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Psychotropic Treatment During Pregnancy: Research Synthesis and Clinical Care Principles

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Abstract

Background: Psychiatric illnesses are common in women of childbearing age. The perinatal period is a particularly high-risk time for depression, bipolar, and anxiety disorders.
Methods: The scope of the public health problem of perinatal mental disorders is discussed followed by an examination of the specific research methods utilized for the study of birth and developmental outcomes associated with maternal mental illness and its treatment. The evidence on exposure to common psychotropics during pregnancy and breastfeeding is reviewed.
Results: Selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitor medications are not associated with higher rates of birth defects or long-term changes in mental development after adjustment for confounding factors associated with underlying psychiatric illness. Lithium exposure is associated with an increased risk for fetal cardiac malformations, but this risk is lower than previously thought (absolute risk of Ebstein's anomaly 6/1,000). Antipsychotics, other than risperidone and potentially paliperidone, have not been associated with an increase in birth defects; olanzapine and quetiapine have been linked with an elevated risk of gestational diabetes. Due to the dramatic physiological changes of pregnancy and enhanced hepatic metabolism, drug doses may need to be adjusted during pregnancy to sustain efficacy. Untreated maternal psychiatric illness also carries substantial risks for the mother, fetus, infant, and family.
Conclusions: The goal of perinatal mental health treatment is to optimally provide pharmacotherapy to mitigate the somatic and psychosocial burdens of maternal psychiatric disorders. Regular symptom monitoring during pregnancy and postpartum and medication dose adjustments to sustain efficacy constitutes good practice.

Keywords: psychotropic medications, antidepressants, SSRI, perinatal depression, pregnancy, breastfeeding

Introduction

The perinatal period is a high-risk time for the occurrence of maternal mental illnesses such as major depressive disorder (MDD), bipolar disorder, and anxiety disorders. Suicide remains a leading cause of mortality in the postpartum period and accounts for 20% of maternal deaths in the first year after birth.[1] With increasing recognition of the public health impact of perinatal illness, organizations such as the U.S. Preventive Services Task Force, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics have recommended screening women for mood and anxiety symptoms during pregnancy and postpartum and either treating (in the role of primary care physician) or referring for psychiatric treatment.[2–4]

Maternal mental illness during pregnancy has been associated with adverse perinatal outcomes, including placental abnormalities, small-for-gestational-age fetuses, fetal distress, preterm delivery, neonatal hypoglycemia, adverse neurodevelopmental outcomes, and disordered attachment.[5–7] Pregnant women with untreated mental illness also are more likely to engage in high-risk behaviors, such as indiscriminate sex and exposure to sexually transmitted infections, smoking, alcohol and drug use, less prenatal care, and poor nutrition.[8] Assessment and treatment for perinatal psychiatric disorders results in better outcomes for the woman, her fetus/infant, and family. Medications and psychotherapy are both evidence-based approaches to the treatment of peripartum depression. However, pregnant women have been labeled ''the last therapeutic orphans'' with respect to pharmacotherapy due to a dearth of research to guide care.[9]

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A well-intentioned focus on limiting harm to the fetus/infant has resulted in a public health inequity of limited data regarding the drug treatment of maternal diseases.

Methods

Consistent with the aim of the 2015 U.S. Food and Drug Administration (FDA) Pregnancy and Lactation Labeling Rule,[10] clinicians must assess the risks of untreated illness as well as potential adverse effects of pharmacotherapy with respect to pregnancy and infant outcomes. Perinatal outcomes include miscarriage, major birth defects, preterm birth, stillbirth, neonatal adaptation signs, and behavioral and developmental effects. These domains are impacted by both psychiatric disorders and the medications used to treat them. Large, well-designed studies that include management of confounding variables are particularly important in establishing the validity of associations between drugs and outcomes.

In this study, recent research on the use of common psychotropic medications in perinatal women is reviewed. Research and statistical methods required to interpret this literature are discussed. We review medications by class with an emphasis on antidepressants. Summary information for mood stabilizers, antipsychotics, stimulants, benzodiazepines, and sleep aids is also provided.

