Pharmacological Treatment of Mood Disorders During Pregnancy: 2015 Update Summary

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Introduction

Treatment decisions during pregnancy should be as collaborative as possible between health care providers and patients, and take into account the individualized risks and benefits of treatment options. In addition to the reproductive safety of psychopharmacologic treatments, the past course of illness and treatment responses should be strongly considered. Specifically, the potential risks of medications must be assessed along with the risks of untreated psychiatric disorders across pregnancy and the postpartum. In assessing the risks and benefits, it is important to keep in mind that the baseline rate of congenital malformations (birth defects) is approximately 3% of all pregnancies in the U.S.[19] In most cases, causes are unknown. Decision making around treatments for psychiatric disorders in pregnancy requires consideration of what is known about the medications in pregnancy, the course and severity of the woman's disorder being treated, and exposures to the baby of both untreated maternal illness and medication. Psychiatric mood and anxiety symptom burden during pregnancy is a major risk factor for serious postpartum illness.

Unplanned pregnancies are common, and the reproductive safety of treatments should be kept in consideration when treating women of reproductive potential. General recommendations for healthy pregnancies should be included in the treatment plan, as some elements are particularly relevant for individuals with mood disorders. These include getting regular exercise, abstaining from tobacco, alcohol, and illicit substances, and maintaining a healthy diet and weight.[20]

Major Depressive Disorder (MDD)

Women are not protected from new onset or recurrence of mood disorders during pregnancy. The risk of relapse appears to be highest when effective maintenance medications are discontinued. Women with histories of postpartum depression and recurrent MDD are at elevated risk for postpartum depression, and women with bipolar disorder are at risk in the postpartum for mood episodes.[21-22] Women with bipolar disorder are also an at-risk group for postpartum psychosis.[23]

Consistent with guidelines from the American Psychiatric Association and the American College of Obstetricians and Gynecologists, psychotherapy is considered a first-line treatment in mild depression.[24] It is also an important part of the treatment plan for women with more severe illness, and the most evidence based non-pharmacologic treatment for depression in pregnancy. A modest amount of evidence supports other non-medication interventions, including acupuncture, massage therapy, and light therapy (which may trigger mania in individuals with bipolar disorder).

The U.S. Food and Drug Administration (FDA) has recently revised labeling for pregnancy and lactation.[25] The letter categories are being discontinued (new drugs will no longer have that categorization and older drugs will have the letter phased out of their labels). This reflects the major limitations of these labels, in which systematic human data are often not available. For example, medications without human data have received Category B labeling, while older drugs with

substantial data regarding pregnancy use typically have had a C or D category label. It is essential for a provider to know the specific safety and efficacy data for a particular medication, rather than use the letter categories for medication selection.

Antidepressants are considered first-line for moderate to severe MDD.[24] Selective serotonin reuptake inhibitors (SSRIs) have received a substantial amount of study in pregnancy regarding safety outcomes. Most studies do not show any increased risk of birth defects with SSRIs, although some studies have shown rare and inconsistent reports of malformations.[26-27] Data have been more inconsistent with paroxetine than other antidepressants, with some studies showing an increased risk of cardiovascular malformations. However, this risk has been seen inconsistently.

The most consistent risk seen in studies of SSRIs in pregnancy is poor neonatal adaptation or "withdrawal", which is reported to affect 20-30% of babies whose mothers used antidepressants in latter pregnancy.[24, 28] Symptoms commonly include jitteriness and fussiness, and other medical symptoms and/or more careful observation after delivery. Generally, these symptoms are mild and transient. While medication labels suggest women should consider stopping antidepressants in the third trimester due to this risk, medication discontinuation in women at-risk for serious postpartum illness may carry grave consequences for women and their newborns.

While SSRI antidepressants are best known in pregnancy, and limited information is available regarding SNRIs, the individuality of treatment responses is paramount. If a woman has had multiple past medication trials, then a woman who has had a good previous response to a lesser known antidepressant in pregnancy may be best treated with that agent to avoid multiple medication trials during pregnancy and to provide optimal benefits. Also, bupropion may be considered in women who are having difficulty with smoking cessation and/or are at risk for relapse of smoking. Antidepressant monotherapy is preferred when possible, although augmentation may be considered with partial treatment responses. Electroconvulsive therapy (ECT) may be considered with severe and/or refractory illness.

Antidepressants are generally considered reasonable for use during breastfeeding when clinically warranted, and SSRIs in particular are one of the best studied classes of medications during breastfeeding.[29] If a new antidepressant is needed, sertraline is often preferred, due to the amount of study in the breastfeeding context and demonstrated low levels of exposure as quantified in breast milk and infant blood levels.[30] If a woman has responded best to a different antidepressant, it should be strongly considered for her treatment in the postpartum.

