Treatment of Mood Disorders During Pregnancy

The Primary Goals of Treating Mood Disorders During Pregnancy

- Optimal functioning of the mother, aiming for remission of illness, with a goal of achieving or maintaining euthymia, and relapse prevention and associated risks of morbidity and mortality, including risk of suicide.
  - ✦ As women with mood disorders are generally at-risk for postpartum psychiatric illness, and illness during pregnancy predicts illness in the postpartum, treatment during pregnancy may alleviate postpartum relapse or worsening of course of illness.
- Managing risk of medication exposure to the infant.
- Individualized consideration of risk/benefit ratio for treatment options, realizing that untreated illness itself poses risks to the mother and baby. Partner with the Ob/Gyn in prenatal care, nutrition and support.

Principles of Pharmacotherapy During Pregnancy

- Collaborative treatment decisions between the patient and her health care providers are essential, grounded on the evidence-base and guidelines that exist.
- Prioritize medications that have worked for the mother in the past.
- Minimize polypharmacy, if possible, as multiple exposures may increase risks to the fetus.
- Maximize non-pharmacologic therapies if effective, to augment pharmacotherapies. Psychotherapy is the most important effective non-medication treatment for mood disorders during pregnancy and the postpartum.
- If the patient has psychotic symptoms, antipsychotic medications are the most effective treatment and have no confirmed increase in birth defects.
- If suicide risk is significant, swift treatment is an especially high priority.

*Note. The U.S. Food and Drug Administration's (FDA) new labeling is detailed in the Pregnancy and Lactation Labeling Rule (PLLR) or "final rule" at -**http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm**. The use of letter labeling (i.e., A, B, C, D, X) for pregnancy categories is being phased out by the FDA. This change is based on the major limitations of the letter category system. Until June 2015, when new drugs were improved by the FDA, the letter was determined based on available data at the time of approval, without a requirement for human pregnancy data. Thus, the letters were assigned primarily after review of available animal data. Also, the letters do not take into account the relative amount or quality of the body of data available for each medication, and do not take into account the risk of the untreated condition for the mother and fetus. Also, context has not historically been provided when risks are reported and any potential risks need to be compared to their occurrence in the general population, and ideally among women who suffer from the disorder for which the drug is utilized. Important in the risk/benefit discussions with patients, pregnancy itself is inherently risky, and obstetrical complications are common. The rate of birth defects in the U.S. approximately 3%.*

Treatment of Major Depressive Disorder in Pregnancy

Refer to the treatment guidelines and dosage tables for major depressive disorder (See pages 20-23). Begin with the lowest therapeutic dose.

Level 1 Initial Treatment:

- Mild to moderate depression may respond to non-pharmacological treatment alone, but severe depression should be treated with effective medication
- Psychotherapy is the most evidence-based non-pharmacologic treatment for depression during pregnancy and the postpartum period
- There are modest data for the use of light therapy, acupuncture, and massage, for mild depression in pregnancy. Light boxes carry the risk of triggering mania or hypomania if a patient has a bipolar disorder
- Monotherapy with a selective serotonin reuptake inhibitor (SSRI) is preferred (with the exception of paroxetine, which may have an increased risk of cardiac and other malformations)*
- Consider bupropion in smokers who are trying to quit/abstain during pregnancy
- If only partial response to first agent, augmentation should be considered

**If a woman has failed medication trials during the course of her illness, a medication that has been most helpful to her may be considered as a first-line option, even if it is not an SSRI. Data (or lack of data) should be discussed with the patient.*

Level 2 If Level 1 is ineffective and/or not well tolerated:

- Switch to a different SSRI
- Consider monotherapy with a serotonin-norepinephrine reuptake inhibitor (SNRI) (good efficacy but less data on birth defects)
- Consider augmenting with a second generation antipsychotic (SGA)

Level 3 If Levels 1 and 2 are ineffective and/or not well tolerated:

- Consider electroconvulsive therapy (ECT): it has proven efficacy in severe depression and can be done with proper safeguards in pregnant women

Level 4 If Levels 1, 2 and 3 are ineffective and/or not well tolerated:

- Augmentation strategies with agents other than SGAs (avoid known teratogens such as valproic acid at any time, and lithium during the first trimester)
- Transcranial magnetic stimulation (TMS) is well-tolerated but has little evidence in this population

Note. Avoid benzodiazepines if possible, although the decision should be made on a case by case basis. There are inconsistent data suggesting that in the first trimester, there may be a small increased risk of oral clefts, and high doses in late pregnancy may be associated with a floppy infant syndrome at birth and withdrawal afterwards.

Herbal or "natural" supplements (for example, St. John's Wort) should not necessarily be considered safe during pregnancy and warrant the same degree of study as pharmaceuticals in pregnancy. They are less regulated and there is a variable degree of quality assurance regarding manufacturing and purity, and efficacy does not require establishment before they are marketed.

