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Pharmacotherapy for Mood Disorders in Pregnancy:

A Review of Pharmacokinetic Changes and Clinical Recommendations for Therapeutic Drug Monitoring

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Abstract

Objective—Pharmacotherapy for mood disorders during pregnancy is often complicated by pregnancy-related pharmacokinetic changes and the need for dose adjustments. The objectives of this review are to summarize the evidence for change in perinatal pharmacokinetics of commonly used pharmacotherapies for mood disorders, discuss the implications for clinical and therapeutic drug monitoring (TDM), and make clinical recommendations.

Methods—The English-language literature indexed on MEDLINE/PubMed was searched for original observational studies (controlled and uncontrolled, prospective and retrospective), case reports, and case series that evaluated or described pharmacokinetic changes or TDM during pregnancy or the postpartum period.

Results—Pregnancy-associated changes in absorption, distribution, metabolism, and elimination may result in lowered psychotropic drug levels and possible treatment effects, particularly in late pregnancy. Mechanisms include changes in both phase 1 hepatic cytochrome P450 and phase 2 uridine diphosphate glucuronosyltransferase enzyme activities, changes in hepatic and renal blood flow, and glomerular filtration rate. Therapeutic drug monitoring, in combination with clinical monitoring, is indicated for tricyclic antidepressants and mood stabilizers during the perinatal period.

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Conclusions—Substantial pharmacokinetic changes can occur during pregnancy in a number of commonly used antidepressants and mood stabilizers. Dose increases may be indicated for antidepressants including citalopram, clomipramine, imipramine, fluoxetine, fluvoxamine, nortriptyline, paroxetine, and sertraline, especially late in pregnancy. Antenatal dose increases may also be needed for lithium, lamotrigine, and valproic acid because of perinatal changes in metabolism. Close clinical monitoring of perinatal mood disorders and TDM of tricyclic antidepressants and mood stabilizers are recommended.

Keywords

pharmacokinetics; pregnancy; antidepressants; mood stabilizers

Untreated mood disorders during pregnancy are associated with health risks to both mother and fetus, making the goal of euthymia paramount.[1–4] Guidelines for the management of major depressive disorder and bipolar disorder during pregnancy stress the importance of preconception treatment planning and close clinical monitoring.[2,5] Most women who discontinue maintenance antidepressants or mood-stabilizer pharmacotherapy for a pregnancy will experience a relapse during the pregnancy. Therefore, immediate and prophylactic treatment of many women with mood disorders will include pharmacologic treatment.[6,7] Treatment during pregnancy is complicated by pharmacokinetic changes, which can result in lowered psychotropic drug levels and/or treatment efficacy.

Therapeutic drug monitoring (TDM) is an integral aspect of the standard of care for medications with established therapeutic ranges, a narrow therapeutic index or significant pharmacokinetic variability, which includes some mood stabilizers and tricyclic antidepressants (TCAs). Given the evidence for changes in perinatal physiology and pharmacokinetics, TDM has the potential to optimize dosing by avoiding supratherapeutic doses that would increase drug exposure to the mother and fetus or subtherapeutic dosing that would expose the dyad to the consequences of undertreated psychiatric illness. A comprehensive discussion that includes the potential risks of undertreated mental illness for the mother and fetus, benefits of nonpharmacologic and potential risks, and benefits to psychopharmacologic treatment[8–16] is essential to quality patient care. In cases of polypharmacy, TDM can be valuable in avoiding adverse effects due to drug-to-drug interactions. For medications without standardized therapeutic ranges, an individual woman's drug level at a time when she is clinically asymptomatic that can be used as a target serum drug level during pregnancy may be useful.[17,18]

The objectives of this review are to summarize the evidence for changes in perinatal pharmacokinetics of psychotropic medications commonly used for mood disorders during pregnancy, consider the implications for clinical and TDM, and make clinical recommendations.

MATERIALS AND METHODS

The English-language literature indexed on MEDLINE/PubMed was searched for the period between 1966 and 2013 using the following key terms: *antidepressant, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, venlafaxine, desvenlafaxine,*

duloxetine, bupropion, mirtazapine, trazodone, vilazodone, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine, amoxapine, maprotiline, selective serotonin reuptake inhibitor (SSRI), *selective norepinephrine reuptake inhibitor* (SNRI), *tricyclic, tetracyclic, mood stabilizer, antiepileptic, lithium, lamotrigine* (LTG), *carbamazepine* (CBZ), *valproic acid* (VPA), *pregnancy, prenatal, delivery, post-partum, female, gender, pharmacokinetics, dosing, therapeutic drug monitoring, and drug level*. Resultant articles were cross-referenced for other relevant articles not identified in the initial search. Original observational studies, case reports, and case series that evaluated or described pharmacokinetic changes or TDM during pregnancy or the postpartum were included.

