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Commentary

A Cautionary Note Against 'One Size Fits all'

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Pregnant women presented with a health concern are often faced with difficult decisions regarding whether or not to take medications during pregnancy. As all medication exposures during pregnancy pose some risk to the developing fetus, this risk must always be weighed against the potential risk/benefit ratio for both fetus and mother. Depending on the type of medication under consideration for use, the dialog surrounding the risk/benefit ratio can be intense. Specifically, antidepressant medication use during pregnancy has been controversial. In many ways, it could be deemed an 'unfair controversy' as the scrutiny encountered by women taking antidepressants likely exceeds that faced by women taking other types of medications for a myriad of different medical illnesses.

In this issue of *Neuropsychopharmacology*, a new article by Mulder *et al* (2011) examines the *in utero* neurobehavioral development of SSRI-exposed infants. The primary aim of this study was to compare behavioral development in a group of fetuses exposed to SSRIs throughout pregnancy compared with a control group of healthy unexposed fetuses. This study examined three groups of participants: (1) low-dose SSRI medication exposed and unmedicated pregnant women with a history of depression/anxiety, (2) women taking average or above average doses of SSRI's with histories of depression/anxiety, and (3) normal controls (pregnant women with no psychiatric history and no medications). The authors conducted a prospective observational study throughout pregnancy and performed detailed ultrasound assessments of fetal behavior during each trimester (T1, T2, T3) including fetal motor behavior, heart rate, and the emergence of behavioral (sleep–wake) states.

The authors report that neurobehavioral development in fetuses of low-dose SSRI-treated pregnant women and unmedicated women with psychiatric problems was indistinguishable from fetal development in the control group of women with no psychiatric history and taking no medications. However, fetuses exposed to standard SSRI dosing or greater than average SSRI doses were noted to have behavioral differences by ultrasound assessment, irrespective of SSRI type. These differences included increased motor activity at the beginning (T1) and end of the second trimester (T2), and lack of inhibitory control of motor output at times fetuses are supposed to be 'at rest' (T2) or in 'quiet' or non-REM sleep (T3). One notable limitation of the study is the significant drop-out rate in both exposed groups (low- and higher-dose SSRI); only 45% of participants in the medication exposed groups attended all three antenatal ultrasound testing sessions. Consequently, developmental trajectories for individual fetuses could not be assessed with the use of longitudinal data analysis.

These newly reported findings are both interesting and important, and the results will need to be replicated in future studies. Certainly, these results are consistent with previous literature documenting neurobehavioral effects of SSRI's during pregnancy and the acute postpartum period, although these findings are largely transient and it is not clear whether these prenatal and postnatal abnormalities persist (Sanz *et al*, 2005). However, it is critical to comment on one of the authors primary recommendations; namely, the authors state that 'the use of above-standard dosage for a particular SSRI type may be discouraged, if possible and safe.' This statement should be taken with great caution for a number of reasons. First, symptom relief or remission of symptoms, and not 'dose' should be the primary guiding principle for antidepressant treatment during both pregnancy and at all other times. Second, antidepressant exposure at sub-therapeutic doses with ongoing symptoms of depression and anxiety is likely counterproductive for both mother and fetus, and may constitute a 'double exposure' (inadequately treated maternal depression and SSRI exposure) for the fetus. Third, one can assume that most women taking 'average or greater than average' doses of antidepressant monotherapy were doing so because that was the necessary efficacious dose for the mother, and therefore, women requiring higher doses may have more severe psychiatric illness in general, that could contribute to a different or altered fetal neurobehavioral pattern, independent of antidepressant use.

Last, and as the authors concur, women who discontinue their antidepressant use during pregnancy have increased risk of relapse of major depression (Cohen *et al*, 2006). This risk deserves to be highlighted and all women with histories of depression/anxiety need to be appropriately counseled on

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an individual case-by-case basis regarding treatment during pregnancy. In particular, appropriate counseling of the patient must include obtaining a comprehensive past psychiatric history, as it will influence the selection of the treatment modality. The literature documents that untreated depression during pregnancy significantly increases risk for the development of postpartum depression, a potentially devastating illness with serious consequences for the mother, infant, and family (O'Hara and Swain, 1996). Moreover, recent work from investigators in British Columbia has demonstrated that third trimester discontinuation of SSRI medications did not alter neonatal outcomes (Warburton *et al*, 2010). Consequently, the timing of treatment throughout the perinatal period needs to be carefully discussed on an individual basis.

Therefore, rather than using a 'one size fits all approach' to counseling pregnant women, it is preferable to consult comprehensive evidence-based practice recommendations to guide treatment of perinatal depression, such as the 2009 publication by Yonkers *et al*, 2009a, b: a joint report on the management of depression during pregnancy endorsed by the American Psychiatric Association (APA) and the American College of Obstetricians and Gynecologists (ACOG). The issue, at hand, is not whether antidepressants during pregnancy have effects on the fetus, but rather, what are the most appropriate treatment recommendations for pregnant women with depression or anxiety to ensure optimal outcomes for both members of the mother–infant dyad.

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