Treatment of Bipolar Disorder in Pregnancy

Refer to the treatment guidelines and dosage tables for bipolar disorder (See pages 11-16).

Begin with the lowest therapeutic dose. Treatment decisions regarding mood stabilizing medications during pregnancy are complex. For some agents, there is limited data on safety in pregnancy. Importantly, there is a lack of human pregnancy data for those agents that are currently in FDA category B. Also, some agents included in FDA categories C or D are often reasonable first-line treatment options, based on a woman's history of response, and characterization of known risks, which may be acceptable in consideration of severe past or present illness. Valproic acid remains the psychotherapeutic medication with the greatest risk of teratogenicity and long-term neurodevelopmental and cognitive deficits. It should be avoided during pregnancy.

Level 1 **Initial Treatment:**

- Second generation antipsychotic (SGA) monotherapy
- Lamotrigine monotherapy*
- Lithium monotherapy ONLY in known lithium responders (consider avoidance during the first trimester due to known association with Ebstein's anomaly)*

**Both lithium and lamotrigine are metabolized during the second half of pregnancy at higher than non-pregnant rates, and declines in blood levels are typical. Many women will need to have doses increased in latter pregnancy.*

Level 2 **If Level 1 is ineffective and/or not well tolerated:**

- Lithium monotherapy*
- Two drug combination – SGA + SGA, or SGA + mood stabilizer**

**Weigh benefits vs risks; has positive evidence of risk.*

***Although monotherapy is preferred in pregnancy, patient with bipolar are usually treated with more than one medication. Risks and benefits of polypharmacy should include consideration of what has helped stabilize the patient in the past, balanced with what is known about each medication's risks and benefits.*

Level 3 **If Levels 1 and 2 are ineffective and/or not well tolerated:**

- Consider electroconvulsive therapy (ECT) if symptom severity is warranted
- Carbamazepine*
- First generation antipsychotic (FGA)

**Weigh benefits vs risks; has positive evidence of risk.*

Note. Lithium is associated with a known risk of cardiac malformations in the first trimester, but the background rate is so low that even the increased risk means the overall rate is still low. Fetal echocardiogram is recommended when there has been lithium exposure in the first trimester.

Carbamazepine in the first trimester has been associated with fetal carbamazepine syndrome – dysmorphic features and major malformations.

Mood Disorders in the Postpartum Period

The new mother is at higher risk for mood episodes or psychosis in the immediate postpartum period, especially if her illness was untreated during pregnancy. Other risk factors include prior episodes, family history, and sleep loss. Close monitoring is advised. A history of bipolar disorder increases the risk of postpartum psychosis. If women stopped mood stabilizers for pregnancy, they should be reinitiated during the third trimester or immediately after delivery for prophylaxis of postpartum illness. Lithium is especially sensitive to the fluid shifts at delivery and should be monitored closely in the mother.

Interconception counseling regarding contraceptive options should occur during the course of pregnancy and at the first post-partum appointment and should include consideration of the use of a long acting reversible contraceptive (LARC) or another form of contraception to avoid an early unintended pregnancy post-partum.

Medications and Lactation

Breastfeeding is an important topic for women with mood disorders, as is sleep. Maternal mental health should be prioritized over breastfeeding. If a woman is exclusively breastfeeding, she is the only one that can feed the baby, and therefore her sleep will be greatly affected. Sleep deprivation is a major trigger for the relapse of mood episodes, particularly in bipolar disorder. It is strongly encouraged that women consider at least supplementing with bottles.

Most medications can cross into breast milk but their levels vary.

- Lithium is the medication most incompatible with breast feeding, due to relatively high levels found in neonates, and multiple adverse event reports.
- Carbamazepine has relatively higher levels in breast milk, with measurable levels in the infant.
- Clozapine also has relatively high levels in breast milk and may affect the infant's complete blood count (CBC)—since weekly blood draws are difficult in neonates, breastfeeding is not recommended in mothers on clozapine.

Formula feeding is an alternative that can allow the mother to use whichever medication works best for her.

Although some antidepressants are better studied in breastfeeding, or may have demonstrated lower levels in breast milk or infant blood levels, if a woman has responded especially well to an antidepressant in the past, it should be considered a reasonable option. Also, a woman should not switch from one antidepressant in pregnancy to another in the postpartum due to breastfeeding concerns. Staying on the same antidepressant limits the exposure that the baby has had to only one agent rather than two, and switching carries a risk of relapse.

Note. There is little benefit for "pump and dump" which significantly increases the new mother's stress levels and time spent feeding, decreases compliance with treatment, reduces the infant's drug exposure only slightly, and is not supported by clinical studies.

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.