RESULTS

Pharmacokinetics During the Perinatal Period

The drug dose–effect relationship is complex, including not only interperson pharmacokinetic and pharmacodynamic variability but also genetic variability controlling the translation of proteins involved in metabolizing enzymes, drug transporters, and drug targets. Small-to-moderate sex differences, which exist in drug absorption, distribution, metabolism, and elimination,[19–21] may be amplified during pregnancy. For example, women have a slower gastric emptying[22] and small bowel and colonic transit time when compared with men, which are further slowed during pregnancy.[23,24] The increased plasma volume, change in protein binding, and lower ratio of lean muscle to adipose tissue in pregnant women may result in a greater volume of drug distribution for lipophilic drugs. Together, these changes likely contribute to a small effect in the peak plasma concentrations.[19] Hepatic clearance of psychotropic medications is also altered, most notably due to pregnancy-associated changes in metabolic enzymes. Of the multiple families of metabolic enzymes,[25] the phase 1 metabolism cytochrome P450 (CYP) family has been best studied in pregnancy. Individual drugs often undergo metabolism by several CYP and/or non-CYP pathways. Other families of enzymes include phase 2 metabolism enzymes such as uridine diphosphate glucuronosyltransferase (UGT) and *N*-acetyltransferase. Increased sex steroids associated with pregnancy may modulate several of the CYP450 and UGT isoforms in a clinically relevant manner. Synthetic analogs of sexsteroids associated with pregnancy, such as those used in hormone replacement therapy or oral contraceptives, modulate several CYP450 isoforms via inhibition (CYP1A2,[26] CYP2C19,[27] CYP2B6,[28] and CYP3A4[29]), induction (CYP2A6[30]), or increasing glucuronidation by UGT1A4 and possibly UGT2B7.[31,32] Cytochrome P450 and UGT changes may also have effects on adverse effect burden for both mother and fetus/infant because drug exposure partially depends on metabolism. Changes in maternal drug pharmacokinetics in conjunction with placental transfer and fetal drug metabolism affect fetal psychotropic drug exposure.[33–41]

Cytochrome P1A2 is less active in women compared with men[42] and is inhibited by sex steroids.[43,44] The activity of CYP1A2 is reduced by 65% to 70% at the end of pregnancy compared with the postpartum period[32] and may affect psychotropics metabolized by CYP1A2 including fluvoxamine, duloxetine, amitriptyline, clomipramine, desmethylimipramine, imipraminem, and doxepin.

Greater CYP3A4 activity in women (via progesterone effects)[42,45] has the potential to accelerate metabolism and reduce plasma levels of some commonly used psychotropics partially metabolized via CYP3A4 including citalopram, escitalopram, fluoxetine, paroxetine, trazodone, venlafaxine, desvenlafaxine, bupropion, mirtazapine, amitriptyline, clomipramine, imipramine, trimipramine, doxepin, and CBZ.

During pregnancy, CYP2C19 activity is reduced by almost 50%.[46] Pharmacokinetic changes associated with CYP2C19 during pregnancy may affect the metabolism of citalopram, escitalopram, sertraline, fluoxetine, vilazodone, venlafaxine, amitriptyline, clomipramine, trimipramine, imipramine, and desmethylimipramine.[47]

Cytochrome P2D6 is generally induced during pregnancy,[32,48] and CYP2D6-associated pharmacokinetic changes may affect the metabolism of numerous psychotropics from the SSRIs, SNRIs, and TCA drug classes. Maternal CYP metabolic phenotype (eg, poor, intermediate, extensive, and ultrarapid) is an important determinate of metabolism. Different allelic forms of CYP2D6 may result in differing therapeutic dosing requirements. In nonpregnant patients, dose adjustments may be required based in part on CYP2D6 phenotype.[49] In pregnancy, phenotype influences metabolic ratios of medications biotransformed by CYP2D6.[48]

Increased renal blood flow and the associated increase in glomerular filtration rate (GFR) may increase drug (eg, lithium) elimination during pregnancy.[50] Although the studies are inconsistent,[51,52] increased hepatic blood flow may account for increased clearance and decreased concentration of high extraction ratio drugs during pregnancy.

The postpartum period is characterized by a rapid decline in sex steroid levels, contraction of plasma volume, reestablishment of hepatic enzyme activity after a period of metabolic refractory activity,[53–56] and a return of the GFR to prepregnancy levels. As a consequence, increased drug blood levels may result and manifest as adverse effects of toxicity, especially when an increased dose used during pregnancy is continued into the postpartum.[57]

In addition to changes in maternal pharmacokinetics, patient-specific psychologic factors and physiologic effects of pregnancy on vulnerability and treatment responsiveness may also influence treatment outcomes. Pregnancy brings about a psychosocial context, which differs among women, aspects of which can affect the risk of mood disorder recurrence during pregnancy or treatment efficacy.[58] Physiologic changes associated with pregnancy may interact with underlying sexual dimorphisms in the localization and concentration of endogenous neurotransmitters and their degradative enzymes and transporters, having the potential to clinically affect antidepressant pharmacodynamics (eg, drug-receptor interactions), particularly if they are sex steroid hormone responsive.[59–62]