Results

Antidepressants

Peripartum depression is common and an estimated 1 in 7 women experience an episode during pregnancy or in the first several weeks postpartum.[11] Many depressive episodes that are identified after birth began before pregnancy (26.5%) or during pregnancy (33.4%) and the majority (40%) begin early postpartum—within 4–6 weeks of birth.[11] The risk for recurrence of depression is elevated during pregnancy, especially for women who discontinue antidepressant medications proximal to conception. Pregnant women who discontinued were more likely to experience a relapse than women who maintained their antidepressant during pregnancy (68% vs. 26%, respectively).[12] Relapses emerged rapidly; 50% relapsed during first trimester and 90% by the end of second trimester.[12] Nonpharmacologic treatments, such as bright light therapy[13] and psychotherapy,[14] are evidence-based treatments for depression with established efficacy in the perinatal period. Interpersonal psychotherapy and behavioral activation have specific evidence of efficacy in this population.[14–16] These nonpharmacologic treatments are often combined with antidepressant medications in women with moderate-to-severe depression and are appropriate as monotherapy for mild depression or due to patient preference.

Medication use during pregnancy is common. During the first trimester, 82.3% of women take at least one medication (prescription or over the counter, such as acetaminophen, antiemetics, antibiotics, antiepileptic, and antihypertensive agents, not including vitamins or iron[17]) and 48.8% of women take a prescription medication.[17] Nearly 30% of women have exposure to four or more medications (prescription or over the counter) during the first trimester.[17] Twenty percent of women will experience a major depressive episode at some point in their lives.[18] Given the high prevalence of depression, antidepressant use during pregnancy is also common and nearly 8% of pregnancies have exposure to an antidepressant[17] and 2.8% of women maintain treatment throughout pregnancy.[19]

Birth defects. The baseline rate of congenital malformations in the general population is estimated at 3%–5%.[20–22] Clinicians prescribing medications during embryogenesis (the first 8 postconception weeks) must determine whether the medication will increase the risk for malformations. Accurately quantifying the level of risk requires large studies that adequately consider confounding variables that may also influence reproductive outcomes. Huybrechts et al. applied a robust study design to a number of reproductive pharmacoepidemiology studies to assess pregnancy outcomes associated with psychotropic medications. Utilizing the Medicaid Database, they included a large number of exposed study participants and adjusted for potential confounders such as sociodemographic disparities, maternal heath factors, maternal age, parity, smoking history, severity of depression, and history of premature births. They applied propensity score matching to adjust for variables that impact both exposure and outcomes.

In Huybrechts et al.'s study using the Medicaid Database and including 949,504 pregnant women, 6.8% were prescribed an antidepressant during the first trimester.[23] The offspring of women exposed and unexposed to antidepressants in the first trimester were compared and the rate of cardiac defects was determined. The unadjusted analyses showed an odds ratio (OR) of 1.25 with a 95% confidence interval (CI) of 1.15–1.36. The CI does not include 1, which suggests that *in utero* exposure to an antidepressant was associated with a 25% increased risk of developing a cardiac defect. However, restriction of the subject pool to women with only MDD and who were exposed versus unexposed to an antidepressant resulted in a reduction in the OR to marginal significance, (adjusted odds ratio [aOR] = 1.12, 95% CI = 1.01–1.25). Performing propensity score stratification within the depression restricted group further attenuated the OR to nonsignificance (OR = 1.02, 95% CI = 0.90–1.15). This careful analysis illustrates the importance of accounting for confounders when assessing reproductive outcomes. Although a woman taking an antidepressant is at greater risk for having a child with a cardiac defect, that risk is largely secondary to factors associated with the underlying depressive disorder and its sequelae and not attributable to the medication. Antidepressants were also examined individually and none was associated with a significant risk of cardiac defects.

