Therapeutic Drug Monitoring in Pregnant and Postpartum Women: Recommendations for SSRIs, Lamotrigine, and Lithium

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Recently, guidelines for antenatal management of depression were published.[1] Psychotherapy alone may be an appropriate treatment for some women, while psychopharmacotherapy may be indicated in others. Use of psychopharmacotherapy during pregnancy and the postpartum involves complex clinical decisions based on the risks and benefits and alternatives to medications. The aim of effective treatment is to minimize maternal and fetal exposure to psychiatric illness by optimally treating it with the minimum effective dose regimen. One variable that complicates psychopharmacotherapy is that dosing often requires adjustment to maintain therapeutic effects, particularly in late pregnancy. The current article focuses on those factors that affect dosing in pregnancy.

Therapies were selected for discussion in this article on the basis of their prevalence in the treatment of mood disorders in pregnancy and the availability of pharmacokinetic studies regarding metabolic changes and/or therapeutic blood monitoring in pregnancy. A full review of the risks and benefits of these therapies is beyond the scope of this article; however, references 2–4 provide information that is important to the decision to use antidepressant or mood-stabilizing medications during pregnancy and the postpartum.

SSRIs

Pregnancy-associated changes in drug absorption, distribution, metabolism, and elimination have been described. In particular, changes in cytochrome CYP450 enzymatic activity, possibly mediated by increased gonadal steroid levels, appear to lower plasma selective serotonin reuptake inhibitor (SSRI) levels and may impact treatment response.[5] CYP3A4 is induced during pregnancy,[6] and CYP2D6 has been hypothesized to be induced, although the mechanism is unclear.[6–8] Pregnancy-associated demethylation of fluoxetine and citalopram by CYP2D6 may contribute to lower trough levels in pregnancy as compared to the postpartum period.[9,10] Similarly, during pregnancy, plasma levels of paroxetine in women with the CYP2D6 extensive or ultrarapid metabolizer genotype decrease steadily and are inversely correlated with depressive symptoms.[11]

Although SSRI concentrations frequently change in pregnancy, the relationship between blood SSRI levels and clinical response is not well established, and there is significant variation in steady-state plasma concentrations of some SSRIs in both pregnant[12] and nonpregnant[13] women. One study found that two-thirds of pregnant women receiving antidepressant monotherapy required dose increases, especially after 20 weeks' gestation,[14] to treat depressive symptoms or maintain euthymia. One contributing factor may be the more rapid metabolism of the medication or, alternatively, other physiologic or psychosocial changes frequently experienced during pregnancy. My practice is to continue the dose that was effective early in pregnancy (or prepregnancy) as the woman progresses through pregnancy, while monitoring for depressive symptoms at least monthly, and base dose adjustments on clinical presentation.

The postpartum-related rapid decline in gonadal steroid levels, contraction of plasma volume, and reestablishment of hepatic enzyme activity and return of glomerular filtration rate to prepregnancy levels may influence antidepressant metabolism. Increased blood antidepressant levels may result as a consequence of these postpartum-related changes and manifest as side effects, especially when an increased dose that was used during pregnancy is continued into the postpartum.

Postpartum depression is a debilitating condition that affects 1 in 8 women.[15] Some authors have suggested, in the absence of adverse effects, continuing the SSRI dose used in pregnancy at least 6 weeks postpartum to provide prophylaxis against postpartum mood exacerbations.[14] My practice is to continue the dose used in pregnancy into the postpartum and monitor patients for the emergence of side effects or depression by telephone communication during the first postpartum week and then via office visits every 2 to 4 weeks as clinically indicated. Dose adjustments are based on clinical presentation, as there is currently insufficient evidence to support routine therapeutic blood level monitoring of SSRIs during pregnancy or the postpartum.

Lamotrigine

Lamotrigine is the most widely prescribed antiepileptic drug in women of reproductive age with epilepsy and is widely used for the maintenance of bipolar disorder.[16] Pregnancy has significant effects on the pharmacokinetics of lamotrigine. The gonadal steroid–associated increase in phase II glucuronidation that takes place during pregnancy to convert lamotrigine to its inactive metabolite, lamotrigine-2-N-glucuronide, is a particularly essential mechanism that affects lamotrigine levels.[17]