Evidence for Change in Perinatal Phase 1 Metabolism: SSRIs

Some women will experience increased metabolism of SSRIs in late pregnancy and may require higher dosing, especially during the third trimester to maintain clinical benefits. Fluoxetine is predominantly metabolized by CYP2C9 to its active metabolite norfluoxetine, which is also pharmacologically active[63,64]; CYP3A4, CYP2D6, and CYP2C19 additionally

contribute to fluoxetine's metabolism.[63–67] Mean fluoxetine-metabolite ratio levels decrease between 20 to 26 weeks and 30 to 36 weeks' gestation, suggesting increased clearance during pregnancy, whereas postpartum fluoxetine-metabolite ratio levels increase, suggesting reduced clearance after delivery.[56] Similarly, higher maternal serum concentrations of fluoxetine and norfluoxetine in the postpartum period, compared with the third trimester, have been reported in women taking the same fluoxetine dose during both periods.[68] Decreased albumin levels in pregnancy may result in low plasma trough concentrations of highly protein-bound fluoxetine and norfluoxetine. Pregnancy-associated induced demethylation of fluoxetine by CYP2D6 may contribute to lower trough levels in pregnancy compared with the postpartum period.[69]

Sertraline and its main weakly active metabolite *N*-desmethylsertraline are substrates of several P450 enzymes, including CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Sertraline dose increases are often required early in the third trimester to treat emergent depressive symptoms or maintain euthymia[70] with some women experiencing increased drug metabolism from second to third trimester.[71]

Paroxetine has no known pharmacologically active metabolites and is predominantly metabolized via CYP2D6 and to a lesser extent via CYP3A4.[72] Steadily decreasing plasma levels of paroxetine and increasing depressive symptoms can occur in pregnancy in women with the CYP2D6-extensive or ultrarapid metabolizer genotype. Cytochrome P2D6 intermediate and poor metabolizers may have increasing plasma levels of paroxetine throughout pregnancy.[73] Antidepressant accumulation in poor and intermediate metabolizers could potentially have adverse effects on the fetus.[74]

Citalopram, a racemic mixture of *R*- and *S*-citalopram, and the more pharmacologically active *S*-enantiomer, escitalopram, are metabolized via demethylation at CYP2C19, CYP2D6, and CYP3A4.[75,76] Main metabolites include desmethylcitalopram and didesmethylcitalopram. Doses of citalopram result in low trough plasma concentrations and metabolites during pregnancy but a significantly higher mean desmethylcitalopram-citalopram metabolic ratio compared with 2 months postpartum, suggesting induced metabolism during pregnancy.[53] Decreased level/dose ratios are associated with lowered drug efficacy and increased dose requirements in the second half of gestation.[55] Enhanced demethylation of citalopram by CYP2D6 may in part contribute to lower trough levels in pregnancy as compared with the postpartum period.[53,77]

Fluvoxamine is an achiral drug without clinically significant active metabolites. It undergoes metabolism via CYP2D6 and CYP1A2, and its main metabolite is fluvoxamine acid.[78] Pharmacokinetic studies during pregnancy were not found for fluvoxamine, but CYP2D6 activity has been shown to be increased during the third trimester and associated with decreased plasma drug concentrations and possibly diminished efficacy. This effect may be offset by the decreased CYP1A2 activity seen throughout pregnancy.[32]

Vilazodone is metabolized through CYP, mainly CYP3A4 with lesser contributions from CYP2C19 and CYP2D6, and non-CYP pathways.[78] Pharmacokinetic studies during pregnancy were not found for vilazodone, but the 2 main CYP isoenzymes responsible for

its metabolism demonstrate different overall changes in activity during pregnancy (ie, CYPC19 is reduced, and CYP2D6 is increased). The net effect of these changes on vilazodone during pregnancy is unknown.

Evidence for Change in Perinatal Phase 1 Metabolism: SNRIs

Venlafaxine is renally excreted and predominantly metabolized by CYP2D6 into *O*-desmethylvenlafaxine (ie, desvenlafaxine) and CYP3A4 to *N*-desmethylvenlafaxine. Although dose adjustments for sex are not generally indicated, women have higher dose-corrected concentrations than men.[79,80] An analysis that compared venlafaxine and its metabolic products in the first and third trimester to the postpartum period did not find concentration differences.[77] In contrast, 1 case report of a pregnant adolescent patient with bipolar II disorder treated with venlafaxine extended release and concomitant psychotropics reported 2-fold higher venlafaxine plasma levels in the postpartum than during pregnancy for the same dose.[57]

Unlike venlafaxine, desvenlafaxine is metabolized by CYP3A4 and is biotransformed to *N*,*O*-didesmethylvenlafaxine and a hydroxylated metabolite.[81] No pharmacokinetic studies during pregnancy were located for desvenlafaxine, but based on studies of CYP3A4 with other antidepressants, its metabolism has the potential to be reduced during pregnancy.

