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SSRIs in Pregnancy –Are they safe?

Commentary on the articles by Oberlander *et al.* on page 443 and Morrison *et al.* on page 433

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An estimated 10% to 20% of women of reproductive age suffer from depression, often necessitating pharmacotherapy. During the last decade, there has been a dramatic shift in the treatment of patients with depression, with the selective serotonin reuptake inhibitors (SSRIs) largely replacing the tricyclic antidepressants. Typical of drug development, fluoxetine entered the market with reassuring animal reproductive studies but with no human experience. Because at least half of all pregnancies are unplanned, coupled with physicians and patients often being reluctant to discontinue effective drug therapy, postmarketing studies have gradually emerged on the safety of fluoxetine in pregnancy. Such studies have not shown evidence of morphologic or functional teratogenicity of fluoxetine (1–4).

Many women cannot discontinue their antidepressant therapy in pregnancy without a major negative impact on their well being. Einarson *et al.* have recently documented that "cold turkey" discontinuation of SSRIs and other psychotropic drugs in pregnancy can lead to substantial morbidity among women, including suicide ideation, hospitalization, and replacement of medications with alcohol (5). Hence, it is most important that the assessment of safety of medications in human pregnancy includes careful evaluation of the maternal and fetal risks of the untreated condition. A recently completed study of pregnancy outcome among children of women taking fluoxetine throughout pregnancy has failed to show any adverse effects on birth weight, preschool IQ, language development, or behavior. The study did find that the maternal level of depression (and not fluoxetine) is negatively associated with measures of child development (6).

This issue of Pediatric Research contains two studies from the University of British Columbia dedicated to the effects of SSRIs in pregnancy (7, 8). One study uses sheep as a model for physiologic changes associated with fluoxetine (7). The second study investigated neonatal pain response associated with SSRIs and benzodiazepines in pregnancy (8).

In their meticulous and well-planned study, Morrison and colleagues (7) detected an acute, but transient effect on uterine blood flow, temporally related to i.v. infusion of fluoxetine. They also monitored blood gases and fetal growth. Animal studies are critical in advancing our understanding of mechanisms of potential fetal or placental pathology. The chronically cannulated sheep model is an important experimental paradigm in establishing mechanisms of fetal safety and placental transfer. With this model one can bridge gaps of knowledge which cannot be obtained ethically in human pregnancy. Yet, before extrapolating such results to humans, one has to acknowledge differences between the experimental design in the animal, and human physiology and pharmacology. Morrison and colleagues should be commended for exhibiting remarkable caution in extrapolating their results with existing human data.

Although the measured long-term (steady state) serum concentrations of fluoxetine and its active metabolite in the sheep were in the range observed in treated patients, the acute observed effects may be related to the i.v. bolus of the drug, which results in high initial serum concentrations falling rapidly, typical of the distribution phase of most drugs. Because women do not receive fluoxetine as an i.v. bolus, it is difficult to decide whether the acute observed effects can be expected in humans. Due to the very long elimination half-life of fluoxetine, and the lack of a loading dose in humans, serum concentrations accumulate slowly over months, possibly avoiding the bolus effect seen in the present animal study. To mimic the human clinical pharmacology of fluoxetine, it will be interesting to repeat a similar protocol, but with oral administration of the drug, or with an infusion rate that avoids the bolus effect, allowing the slow accumulation of fluoxetine.

Oberlander and colleagues investigated the effects of SSRIs and benzodiazepines in pregnancy on neonatal pain response (8). Using a validated tool for measurement of pain response in neonates, they have shown an apparently attenuated pain response in babies exposed *in utero* to a variety of psychoactive drugs when compared with an unexposed control group. This is the first study to assess pain response in neonates as related to their prenatal drug exposure. It is also the first study to explore potential alterations in sensory functions following *in utero* exposure to SSRIs with or without benzodiazepines. Hence, the ramifications of this study may be far-reaching. If prenatal exposure to SSRIs or benzodiazepines affect neuronal development, then one needs to be very restrictive in their use, even beyond first trimester embryogenesis.

However, before such effects can be inferred, future work will have to address the possibility that what Oberlander and colleagues observed is a *direct* neonatal drug effect. The authors report that all women took their psychotropic drugs up to birth and during the first few days of breastfeeding. Benzodiazepines and SSRIs have much longer elimination half lives in the neonate than in the mother, and hence all neonates likely had clinically significant levels at the time of measurement of pain response. Without measuring directly the concentrations of these drugs in the neonate, it may not be possible to conclude that these psychoactive drugs affect intrauterine "wiring" of neurons.

A possible way to separate potential *in utero* effects on CNS development *versus* direct postnatal pharmacological effects would be through correlation of serum drug concentrations in the neonate and attenuation of pain response, and/or changes in autonomic responses.

Should these studies lead to changes in the way one counsels pregnant women about safety of SSRIs in pregnancy? I do not believe so. One of the studies reported transient changes in uterine blood flow after IV bolus of fluoxetine, a schedule not used in humans. The other study described changes in pain response that may well be caused by direct pharmacological effects on the newborn. It is critical that these two important studies be read in their context, and not interpreted separately as proofs of increased fetal risks. Two years ago Pediatric Research published experiments in chick embryos showing inhibition of NMDA receptors by dextromethorphan (9). Much publicity ensued (10), and unnecessary havoc was caused for thousands of women and their health providers. Not surprisingly, epidemiologic human studies that followed, have failed to show increased human risks (11, 12).

One has to be very careful when incorporating research findings into the reproductive risk-benefit equation. New findings should not be looked independently, but rather within the context of all available data, and this will create the appropriate balance in their interpretation.

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