such as fluoxetine (IC50 = 17 nM) and paroxetine (IC50 = 23 nM), and less potently by cocaine (IC50 = 182 nM). 5-HT profoundly affects vascular function by contracting vascular smooth muscle and enhancing the effects of other vasoconstrictors. Thus, clearance of 5-HT by the placental 5-HT transporter plays an important role in optimizing uteroplacental blood flow. Cocaine produces placental ischemia, depriving the fetus of oxygen and nutrients, and it has been suggested that “impairment of such a vital function [placental 5-HT transport] by cocaine is expected to be highly relevant to the pathogenesis of fetal and placental complications of cocaine abuse during pregnancy.” Such concerns are even more relevant to SSRIs because they inhibit placental 5-HT transport much more potently than cocaine does;
- fluoxetine reduces hunger and food intake in humans, produces hypophagia in rats and increases resting energy expenditure and basal body temperature in humans.

Hopefully, these few thoughts can serve as a reminder that the use of antidepressants during pregnancy is a complex and controversial issue. The fact that antidepressants are not major teratogens does not prove that they are without effect on the developing CNS — these drugs are more likely to affect CNS biochemistry or the microscopic organization of brain circuits, rather than gross brain structure. The role of 5-HT in normal CNS development, as well as the effects of altering 5-HT transmission at critical periods, remain to be further clarified. Although my comments have concentrated on fetal risk, the decision to use antidepressants during pregnancy is a multifaceted problem, involving benefits and risks of either using or abstaining from the medication to both mother and child. Given our current level of uncertainty, we can only benefit from more individuals performing their own critical appraisals of the
existing literature, and from further research, to reach the goal of a truly informed decision as to relative benefits and risks of antidepressant use during pregnancy.

References