Duloxetine undergoes oxidative metabolism to 4-, 5-, and 6-hydroxy duloxetine by CYP2D6 and CYP1A2 and subsequent sulfate and glucuronide conjugation.[82] Nonpregnant women have a 64% higher average steady-state concentration than men, in part because of lower CYP1A2 activity in women.[83] No pharmacokinetic studies during pregnancy were located for duloxetine; however, 1 study reported duloxetine plasma levels in healthy lactating postpartum women comparable with those observed in healthy adults.[84]

Evidence for Change in Perinatal Phase 1 Metabolism: Other Antidepressants

Bupropion is extensively metabolized in the liver primarily by CYP2B6 to its main active metabolite, hydroxybupropion, and to threo- and erythrohydrobupropion via carbonyl reduction. During pregnancy, the placenta is a site of bupropion biotrans-formation, although carbonyl reduction is favored over oxidative biotransformation at this tissue site.[38,85,86] To a lesser extent, the CYP1A2, 2A6, 2C9, 2D6, 2E1, and 3A4 isoforms are also involved in bupropion metabolism.[87–89] Sex hormones inhibit up to 50% of bupropion hydroxylation via CYP2B6,[28] but the isoform shows high interindividual variability.[90] No systematic studies have been published that inform the pharmacokinetics or TDM for bupropion in pregnancy.

Mirtazapine is a tetracyclic antidepressant that is rapidly and completely absorbed. Major pathways of biotransformation include demethylation and oxidation followed by conjugation. Mirtazapine undergoes *N*-demethylation via CYP3A4 into the pharmacologically active desmethylmirtazapine and hydroxylation by CYP2D6 and CYP1A2. Because several metabolic pathways contribute to mirtazapine's biotransformation, genetic polymorphisms affecting activity in any one of the pathways are not hypothesized to result in clinically significant changes in mirtazapine plasma

concentrations[91–93]; however, CYP2D6 genotype may influence the concentrations of the enantiomers of mirtazapine and its metabolites.[94] Nonpregnant women exhibit longer elimination half-lives and a 15% lower drug disposition as compared with men.[95] Women show higher plasma concentrations compared with men,[94] but it is unknown if this results in differences in clinical efficacy. No pharmacokinetic studies during pregnancy were located for mirtazapine.

Trazodone is highly lipophilic, well absorbed, and extensively metabolized by the liver via hydroxylation, *N*-oxidation and *N*-dealkylation. Cytochrome P3A4 mediates the *N*-dealkylation that results in the formation of the active metabolite 1-*m*-chlorophenylpiperazine, which then undergoes hydroxylation by CYP2D6.[96] Therapeutic response has been associated with plasma trazodone concentrations of approximately 700 ng/mL but not with 1-*m*-chlorophenylpiperazine[97] plasma levels. Cytochrome P1A2 may also be involved in trazodone metabolism. Higher drug concentrations have been found in females[98] as compared with men. Pharmacokinetic data are limited to 1 case report of a pregnant patient treated with trazodone extended release of 150 mg/d in conjunction with other psychotropics. Plasma trazodone drug levels and the elimination half-life remained stable throughout pregnancy.[57]

Evidence for Change in Perinatal Metabolism: TCA

Tricyclic antidepressants metabolism is complex, and the pharmacokinetic changes observed in pregnancy likely reflect a summation of multiple metabolic effects including phase 1 and 2 metabolism. Generally, tertiary TCAs are demethylated by varying CYP450 enzymes into secondary TCAs and then undergo hydroxylation by CYP2D6 and glucuronidation by UGT. No pharmacokinetic or TDM studies during pregnancy were located for amitriptyline, desipramine, doxepin, protriptyline, trimipramine, amoxapine, or maprotiline.

A landmark study by Wisner et al[99] (1993) evaluated nortriptyline, clomipramine, and imipramine levels during pregnancy compared with nonpregnancy doses and levels. The final dose required during pregnancy to maintain therapeutic drug levels was an average of 1.3 to 2.0 times the dose required when not pregnant. Doses increased over the second half of pregnancy, especially in the third trimester. The third trimester was associated with rapid acceleration of the required dose increase,[99] and patients responded at plasma levels similar to those before pregnancy. Subsequent case reports of decreased plasma levels of nortriptyline and imipramine during pregnancy associated with recurrence of depressive symptoms confirm these findings.[100] Nortriptyline level/dose ratios rise during the 2 to 6 postpartum weeks and then decline and stabilize around week 11 and beyond (Table 1).[54]

Evidence for Change in Perinatal Metabolism of Mood Stabilizers: Lithium, LTG, CBZ, and VPA

Lithium—Although effects of pregnancy on the pharmacokinetics of antidepressant metabolism are variable, pregnancy more clearly affects the pharmacokinetics of lithium and some antiepileptic drugs (AEDs). Lithium is rapidly absorbed through the upper gastrointestinal tract and is almost exclusively renally eliminated without undergoing biotransformation. It is filtered through the glomeruli as a free ion, and 80% is reabsorbed

by the proximal tubule.[102,103] The pharmacodynamics of lithium is influenced by weight, renal function, age, coadministered medications, pregnancy, and lactation.[102,104] If the excretion of lithium is impaired, plasma ion concentrations can increase dramatically and precipitate toxicity.[103] Lithium has an established therapeutic drug level and a narrow therapeutic index of 0.6 to 1.2 mEq/L. Lithium clearance is 20% to 30% of the GFR and thus varies with GFR. During pregnancy, lithium increases by 30% to 50% because of increased renal blood flow and GFR, particularly in the last months of gestation,[50,104,105] causing plasma levels to decrease substantially, increasing the risk of maternal relapse.[106] At delivery, vascular volume rapidly decreases, and lithium clearance precipitously decreases to prepregnancy levels.[102,107]