Preterm birth. Both depression and antidepressants have been associated with preterm birth, which is defined as birth before 37-0 gestational weeks. Patients with MDD and who are medicated or unmedicated have higher rates of preterm birth (23% and 21%, respectively) than women without MDD or antidepressant treatment (6% preterm birth).[24] In a systematic review and meta-analysis of preterm birth and antidepressant medications, an adjusted pooled OR for the risk of preterm birth following antidepressant exposure in pregnancy was 1.61 (95% CI = 1.26–2.05; $p = 0.039$) after adjusting for confounding variables and risk of maternal psychiatric illness.[25] In contrast, a population-based Scandinavian

study reported that selective serotonin reuptake inhibitors' (SSRI) use was associated with a significantly lower rate of late preterm birth (OR = 0.84, 95% CI = 0.74–0.96), very preterm birth (OR = 0.52, 95% CI = 0.37–0.74), and cesarean section (OR = 0.70, 95% CI = 0.66–0.75) compared with individuals with psychiatric disorders who were not taking an antidepressant. A potential explanation for this finding is that successful treatment of depression is protective; however, a measure of depressive symptoms was not included.[26] These results suggest that determining the association between antidepressant exposure and preterm birth is challenging and depends upon disentangling contributions from medication versus disease exposure.

Neonatal adaptation syndrome. Neonatal adaptation syndrome (NAS) refers to signs exhibited by the newborn exposed *in utero* to SSRI. No consensus definition or measurement tool has been developed for SSRI-associated NAS. Signs include neuromuscular, central nervous system, gastrointestinal, and respiratory difficulties. Malm et al. observed an increased risk for neonatal complications in infants exposed to SSRI medications, including a risk for lower Apgar scores (OR = 1.68, 95% CI = 1.34–2.12) and admission to the neonatal intensive care unit (OR = 1.24, 95% CI = 1.14–1.35).[26]

NAS occurs in 0%–30% of infants exposed to antidepressants *in utero*.[27] This highly variable rate is indicative of the difficulty measuring and describing the syndrome and the lack of understanding of the mechanism. It occurs more commonly in infants exposed to paroxetine, venlafaxine, and fluoxetine than in infants exposed to other serotonergic antidepressants. Paroxetine is highly anticholinergic, venlafaxine has a well described discontinuation syndrome, and fluoxetine and its active metabolite have long half-lives, which tax the newborn's metabolic capacity.

The mechanism underlying SSRI-associated NAS has not been elucidated. It has been hypothesized to be secondary to rapid drug decline after birth (withdrawal), increased serotonergic tone as a side effect from the medication (serotonin toxicity/syndrome), and neurobehavioral teratologic effects in the fetal central nervous system. These mechanisms are not mutually exclusive and are associated with the pharmacologic characteristics of the specific drug. Concomitant mixed exposure to benzodiazepines and serotonergic antidepressants *in utero* results in a higher likelihood of NAS signs, and some of these persist at 30 days postdelivery.[28]

Developmental outcomes. Serial assessments using the Bayley Scale of Infant Development at 12, 26, 52, and 78 weeks of age[29] were completed to compare infants with *in utero* exposure to SSRI to those with exposure to maternal depression (without antidepressant treatment) and infants without exposure to either antidepressants or maternal depression. At 26 and 52 weeks of age, SSRI-exposed infants had significantly lower psychomotor developmental scores compared with infants exposed to depression or neither exposure. By the 78-week assessment, no difference in psychomotor function among the groups remained. There were no differences in cognitive development scores between the groups and this finding has been consistent across several investigations.[29–33] Standardized assessments of intelligence quotient (IQ) and behavioral symptoms in 3 to 7-year-olds have not demonstrated significant differences between individuals exposed versus nonexposed to SSRI.[34]

In utero exposure to antidepressants was associated with higher rates of speech and language disorders in children studied in early adolescence compared with children whose mothers had a history of maternal psychiatric disorders without antidepressant treatment.[35] Severity of maternal depression prenatally and in childhood has also been found to predict internalizing and externalizing behaviors in offspring; however, SSRI exposure *in utero* was not associated with these behavioral concerns.[34] A higher incidence of depression has been reported in teenagers with a history of gestational exposure to antidepressant medications and this remained significant after efforts to control for severity of maternal depression.[36] The same authors did not find a significant association with *in utero* exposure to antidepressants and later development of attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder, after controlling for maternal psychiatric illness.[36]