Lamotrigine clearance progressively increases through the 32nd gestational week.[18] There is a greater than 330% increase in lamotrigine clearance between preconception and the third trimester. An average dose increase of 250% was required to sustain therapeutic drug levels across pregnancy in women with epilepsy.[2] Within days after delivery, the elimination rate of lamotrigine drops rapidly, and plasma concentrations increase significantly during the first 2 to 3 weeks postpartum.[2] The vast majority of pregnant women require higher doses of lamotrigine to maintain therapeutic drug levels and treat increased frequency of seizures; postpartum lamotrigine toxicity is common in women who require a dose increase during pregnancy and subsequently a decrease to preconception dose in the postpartum.[19]

The American Academy of Neurology recommends that therapeutic drug monitoring of lamotrigine should be considered in pregnant women with epilepsy.[20] Other authors have recommended such monitoring for women with epilepsy at least monthly during pregnancy and weekly during the puerperium.[2] In contrast to the use of lamotrigine in the treatment of epilepsy, lamotrigine dosing in bipolar disorder is typically driven by clinical response. Blood drug levels are not routinely obtained, and target therapeutic blood drug levels are not defined. Pregnant and postpartum women with bipolar disorder are at high risk for relapse and postpartum psychosis,[21] but currently there are no established guidelines for therapeutic drug monitoring of lamotrigine in bipolar disorder: dosing is based on patient symptomatology. Clinically, I find that many women with bipolar disorder require lamotrigine dose increases during pregnancy, and it is my practice to check a patient's lamotrigine level 2 weeks postpartum to prevent lamotrigine toxicity.

Lithium

Lithium is renally eliminated without biotransformation. Unlike SSRIs and lamotrigine, lithium has an established therapeutic drug level that guides management during pregnancy and the postpartum. In pregnancy, renal lithium clearance almost doubles, thus

lowering serum concentrations and potentially increasing the risk of relapse.[22] More frequent therapeutic drug monitoring, at intervals ranging from every 2 to 4 weeks[23,24] during pregnancy and weekly[25] in the last month of pregnancy, has been recommended. At delivery, vascular volume rapidly decreases by approximately 40% and renal lithium clearance falls to prepregnancy levels, increasing serum concentrations and placing women at risk of lithium toxicity.[24] To avoid toxicity, it has been suggested that clinicians check a lithium level when a patient presents for delivery; either decrease the dose of lithium at labor onset[22] or briefly withhold lithium therapy for 24 to 48 hours before a scheduled cesarean section or induction or at the onset of labor.[26] As the maternal glomerular filtration rate quickly returns to prepregnancy levels after delivery, the preconception dose may then be reinitiated; blood lithium levels will then approximate preconception levels.[26] Therapeutic drug levels can be checked 24 hours after and every few days after delivery.[23] If the neonate exhibits signs of lithium toxicity, serum lithium monitoring may be indicated, but neonatal care providers should be advised against using test tubes that contain lithium heparin, which could give spurious results.[27]

Summary

The physiologic and pharmacokinetic changes that are associated with pregnancy and the postpartum period can affect the psychopharmacologic treatment of women. All women taking psychotropic drugs should be closely monitored for recurrence of symptoms or emergence of side effects throughout pregnancy and during the postpartum period as dose adjustments may be necessary. To facilitate clinical assessment, it is my practice to have all women complete standardized assessments of depression (eg, Edinburgh Postnatal Depression Scale, Quick Inventory of Depressive Symptoms–Self Report), anxiety (eg, Zung Self-Rating Anxiety Scale, Sheehan Patient-Rated Anxiety Scale), and, if applicable, hypomania/mania (eg, Altman Self-Rating Mania Scale) at every visit. At this time, there is robust evidence to support routine therapeutic drug monitoring for lithium. In the treatment of epilepsy, therapeutic drug monitoring of lamotrigine is commonplace, but the application to the treatment of bipolar disorder during pregnancy and the immediate postpartum period requires further study. There is currently insufficient evidence to support widespread drug level monitoring for SSRIs.

Evolving treatment guidelines for psychopharmacologic treatment of depression throughout pregnancy and the postpartum period are needed, as is research that will aid clinicians in determining which women may need an increase in antidepressant or mood-stabilizing medication to prevent reemergence or worsening of mood symptoms. Eventually, individualized psychopharmacologic treatment that takes into account a mother's and fetus's genotype and plasma drug levels throughout pregnancy may become standard of care to maximize drug benefit and minimize risks to the mother or fetus/infant.

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Free Resources on Drug Treatment During Pregnancy

Organization of Teratology Information Specialists
www.otispregnancy.org

National Library of Medicine–Toxnet
http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC

Food and Drug Administration Guidance for Industry Pharmacokinetics in Pregnancy
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072133.pdf

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