Lamotrigine—Lamotrigine is the most widely prescribed AED for epilepsy in women of reproductive age[108] and is often used for maintenance treatment of bipolar disorder. Lamotrigine almost entirely undergoes hepatic glucuronic acid conjugation to its inactive metabolite LTG 2-*N*-glucuronide via UGT1A4. The sex steroid changes that occur in pregnancy increase phase 2 glucuronidation, which leads to increased LTG clearance.[109,110] 2-*N*-glucuronide/LTG ratios are reported to be 175% higher in the third trimester than at baseline. Less significant pregnancy-induced changes can also affect LTG levels, such as the degree of plasma protein binding, absorption, or transplacental transfer.[109,111]

Although there is substantial variability in the pharmacokinetics of LTG among women,[112–114] plasma concentrations consistently decline in pregnancy.[17,113–117] Lamotrigine clearance increases substantially at pregnancy onset[118] and continues to increase progressively through the third trimester.[17,18,113] Lamotrigine clearance potentially increases greater than 330% between preconception and the third trimester. An average dose increase of 250% is required to sustain therapeutic drug levels across pregnancy in women with epilepsy.[113] Beginning within days of delivery and continuing during the first weeks post-partum, LTG elimination rate drops rapidly and plasma concentrations increase dramatically.[109,113,115,116,119]

Carbamazepine—Carbamazepine is metabolized hepatically mainly via conversion to an active metabolite, 10,11-epoxide. The 10,11-epoxide is then metabolized to inactive compounds via glucuronidation, conjugation, and hydroxylation. Carbamazepine induces the P450 system, which can increase the metabolism of medications administered concurrently.[120] Carbamazepine clearance seems to increase in pregnancy,[121] with some studies reporting declining total concentrations of CBZ during the second and third trimester,[122–127] whereas others have not found a significant change in CBZ plasma clearance.[128] A study of 22 pregnancies reported a 42% decline in total plasma level and a 22% decline in free concentration.[129] The measurement of total plasma concentrations of CBZ may be misleading, given that studies suggest that although the total concentration of CBZ decreases significantly in pregnancy, free-CBZ levels may not change when compared with baseline[123,129] until delivery.[129] The decrease in protein binding is likely the cause of the decrease in total CBZ concentration because the free concentration is less affected.[129]

Valproic Acid—Of all the mood stabilizers, VPA has the greatest risk of teratogenicity including neural tube defect and neurocognitive impairment[15,16] and should not be

considered a first-line mood stabilizer in women of reproductive potential. However, VPA is often prescribed to women of childbearing age.[130] If the decision is made that VPA is the appropriate medication for perinatal mood stabilization, despite the risks, a number of measures can be taken to minimize fetal risk.

Highly protein bound, VPA pharmacologic activity is due to the free or unbound drug that crosses the blood-brain barrier. Valproic acid metabolism is complex because it undergoes a variety of different metabolic processes including mitochondrial beta-oxidation, CYP450-dependent processes including CYP2C9, CYP2C19, and CYP2A6, and glucuronidation. The half-life of VPA can be altered dramatically when administered with other medications that affect these pathways.[120]

An increase in VPA clearance resulting in a decrease in serum VPA levels has been observed particularly at the end of the third trimester.[128,131,133] The plasma concentration of VPA decreases by as much as 50% in the last few weeks of pregnancy; however, no significant changes have been found in unbound concentrations.[131,134] Concentration-dependent, VPA plasma protein binding decreases during pregnancy, and the free fraction increases as serum concentrations rise.[134] Although VPA is highly protein bound, several authors[133–136] have noted that while the total VPA levels decline, free levels do not and in fact remain unchanged or even increased. This suggests that both free and total plasma levels of VPA should be measured during pregnancy.[134,135] Valproic acid concentration decreases sharply in the immediate postpartum period (Table 2).[131]

DISCUSSION AND CLINICAL RECOMMENDATIONS

Antidepressants

The relationships between drug dose, TDM, and therapeutic effects are complex. Interindividual differences result from pharmacokinetic and pharmacodynamic variability, as well as genetic variants influencing the translation of proteins involved in metabolizing enzymes, drug transporters, and drug targets. At the level of the individual, perinatal changes in pharmacokinetics may or may not lead to changes in drug or metabolite levels. In addition, changes in drug or metabolite levels do not necessarily lead to alternations in clinical status.

