Balancing Risks: Dosing Strategies for Antidepressants Near the End of Pregnancy

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One of the most difficult balancing acts in clinical psychopharmacology practice is minimizing the risks of untreated depression in pregnant women while also minimizing the risks of antidepressant treatment. Major depression is estimated to occur in 9.4% to 12.7% of pregnant women[1] and to recur in over two thirds of women who discontinue antidepressant medication while pregnant.[2] Antenatal depressive symptoms can compromise outcomes for women and their offspring.[3] Antidepressant medications can alleviate depressive symptoms, improve functioning, and prevent symptom relapse during pregnancy, but can also pose risks to fetuses and neonates.

Added to long-standing efforts to determine the risks of first-trimester drug exposure, recent studies have highlighted adverse effects on neonates of antidepressant exposure near the end of pregnancy. These studies have led the U.S. Food and Drug Administration to issue a Public Health Advisory noting the complexity of weighing the risk of maternal depression against the neonatal risks of late-pregnancy antidepressant exposure.[4]

The extremes of stopping antidepressants altogether or medicating exactly as if a woman were not pregnant may be riskier than a balanced approach. Is there a dosing strategy near the end of pregnancy that minimizes the risks of both medications and symptoms? A risk-benefit analysis suggests that there may be.

Risks of Untreated Antenatal Depression

In addition to general risks of major depression, such as suicide, untreated antenatal depression is associated with increased risks of preterm labor[5] and low birth weight.[6] Compared to controls, offspring of women who are depressed during pregnancy have more irritability[7] and higher cortisol levels[6] as newborns, poorer growth and increased risk of infection as babies,[8] and more difficult temperaments as children.[9]

Risks of Antidepressant Medications in Late Pregnancy

Near the end of pregnancy, potential types of risks include transient neonatal side effects and effects on organ maturation. Side effects in neonates exposed prenatally to antidepressants, as described in small studies and case reports,[10–16] include respiratory distress, hypotonia or hypertonia, tremor, jitteriness, weak cry, changes in sleep or behavioral state patterns, nystagmus, irritability, and, rarely, cardiac arrhythmias or seizures. These symptoms typically begin within the first 24 hours after birth and resolve within 1 to 2 days. Up to 30% of neonates exposed to antidepressants in late pregnancy have side effects.[14,16] Most of these side effects are posited to be due to abrupt medication withdrawal, but another possible explanation is that neonates are slow to metabolize lingering medication due to hepatic immaturity.

The primary concern about antidepressant effects on maturation of fetal organ systems arises from 1 case-control study of persistent pulmonary hypertension of the newborn (PPHN).[17] That study showed a statistically significant link between selective serotonin reuptake inhibitor exposure during the second half of pregnancy and PPHN. The study is inconclusive due to its retrospective design, the incomplete ruling out of confounds, and the small number of exposed mothers with affected infants (14 out of 377 whose infants had PPHN, with 1213 total study participants). Nevertheless, its findings are notable due to the potentially life-threatening nature of PPHN.

Pregnancy-Linked Pharmacokinetic Changes

During pregnancy, antidepressant pharmacokinetics can be altered by decreased gastric motility, increased extracellular fluid space and total body water, decreased albumin concentrations, increased or decreased concentrations of α-1-acid glycoprotein, and altered activity of hepatic drug-metabolizing enzymes.[18,19] The activities of CYP2C19, CYP2D6, and CYP3A4 increase during pregnancy.[20–22] In one study, dose-corrected plasma concentrations of fluoxetine (demethylated by CYP2D6) were approximately 50% lower at 36 to 37 weeks' gestation compared to 2 months postpartum.[23] Similarly, plasma concentration of citalopram (metabolized by CYP2C19 and CYP3A4) was about 40% lower during pregnancy versus the postpartum period.[24] There is substantial individual variability in the degree of pharmacokinetic change during pregnancy, perhaps influenced by polymorphisms in the genes encoding the enzymes responsible for metabolizing these medications.

Implications for Antidepressant Dosing

If a pregnant woman has unexplained breakthrough symptoms while taking a previously effective antidepressant dose, she may be among the subset of women with clinically significant pharmacokinetic changes. This may necessitate a dose increase. Therefore, pregnant women's antidepressant doses are generally at least as high as, and sometimes higher than, those needed in the nonpregnant state.

Near the end of pregnancy, the risk of maternal symptom relapse must be weighed against the risk of dose-dependent neonatal side effects, including effects of abrupt medication withdrawal. One way of balancing these risks is by considering a partial dose taper, to allow for more gradual medication discontinuation for the baby and reduced medication exposure during the period of most rapid fetal pulmonary maturation. At about 35 weeks' gestation, the patient can be assessed for her ability to withstand temporary subtherapeutic antidepressant levels. Candidates for a partial dose taper are characterized by the 6 "*S*s":

- ***Symptom status:*** Sustained remission of major depression for at least 4 weeks prior to initiating the taper
- ***Savvy:*** Excellent insight into illness; can recognize early signs of recurrence
- ***Seeks help:*** History of promptly contacting health care providers when symptoms recur
- ***Stress:*** Not subject to excessive stress (beyond the inevitable stresses of being pregnant)
- ***Social support:*** Significant others are aware of the illness, the dose taper, and the risk of recurrence and are prepared to help
- ***Severity:*** History does not include severe, high-risk, treatment-refractory episodes

Medication dose can be reduced by approximately 25% for 2 weeks, then by

another 25% until the end of the pregnancy. A full therapeutic dose can be resumed immediately postpartum. For example, a woman taking fluoxetine 40 mg/day could reduce to 30 mg/day at week 36 and 20 mg/day at week 38, with a return to 40 mg/day immediately postpartum. A woman taking sertraline 200 mg/day could reduce to 150 mg/day at week 36 and 100 mg/day at week 38, with a return to 200 mg/day immediately postpartum.

Summary and Conclusions

There are risks inherent in failing to adequately treat major depression during pregnancy, and there are risks associated with antidepressant medication during pregnancy. Near the end of pregnancy, a partial dose taper may reduce the risk of neonatal adverse effects for women who can tolerate a brief period of subtherapeutic medication levels.

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Dr. Bishop has received grant/research support from the American College of Clinical Pharmacy and the Valteich Foundation and has received honoraria from Eli Lilly. Drs. Miller, Geller, and Macmillan report no financial or other relationship relevant to the subject of this column.

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