Metabolism and pharmacology considerations during pregnancy. The goal is to reduce the burden of maternal disease through optimal treatment of pregnant women. The disease must be treated maximally to adequately decrease the disease burden and justify the fetal medication exposure. Unfortunately, many women who take antidepressant medications continue to experience depressive symptoms. This exposes the fetus to both maternal depression and to antidepressant medications. Inadequate dosing of antidepressant medications in an effort to limit the medication exposure to the fetus contributes to partial response. Additionally, the plasma concentrations of the majority of antidepressant drug concentrations decline across gestation. The plasma concentrations of paroxetine, fluoxetine, sertraline, citalopram, and escitalopram decline across pregnancy secondary to physiological changes.[37–40] Doses of these antidepressants may need to be increased during second and third trimester to maintain adequate control of depressive symptoms.

Weight gain, plasma volume expansion, and increases in renal clearance impact drug concentrations. Plasma volume increases to 40% above in nonpregnant state and peaks around 32 weeks of gestation. Renal blood flow and glomerular filtration rate increase, which result in an elevated renal clearance of around 30%–50% during pregnancy. Additionally, total body water increases and drug concentration decreases. A major factor that contributes to changes in plasma concentrations in pregnant women is the activity of cytochrome P (CYP) 450 isoenzymes. The activities of specific CYP 450 enzymes vary during pregnancy and contribute to changing plasma drug concentrations.[41] CYP3A4, CYP2B6, and CYP2C9 are characterized by increased activity in pregnancy.[42–45] CYP2D6 demonstrates variable changes in pregnancy.[37,46] During pregnancy, CYP2D6 extensive and ultrarapid metabolizers experience higher enzymatic activity while intermediate and poor CYP2D6 metabolizers have lower enzymatic activity.[37] CYP1A2 and CYP2C19 have been associated with lower activity in pregnant women.[39,41,42,47] After birth, metabolism reverts to prepregnancy status within 11 weeks after delivery and this can result in drug concentrations increasing postpartum.[39,40,48] Given the dramatic changes during pregnancy,

symptoms must be monitored monthly so that prescribers can respond and adjust drug doses to maintain remission.

Ververs et al. demonstrated that genetic polymorphisms in CYP2D6 affect the valence and magnitude of plasma concentration changes in prengancy.[37] Serum concentrations of paroxetine, which is metabolized solely through the CYP2D6, were associated with CYP2D6 metabolizer genotype in pregnant women. Women who were extensive or ultrarapid metabolizers demonstrated decreasing paroxetine plasma concentrations throughout pregnancy and also reported an increase in mean depression scores during pregnancy. Plasma concentrations of intermediate and poor metabolizers increased during pregnancy. Side effects were not assessed, but the authors commented that the potential accumulation of paroxetine and increased fetal exposure may occur. Knowledge of a patient's CYP2D6 genotype may help guide management of paroxetine and other 2D6 substrates during pregnancy.

The NICHD-funded Optimal Medication Management for Mothers with Depression (OPTI-MOM),[49] aims to evaluate antidepressant doses, plasma concentration changes, and symptom expression across pregnancy and postpartum to generate treatment guidelines for proactive, rather than reactive, dose management across pregnancy.[50] Women taking SSRI medications during pregnancy are genotyped for CYP P450 metabolizer status (ultrarapid, extensive, intermediate, or poor metabolizer) on key CYP P450 enzymes (2D6, 2C19). Plasma concentrations are followed monthly, and depression/anxiety symptoms as well as side effects are monitored monthly.

Additionally, neonatal outcomes are recorded. A partner study, Fetal and Newborn Signs After Maternal Antidepressant Treatment (FANSMAT) focuses on measuring and understanding fetal and infant impact of SSRI exposure *in utero*. Participants have fetal ultrasound evaluations completed during the second and third trimesters to record fetal neurobehaviors and breathing movements. The infant is also observed during the first 24 hours of life and again during two home visits and when developmental assessments are completed. Once completed, OPTI-MOM and FANSMAT will yield data to improve care of women with perinatal depression and provide more information on fetal and infant implications of both the disease and its treatment.