Although SSRI concentrations fluctuate in pregnancy, the relationship between SSRI blood levels and clinical response is not well established.[142–144] Despite the lack of clarity in the relationship between SSRI blood levels and clinical response, data suggest that many pregnant women on antidepressant monotherapy may require dose increases, especially after 20 weeks gestation,[70] to treat depressive symptoms or maintain euthymia. Studies to date suggest broad interindividual variability in pharmacokinetic changes, with some but not all women experiencing faster SSRI metabolism in late pregnancy. To maintain euthymia for some women in late pregnancy, the SSRI dose may need to be increased almost 2-fold the dose required earlier in pregnancy.[70] Based on population data, at this time, there is insufficient evidence to support routine therapeutic blood level monitoring of antidepressants other than TCAs during pregnancy or the postpartum. Therapeutic drug monitoring is especially helpful with the TCA class, not only to monitor efficacy but also

toxicity. Clinical presentation, ideally in combination with the use of measurement-based care using standardized assessments[145–147] during the perinatal period, should primarily inform treatment decisions.

Although not studied with most non-TCA antidepressants, a potential patient-specific option is to use the individual woman's antidepressant level at a time when she is clinically asymptomatic as a target serum level during pregnancy. Although these antidepressants do not have an established therapeutic range, the individual woman's antidepressant level can be used as a guide for adjusting dosage during pregnancy and in the postpartum. However, studies are necessary to determine if this strategy would improve clinical care and whether it would be cost-effective. In 2004, the Food and Drug Administration suggested that physicians may consider tapering antidepressants in the third trimester to lower the risk of complications associated with late gestational exposure to SSRIs;[148] however, research does not support that discontinuing antidepressants in the third trimester diminishes the risk for neonatal symptoms.[149] Postpartum pharmacokinetic changes can result in the emergence of antidepressant adverse effects soon after delivery for women who are required for a dose increase during pregnancy. We recommend close clinical monitoring; if adverse effects emerge, the dosage can be lowered. We do not recommend immediately decreasing the antidepressant to the preconception dose in the absence of adverse effects.

Standards have been established for TDM for TCAs outside the perinatal period, and these serve as a basis for the measurement and interpretation of perinatal drug levels. During pregnancy, we recommend monthly monitoring of trough drug levels. Monitoring is especially important in the third trimester when dose increases may be necessary. In the postpartum period, we recommend careful monitoring for adverse effects and tapering to the preconception dose to mitigate adverse effects that may be associated with rising serum levels 2 to 6 weeks after delivery. We recommend checking a blood level whenever adverse effects emerge in the early postpartum or at least at week 6 when drug levels have been reported to peak before eventual stabilization around week 11.[54] Dose decreases may be indicated around week 6 to ameliorate adverse effects.

Mood Stabilizers

Women with bipolar disorder are at a heightened risk of relapse in the postpartum,[150] and therefore, clinical monitoring and optimization of treatment is imperative in late pregnancy and early postpartum. Pregnancy markedly affects the pharmacokinetics of both LTG and lithium, with plasma concentrations declining throughout pregnancy.[17,113–116] Therapeutic drug monitoring of AEDs is common in the treatment of epilepsy during pregnancy and may also be useful in the treatment of bipolar disorder during the perinatal period.

Therapeutic drug monitoring for lithium is well established, and in pregnancy, renal lithium clearance almost doubles, lowering serum concentrations and increasing the potential for relapse.[137] Several authors[106,138] recommend frequent TDM of lithium in pregnancy, up to monthly during pregnancy and up to weekly or biweekly in the last month of pregnancy. This frequency of monitoring may be indicated in women who have discontinued lithium and require reinitiation of the drug or in women with medical comorbidities affecting lithium absorption or clearance, such as hyperemesis gravidarum or dehydration. For

euthymic women on stable doses of lithium, we recommend checking a lithium level every trimester. Although 0.8 to 1.0 mEq/L is widely cited as a target effective level,[151] during pregnancy, women should be maintained at the lowest effective level.[139] Therapeutic drug monitoring can also be used to prevent women from lithium toxicity that can occur during immediate changes in physiology from acute illnesses such as gastroenteritis or other causes of volume depletion including hyperemesis gravidarum.[14] Although the evidence is equivocal, some authors recommend a sustained-release preparation during pregnancy[152] because they are often thought to produce more stable lithium levels than immediate release preparations.[104]

A maternal lithium level should be checked when women present for delivery, and adequate hydration should be ensured; nephrotoxins and nonsteroidal antiinflammatory drugs should be avoided.[153] Although some authors have recommended holding lithium at labor onset[137,139] or 24 to 48 hours before a scheduled cesarean delivery or induction,[104,106,107,139] this has not been found to mitigate adverse perinatal outcomes and infant complications. Others have recommended increasing hydration around delivery to avoid lithium toxicity.[104] Therapeutic drug levels should be checked 24 hours after delivery and then after each dose adjustment.[138]