Bipolar Disorder

Studies have consistently demonstrated that the risk of relapse for bipolar disorder mood episodes in women is at least as common during pregnancy as in the non-pregnant state, and that discontinuation of medications increases the risk of relapse during pregnancy.[22] The majority of women who stop taking mood stabilizers during pregnancy do experience relapse. Discontinuation of a mood stabilizer, especially abruptly during pregnancy, carries a high risk for mood episodes.[22] Risk of relapse is especially high in the postpartum, and if women have stopped medication for pregnancy, it is attenuated by prophylactic mood stabilizer treatment starting in late

pregnancy or immediately postpartum. Regardless of patient choice of treatment, close monitoring is warranted during pregnancy and the postpartum.

The anticonvulsant valproic acid carries a much higher risk of teratogenesis compared with most medications commonly used in psychiatry, with rates of neural tube defects ranging from 1 to 12%.[31] Longer-term neurocognitive deficits with valproate have also been observed after in utero exposure. Because very early pregnancy exposure can contribute to neural tube defects, it is highly recommended to avoid use in women of reproductive age (as many pregnancies are unplanned). Carbamazepine may also increase the risk of neural tube defects, although the risk appears lower than with valproic acid.[32]

The risk of teratogenicity with lithium appears much lower than was once historically thought.[33] While lithium is associated with a rare cardiovascular defect, Ebstein's anomaly, the absolute risk is low, reported as 0.05 - 0.1% risk with first trimester exposure. This is much lower than the risk of neural tube defects observed with valproate. Lithium clearance is increased during pregnancy, and for some women, dose increases may be required later in pregnancy to maintain therapeutic benefits.

Most studies do not show an increased risk of malformations after first trimester exposure to lamotrigine. While there has been a small and inconsistently reported risk of oral clefts with lamotrigine in the first trimester, the largest and newest reports from pregnancy registries did not find any association between oral clefts and lamotrigine.[31] A recent prospective study of children who were exposed to anticonvulsants in utero did not find any neurocognitive problems among those exposed to lamotrigine, with those exposed to lamotrigine having testing scores similar to the general population at ages 3 and 6 years old.[34] There are pharmacokinetic changes of lamotrigine metabolism during pregnancy – lamotrigine is cleared more rapidly during pregnancy, and some women will require higher doses in later pregnancy to maintain therapeutic benefits.

Regarding atypical antipsychotics as a class, there have been several prospective studies to inform safety during pregnancy.[35-36] Prospective studies have generally not shown an increased risk of major congenital malformations among babies whose mothers took atypicals during pregnancy, compared to controls. In one study, there were no differences in outcome between mothers who took atypicals compared to mothers who took older "typical" antipsychotics, although there was a small increased risk of cardiovascular malformations compared to healthy controls. At this time, we have limited data for each individual antipsychotic medication, with those that are newest having the least amount of information about use during pregnancy.

For women with bipolar disorder, breastfeeding is a complex issue. Mood stabilizers such as lithium are associated with adverse events in nursed infants, and atypical antipsychotics are not well studied in breastfeeding.[37] Lamotrigine has been studied, and demonstrated to yield higher blood levels in infants than are seen with SSRIs, but publications generally do not show clinical adverse effects in babies when breastfed while mothers were treated with lamotrigine.[38] Although valproic acid has received some study in breastfeeding women, it is strongly discouraged to start a woman of reproductive potential on valproic acid.

Sleep deprivation is destabilizing for those with bipolar disorder and may trigger a relapse during this vulnerable time. Thus for women with bipolar disorder, it is desirable that somebody else assist with the nighttime feedings in order to protect the mother's sleep and to promote euthymia. For mothers who choose to breastfeed while using medications with incomplete safety profiles during lactation, the baby should be monitored closely for signs of toxicity.

Postpartum Psychosis

The rate of postpartum psychosis is relatively rare, occurring in about 1 out of 1,000 births. However, the risk is much higher in women who have histories of bipolar disorder or a previous history of postpartum psychosis.[39] Previous psychiatric hospitalization is associated with an increased risk of postpartum psychosis. Postpartum psychosis must be considered an acute emergent condition. The mother and her baby are at risk of harm, as well as others in the family. Postpartum psychosis can include many symptoms of psychosis, including delusions, hallucinations, and paranoia. Women with postpartum psychosis are often agitated, and have many symptoms consistent with mania, such as decreased sleep, irritability, increased activity, and thought disorder.

Strategies for prevention and early intervention include psychoeducation of patient and family about postpartum psychosis. If mood stabilizers or antipsychotics were discontinued for pregnancy, they should be restarted immediately after delivery or during the third trimester. Because postpartum psychosis can occur very early in the postpartum, re-initiation of mood stabilizing medication may be too late after delivery, although there have not been adequate studies to advise exact timing of re-initiation.