Breastfeeding. Antidepressants are transferred to the infant through breastmilk, but the relative exposure is much lower than *in utero* exposure. Standard pediatric practice monitoring is appropriate for healthy, full-term infants receiving breastmilk from antidepressant-treated women.[51] Sertraline is the most studied antidepressant in breastfeeding and has minimal transfer into breastmilk. The relative infant dose (infant dose [mg/kg]/maternal dose [mg/kg]) of sertraline is $\sim$0.5% of the maternal dose.[51] Sertraline is well tolerated by breastfeeding infants.[52] Fluoxetine is present in the breastmilk at a higher concentration than other SSRI medications and the relative infant dose is up to 12% of the maternal dose.[51] However, it is generally well tolerated. Evidence to support disposal of breastmilk based on the timing of medication administration has not been published. Currently, limited data exist on the effects of SSRI medications and preterm infants with breastmilk exposure. There is one case report of serotonin syndrome in a late-preterm infant whose mother took fluoxetine 60 mg throughout pregnancy and continued during breastfeeding.[53] The infant's symptoms resolved with time and also after switching to formula. Fluoxetine has active metabolites with long half-lives and the *in utero* exposure was likely the substantial contributor to the infant's presentation rather than the relatively minimal exposure from breastmilk.

Mood stabilizers

Lithium is the standard treatment for bipolar disorder but its association with fetal cardiac malformations makes its use for pregnant women challenging. As a result, many psychiatrists, obstetricians, and patients avoid its use during pregnancy. However, women with bipolar disorder who discontinue treatment with lithium are at high risk for relapse. About 85% of women who discontinued lithium proximal to pregnancy experienced at least one mood episode during pregnancy.[54] When women discontinued their lithium abruptly upon learning they were pregnant, 50% had a recurrence within 2 weeks.[54]

With a large Medicaid database, Patorno et al. evaluated the risk for cardiac defects associated with lithium.[55] They compared first trimester lithium-exposed infants ($n = 663$) to those exposed to the mood stabilizer lamotrigine ($n = 1{,}945$) and to unexposed infants. Lithium-exposed infants had an increased relative risk of cardiac defects (adjusted relative risk (aRR) = 1.65, 95% CI = 1.02–2.68). The lamotrigine-exposed infants and the unexposed reference group had similar rates of cardiac defects. Interestingly, the relative risk of cardiac defects in the lithium-exposed infants increased as the daily dose of lithium increased, which demonstrates a dose–response effect and adds to the validity of the findings. However, higher doses are also likely to designate greater illness severity. Higher severity of illness potentially introduces other confounding variables such as lack of prenatal care or worse overall physical health. Additionally, serum lithium concentrations are more accurate measures of exposure than dose. Lithium use during first trimester is associated with an increased risk of cardiac malformations, including Ebstein's anomaly, but the magnitude of this effect is smaller than what has previously been reported.[55] The incidence of cardiac malformations after first trimester exposure to lithium is 2.41% with an absolute risk of Ebstein's anomaly of 6/1,000 compared with 1.8/1,000 in unexposed infants.[55] In pregnancies with first trimester lithium exposure, fetal echocardiography and a level 2 ultrasound are recommended at 16–18 weeks' gestation.[56,57]

Lithium serum concentrations change across pregnancy.[58] Prepregnancy concentration at stability as well as monthly concentration determinations during pregnancy are recommended.[59,60] Dosing can be changed from once daily dosing to twice or three-times-a-day dosing to stabilize plasma concentrations due to rapid clearance and the resulting decreased drug half-life in pregnancy.[61] Infants exposed to higher lithium concentrations (>0.64 meq/L) at the time of delivery are at risk for lower Apgar scores, longer hospital stays, and higher rates of central nervous system and neuromuscular complications.[61] This risk can be mitigated by discontinuing lithium 24–48 hours before delivery.[59,61] After delivery, fluid shifts and metabolism changes occur and maternal creatinine clearance returns to prepregnancy levels.

To avoid toxicity, lithium dose can be decreased back to the prepregnancy dose immediately after delivery and concentration monitored.