At delivery, the risk of some lithium-induced perinatal complications may also be related to neonatal serum levels, especially for levels greater than 0.64 mEq/L.[139] Thus, using the lowest effective dose that is still within therapeutic range is recommended.[14] If neonatal lithium toxicity is suspected, the neonate's serum lithium level should be monitored. Lithium containing sampling devices should be avoided because they can yield inaccurate lithium levels.[154,155] Maternal GFR returns to pregravid levels immediately after delivery, and lithium levels return to preconception levels.[139] Vascular volume rapidly decreases by approximately 40% and renal lithium clearance decreases to prepregnancy levels, leading to increased serum concentrations and risk of maternal lithium toxicity;[106,107,156] thus, preconception doses should be restarted immediately after delivery.[14]

The American Academy of Neurology states that evidence supports active monitoring of LTG levels during pregnancy.[114] In view of the interpatient variability, some authors recommend the establishment of a baseline LTG concentration in any woman of childbearing age with epilepsy[116,118] and at least monthly monitoring during pregnancy and weekly during puerperium.[113,118] In contrast to the use of LTG in the treatment of epilepsy, LTG dosing in bipolar disorder is typically guided by clinical response. Blood levels are not routinely obtained, and target therapeutic blood levels are not defined because they are for other mood stabilizers such as lithium and VPA. However, an individual's preconception level could potentially be used as a guide for prophylactically increasing dosage during pregnancy[18,140,157] because LTG levels decline and potentially reduce risk of relapse and postpartum psychosis.[140,158,160]

If a preconception LTG level is not available for reference, increases in LTG dosing in late pregnancy should be driven by clinical response with a low threshold for increased dosage. Post-partum LTG toxicity is common and can occur in more than 25% of women, whereas LTG's elimination rate drops rapidly and plasma concentrations increase dramatically

immediately after delivery until 2 to 3 weeks postpartum.[109,113,115,116] Empirically tapering to the preconception dose in the postpartum period can reduce toxicity.[111,113,116]

For women receiving CBZ, both free and plasma concentrations should be monitored[122–124,129] in combination with close clinical monitoring; both should guide dose adjustments.[129] Similar to the other mood stabilizers, the lowest effective dose should be used in pregnancy. After delivery, the dose should be tapered rapidly to avoid toxicity and maintain prepregnancy CBZ levels.

For women who plan to conceive while using VPA for mood stabilization, baseline VPA levels should be obtained before conception to identify the optimal serum concentration for mood stabilization and guide the dose adjustments during pregnancy. Free and plasma levels should be checked at least monthly to maintain the preconception serum concentration.[141] Valproic acid easily transfers across the placenta, and congenital malformations correlate with maternal VPA concentrations and daily dose.[131,161,163] The lowest effective dosage of VPA, preferably less than 1000 mg/d, should be used in pregnancy.[135] To decrease the incidence of neural tube defects, all women of childbearing age taking most anticonvulsants should be treated with up to 4 to 5 mg/d of folic acid. After delivery, the dose should be tapered rapidly to avoid toxicity buildup and to maintain preconception VPA levels.

Therapeutic drug monitoring can also be used to mitigate some of the risks associated with drug interactions, which lithium, LTG, VPA, and CBZ are all very sensitive to. Therapeutic drug monitoring is imperative to monitor for changes in lithium levels that can occur secondary to drug-to-drug interactions. Lamotrigine, VPA, and CBZ are AEDs that can induce or inhibit other drugs and thereby diminish or enhance the pharmacologic effect of other drugs. Carbamazepine induces enzyme activity and thus decreases drug concentrations and the effect of other drugs. In contrast, VPA inhibits enzyme activity and increases drug concentrations, which carries the risk of causing drug toxicity. Therapeutic drug monitoring can be used to monitor drug concentrations and optimize treatment.[164]

Further Recommendations for Clinical Care

The use of antidepressant or mood-stabilizing medications during pregnancy involves complex clinical decisions based on the risks and benefits of medications as well as clinical status, history, and treatment preferences of each woman.[4,5,106,113,139,165] Data-driven clinical recommendations for frequency of clinical monitoring and TDM across pregnancy and the postpartum are urgently needed, whereas therapeutic ranges have typically been derived in nonpregnant populations and have not yet been validated in pregnancy.[166] The available data support frequent clinical monitoring of symptoms throughout pregnancy and postpartum; therefore, this is strongly recommended.

Further research is critically needed to examine how TDM of antidepressants and mood stabilizers in pregnancy will inform the efficacy and safety of psychotropic use for women and their infants. The literature reflects great interindividual variability regarding the effects of pregnancy on metabolism of medications where such data are available. Research is required to identify biomarkers that would specifically inform which women are at risk for

clinically significant pharmacokinetic changes in their medications across pregnancy and postpartum.

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TABLE 1

Change in Perinatal Antidepressant Phase 1 Metabolism and Indications for Perinatal Dose Adjustments

Antidepressant	Main Isoenzymes Involved in Metabolism[101]	Evidence of Change in Metabolism in Pregnancy
Dose increase may be indicated after 20 weeks gestation		
Citalopram	CYPC19, CYP2D6, CYP3A4	Increased drug metabolism between 20 weeks and delivery[53,55]
Clomipramine	CYP1A2, CYP2C19, CYP2D6, CYP3A4	Decreased plasma levels[99,100]
Imipramine	CYP1A2, CYP2C19, CYP2D6, CYP3A4	Decreased plasma levels[99]
Dose increase may be indicated in third trimester		
Fluoxetine	CYP2C9, CYP2C19, CYP2D6, CYP3A4	Higher maternal serum concentrations in the postpartum period compared with the third trimester[68,69]; mean ratios of fluoxetine to metabolite levels decreased during pregnancy.[56]
Fluvoxamine	CYP1A2, CYP2D6	Increased CYP2D6 activity in third trimester[32]
Nortriptyline	CYP2D6	Decreased plasma levels[99,100]
Paroxetine	CYP2D6, CYP3A4	Plasma levels may increase or decrease, varies with metabolizer genotype.[73,74]
Sertraline	CYP2B6, CYP2C9, CYP2C19, CYP2D6,CYP3A4	Marked heterogeneity in range of pharmacokinetic changes[70,71]
Dose adjustments generally not indicated		
Venlafaxine	CYP2D6, CYP2C19, CYP3A4	Metabolism consistent across pregnancy and the postpartum[77]; report of 2-fold increase plasma level in postpartum[57]
Insufficient data on need for dose adjustment		
Amitriptyline	CYP1A2, CYP2C19, CYP2D6, CYP3A4	
Bupropion	CYP2B6, CYP2D6, CYP1A2, CYP2A6, CYP2C9, CYP2E1, CYP3A4	
Desipramine	CYP2D6	
Desvenlafaxine	CYP3A4	
Doxepin	CYP1A2, CYP2D6, CYP2C19, CYP3A4	[Insufficient data for change in metabolism in pregnancy.]
Duloxetine	CYP1A2, CYP2D6	
Mirtazapine	CYP1A2, CYP2D6, CYP3A4	
Trazodone	CYP3A4	
Trimipramine	CYP2C19, CYP2D6, CYP3A4	
Vilazodone	CYP3A4, CYP2C19, CYP2D6	

TABLE 2

Change in Perinatal Metabolism of Mood Stabilizers and Recommendations for TDM or Dose Adjustments

Mood Stabilizer	Main Mechanisms of Metabolism	Evidence of Change in Metabolism in Pregnancy	Recommendations for Clinical Monitoring and TDM
Lithium	GI absorption Excreted via urine	Increased renal blood flow and GFR[50,105] Increased renal lithium clearance[137] Lower serum concentrations[137,138]	TDM up to monthly during pregnancy and up to weekly or biweekly in the last month of pregnancy[106,138] for women who are required for reinitiation of lithium and have unstable mood symptoms or concurrent medical conditions affecting lithium serum concentrations TDM each trimester for euthymic women on stable doses of lithium Maintain lowest effective level.[139] Check maternal lithium level before delivery. Check therapeutic drug levels immediately after delivery and for any clinical worsening or change in clinical status related to obstetrical, medical, and psychiatric condition.[138] Once medically stable, restart preconception dose.
LTG	Hepatic glucuronic acid conjugation via UGT1A4	Increased phase 2 glucuronidation[109] LTG clearance increases and plasma concentration decreases across pregnancy.[109,111,112,114–116,118] Postpartum LTG elimination rate drops rapidly.[109,113,115,116]	Mean dose increase of 250% required to sustain therapeutic drug levels across pregnancy in women with epilepsy[113] Use option preconception drug level as a guide for adjusting dosage.[140] Use lowest effective dose[15] Empirically taper to preconception dose in the postpartum period[111,113,116]
CBZ	CYP3A4, CYP2B6, CYP2C8, CYP2E1, CYP2C9, CYP1A2, UGT Excreted via urine (72%) and feces (28%)	Data are conflicting; CBZ clearance may increase in pregnancy, whereas total CBZ concentration decreases significantly in pregnancy.[122–127] Free CBZ levels do not change when compared with baseline[123,129] until delivery.[129]	Both free and plasma concentrations should be monitored.[122–124,129] Lowest effective dose should be used.[15] After delivery, the dose should be tapered rapidly to avoid toxicity buildup and maintain prepregnancy CBZ levels.
VPA	Highly protein bound; complex hepatic metabolism via mitochondrial beta-oxidation, CYP450 (eg, CYP2C9, CYP2C19, and CYP2A6), and glucuronidation	Plasma concentration decreases.[128,131–133] No significant changes in free or unbound concentrations in pregnancy[131,134] Sharp decrease in VPA concentration in the immediate postpartum period[131]	Both free and total plasma levels of VPA should be measured during pregnancy.[134,135] Baseline VPA levels should be obtained before conception to identify the optimal serum concentration for mood stabilization. Use optimal drug level to dose adjustments during pregnancy. Levels should be checked at least monthly to maintain the preconception serum concentration.[141] After delivery, the dose should be tapered rapidly to avoid toxicity buildup and to maintain preconception VPA levels.

GI indicates gastrointestinal.