Lamotrigine is another commonly used mood stabilizer and has been studied extensively in pregnant women treated for epilepsy. While data from one study suggested an increased risk of cleft lip/cleft palate, extensive additional data have not replicated this finding.[62–64] Folic acid intake can be increased to potentially mitigate this risk. In the United States, 0.4–4 mg is recommended.[65–68] For preconception or pregnant women taking lamotrigine, our center generally recommends 1.2 mg (a prenatal vitamin which includes 800 mcg of folic acid with an additional 400 mcg of folic acid). Due to estrogen-induced metabolism, lamotrigine dose usually needs to be increased during pregnancy, sometimes as high as 330% of prepregnancy dose,[69] and then rapidly decreased postpartum.[70,71] Lamotrigine transfers at a relatively high rate to breastmilk. Infant plasma levels may reach 20% of maternal levels.[72] However, breastfeeding is generally well tolerated with good cognitive outcomes in the offspring.[73] There is one case of respiratory difficulties in an infant whose mother had lamotrigine toxicity due to an elevated plasma concetration.[74]

Carbamazepine therapy during pregnancy probably does not increase the risk of congenital malformations.[75] Valproic acid is a commonly used mood stabilizer outside of the peripartum period, but is contraindicated for use in pregnant women, women planning pregnancy, or women of childbearing age who are not protecting against pregnancy. *In utero* exposure to valproic acid is associated with an increased risk of major congenital malformations, dysmorphic features, behavioral issues in childhood, autism, and developmental delays, including lowering of IQ.[76–83]

Antipsychotics

Antipsychotics are used during pregnancy for FDA approved indications of schizophrenia, bipolar disorder, psychosis, and depression and are commonly used off-label for sleep and anxiety disorders.[84] An estimated 1.3% of pregnancies are exposed to atypical antipsychotics and 0.1% of pregnancies are exposed to typical antipsychotics.[85,86] In a population derived from a Medicaid database, antipsychotic use during the first trimester of pregnancy did not significantly increase the rate of malformations after adjusting for confounding variables. An exception was risperidone, which was associated with a small increase in overall malformations (aRR = 1.26, 95% CI = 1.02–1.56) and a nonsignificant risk specifically for cardiac malformations (aRR = 1.26, 95% CI = 0.88–1.81).[87] The study authors interpreted this as a potential safety signal for first trimester risperidone use. This relationship also may be applicable to paliperidone, which is the primary active metabolite of risperidone. Additionally, there is an increased risk of gestational diabetes with some atypical antipsychotics related to the adverse metabolic effects associated with these medications. Specifically, olanzapine and quetiapine have been associated with increased rates of gestational diabetes when continued during pregnancy.[88]

Stimulants

Adults with ADHD frequently develop coping strategies or work with therapists who specialize in nonpharmacologic treatment of ADHD. However, severe ADHD and other conditions may require treatment with stimulants during pregnancy. Investigators using the Medicaid database assessed the risk for birth defects with first trimester exposure to stimulants.[89] They noted a nonsignificant aRR for cardiac defects after exposure to methylphenidate [aRR = 1.28 (95% CI = 0.94–1.74)]. They pooled their results with health information collected from the Nordic Health Registries (Denmark, Finland, Iceland, Norway, and Sweden) that had similarly examined the risk of congenital malformations with intrauterine exposure to stimulants. Combining data sets allowed the investigator to achieve sufficient statistical power to identify a small effect. The U.S. data combined with the Nordic data resulted in an aRR of 1.28 (95% CI = 1.00–1.64). This suggests a small increase in cardiac malformations associated with first trimester exposure to methylphenidate derivatives. No increased risk of malformations with first trimester exposure to amphetamine-based derivatives was observed.

Benzodiazepines and hypnotics

Benzodiazepines are used by women both on an as-needed basis and as scheduled medications primarily for anxiety. While initial studies reported an elevated risk of cleft lip/cleft palate,[90] larger studies have not supported this association.[91,92] A large European database review, including nearly 2,000 pregnancies with first trimester exposure to benzodiazepines or other hypnotics found no increased risk in congenital malformations.[92] Benzodiazepines have been associated with neonatal adaptation signs, including respiratory distress, infections, cardiac abnormalities, and neurobehavioral changes, and these symptoms may persist up to a month postpartum.[28] Lorazepam is the preferred benzodiazepine in breastfeeding due to its relatively shorter half-life and lack of active metabolites.[93,94]

Insomnia is a common complaint during pregnancy. While melatonin is a reasonable choice of outside of pregnancy, there is a paucity of data on its use during pregnancy.[95] Trazodone at a low dose (50–150 mg at bedtime) is frequently used as a hypnotic. It does not increase the risk for congenital malformations and has acceptable safety data in breastfeeding.[96,97] Zolpidem has not been associated in an increased risk of congenital malformations[92,98] and has minimal excretion into the breastmilk and can be used in breastfeeding.[99] From a practical safety standpoint, parents should avoid cosleeping while taking sleep aids.

Clinical Guidance

At the time of initial assessment, clinicians should engage women in a discussion around their preferences for treatment and provide a referral to psychotherapy, when appropriate. For many women, mental illness is chronic and requires maintenance medications. None of the antidepressants is associated with an increased risk of congenital malformations and all are compatible with breastfeeding. The first-choice antidepressant for use during pregnancy is the one that has been most effective for the individual patient. The use of medications during pregnancy requires careful discussion and documentation so that both the prescriber and the patient have a clear understanding of the factors leading to the decision and its likely outcomes.[100] Documentation of perinatal

exposures (*i.e.*, medical conditions, substance use, medications, supplements, environmental contaminants), the risks of untreated psychiatric illness, as well as the risks of psychotropic exposure in pregnancy at the initial assessment and updating as relevant emphasizes the importance of the physician/patient discussion around treatment choices and provides medicolegal documentation.

Standardized measures (Patient Health Questionnaire-9 or EPDS; Generalized Anxiety Disorder-7)[101–103] completed at monthly visits across pregnancy generate quantitative data and monitoring for emergence of new symptoms. The Mood Disorders Questionnaire[104] is a useful tool to help screen for bipolar disorder and alert clinicians to potentially avoid the use of an antidepressant medication which could further destabilize a patient.[105] Patients can be engaged in mood tracking to self-monitor for symptom change.

Dosing changes in pregnancy and postpartum:

- If the antidepressant has been increased during pregnancy, the patient may experience side effects postpartum as her metabolism reverts to prepregnancy status. If depression and anxiety symptoms remain under good control, the dose can be tapered back to the prepregnancy dose within the first 4–8 weeks postpartum during a period of recovery and manageable stress.[39,40,48]
- If lithium dose is increased during pregnancy, this should be decreased to prepregnancy dose after delivery.[59,61]
- Lamotrigine doses that have been increased during pregnancy can be decreased back to prepregnancy dose within 10 days postpartum.[59,106] If the lamotrigine dose was increased four or more times during pregnancy, it should be decreased by 20%–25% immediately upon delivery to avoid toxicity.[107]

Resources that can be provided to the patient include: www.mothertobaby.org (drug information); www.postpartum.net (support and education network).

Conclusions

Psychiatric disorders during pregnancy and postpartum are common and 14% of women experience peripartum depression. Adequate evaluation and treatment of psychiatric disorders optimizes women's health, pregnancy, and infant outcomes. Treatment involves a discussion with the patient about the potential exposures of maternal mental health disorders as well as the risks and benefits of pharmacotherapy and documentation of this decision making. Large, well-designed studies that account for confounding variables are the most valuable for understanding risk and counseling patients regarding *in utero* exposure to psychiatric medications.

New conceptualizations of the impact of depression and drug exposure for maternal/infant pairs invoke a broad spectrum of potential outcomes. Some pairs may have highly favorable outcomes associated with drug exposure; for example, recent evidence suggests that citalopram exposure *in utero* reverses the adverse effects of maternal gestational stress on fetal brain development.[108] Antidepressant use during pregnancy may protect some fetuses from adverse effects of maternal mental illness. Other pairs may have adverse effects from drug exposure. As the literature evolves, identification of characteristics of mothers who are likely to benefit from pharmacotherapy (or alternatively to experience adversity) will provide physicians with critical information. The goal of perinatal mental health is to treat women optimally to decrease the burden of the maternal psychiatric disorders on the mother, fetus, infant, and family.

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