Chapter 15
The Management of Bipolar Disorder During and After Pregnancy

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Abstract This chapter will discuss the issues of psychiatric management of bipolar disorder (BD) both during and after pregnancy. The risks and benefits of medication use during pregnancy will be discussed along with the risks of discontinuation of medications for pregnancy. Pharmacological treatments will be discussed in detail. The postpartum time period and its risks for depression, mania, and psychosis will be described, and recommendations for management during this critical time period will be detailed. Medication use during breastfeeding will also be discussed.

Keywords Pregnancy • Postpartum depression • Postpartum psychosis

15.1 Prevalence of Bipolar Relapse During and After Pregnancy

The risk of relapse of bipolar disorder (BD) during pregnancy appears to be approximately the same as at any other time in a woman's life. Viguera and colleagues (Viguera et al. 2000) retrospectively compared the risks of recurrence in pregnant and nonpregnant women with BD when tapered off lithium. They found no difference in the risks of recurrence between pregnant and nonpregnant women over the same time period with rates of 52 % in pregnant women and 58 % in nonpregnant women, thus demonstrating that pregnancy does not appear to increase the risk of relapse in women with BD (Viguera et al. 2000).

Although pregnancy appears to be risk-neutral for recurrence of mood disorders, it is not risk-free. This is especially true in women with preexisting mood disorders. Many women experience relapse during pregnancy—both on and off medication. In one study, approximately 50 % of women with either major depressive disorder (MDD) or BD reported significant mood symptoms during, after, or both during and after pregnancy (Payne et al. 2007). Further, the risk for relapse during pregnancy increases in the setting of discontinuation of medications. In women with BD,

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Viguera reported that pregnant women who discontinued mood stabilizers had a recurrence risk of 81–85.5 % while women who continued mood stabilizer treatment had a much lower risk of 29–37 % (Viguera et al. 2000, 2007). Similarly, the recurrence risk in a study comparing discontinuation of any mood stabilizer to lamotrigine treatment during pregnancy was 100 % in the group of women who discontinued medications (Andersson et al. 2003). The finding that at least 80 % of women with BD will relapse when taken off of medication suggests that treatment during pregnancy for many patients is necessary in order to prevent recurrence of psychiatric illness.

The risk of relapse for BD during the postpartum time period is clearly elevated, with many women developing a postpartum depressive, hypomanic, manic, or psychotic episode. In general, there are three types of postpartum mood disorders: Postpartum Blues, Postpartum Depression (PPD), and Postpartum Psychosis. Some women with BD may also develop a postpartum hypomanic episode. Postpartum Blues is a relatively common phenomenon occurring in up to 80 % of women, generally within a few days of labor and delivery. It is usually a self-limited process, resolving over the course of several days. Symptoms include tearfulness, mood lability, and feelings of being overwhelmed, but can also include more positive feelings of happiness or elation (Payne 2003). Postpartum Blues generally requires only supportive interventions such as social support, getting adequate sleep, and time to care for oneself. PPD, in contrast, is less common, occurring in 10–20 % of the general population. PPD meets DSM criteria for a major depressive episode lasting for at least two weeks (Campbell and Cohn 1991). The risk for PPD is increased in women with a history of MDD (Frank et al. 1987), BD, or PPD after previous pregnancies (Cox et al. 1993). While the etiology of PPD is not known, it is likely to be multifactorial with psychological factors, biological factors (including hormonal changes), and social factors all playing a role. Finally, Postpartum Psychosis is a rare phenomenon, occurring in approximately 0.1 % of all births (Kendell et al. 1987). It is more common in women with BD-I, occurring in up to 30 % of those who have children. Postpartum Psychosis is considered a psychiatric emergency and resembles a manic or mixed episode with decreased sleep, psychosis, and agitation (Jones et al. 2010).

15.2 Controversies Surrounding Psychiatric Medication Use During and After Pregnancy

The treatment of psychiatric disorders during pregnancy is complicated by a dearth of studies on what medications work, how changes in body weight and metabolism affect dosing, how to manage medications both during and after pregnancy, and also on what the long-term effects of exposure may be on the developing fetus. There has been a long and appropriate tradition of minimizing the use of medications during pregnancy—however, unlike medications used for purely medical

conditions such as asthma and hypertension, psychiatric medications are often considered expendable and are recommended for discontinuation. Abrupt discontinuation of psychiatric medication can result not only in withdrawal symptoms, but in relapse of the psychiatric illness; multiple studies have demonstrated that exposure to psychiatric illness in utero results in poorer outcomes for both mother and child. Relapse is especially common in women with BD.

One significant limitation of the literature is the fact that the use of psychiatric medications during pregnancy is essentially a "marker" for a population of women who have different risk factors than the general population of pregnant women, and these risk factors may influence the outcomes of studies attempting to examine the risks for a child exposed in utero to a particular psychiatric medication. For example diabetes, obesity, smoking, and substance use are more common in the psychiatric population than in the general population as a whole. Studies that have not controlled for the underlying psychiatric illness and its attendant risks may find associations between psychiatric medications and outcomes that are not due to exposure to the medication itself, but to other risk factors that are highly prevalent in the population of patients who take psychiatric medications during pregnancy. This not only complicates interpretation of the literature but also complicates recommendations for women who have psychiatric illness but no other inherent risk factors or behaviors. Studies in different populations of women with psychiatric illness and different levels of associated risk factors and behaviors need to be conducted with the goal of being able to make intelligent recommendations for individual patients.

Another area that is frequently overlooked in the risk-benefit analysis of whether or not to use psychiatric medications during pregnancy is the risk to the fetus and newborn associated with untreated maternal psychiatric illness. There is a strong literature demonstrating that, in addition to presenting risks to the mother, untreated maternal psychiatric illness during pregnancy is associated with poorer outcomes for the exposed child. For example, depression during pregnancy has been associated with low maternal weight gain, increased rates of preterm birth (Li et al. 2009), low birth weight, increased rates of cigarette, alcohol, and other substance use (Zuckerman et al. 1989), increased ambivalence about the pregnancy, and overall worse health status (Orr et al. 2007), including higher rates of preeclampsia and gestational diabetes (Field et al. 2006, 2010). In addition, prenatal exposure to maternal stress has been shown to have consequences for the development of infant temperament (Davis et al. 2005). Children exposed to perinatal (either during pregnancy or postpartum) maternal depression have higher cortisol levels than infants of mothers who were not depressed (Ashman et al. 2002; Diego et al. 2004; Essex et al. 2002; Halligan et al. 2004), and this finding continues through adolescence (Halligan et al. 2004). Importantly, treatment of depression during pregnancy appears to help normalize infant cortisol levels (Brennan et al. 2008). These findings may partially explain the mechanism for increased vulnerability to psychopathology in children exposed to depression in utero (O'Connor et al. 2005).

The literature regarding maternal illness during the postpartum period is even stronger. Adverse outcomes associated with PPD include lower IQ, slower language development, increased risk of Attention Deficit Hyperactivity Disorder, increased risk of behavioral issues, and increased risk of psychiatric illness in the exposed offspring (Grace et al. 2003). These findings often seem to get lost or even ignored in the debate of whether to use psychiatric medications during pregnancy. The inclination is to compare the risk of exposure to psychiatric medication to the risk of no exposure to medication rather than comparing the risk associated with medication exposure to the risk associated with maternal psychiatric illness which clearly also has consequences for the child. Psychiatric illness during pregnancy should be considered an exposure for the child in the same way that medication use during pregnancy is an exposure for the child.

15.3 FDA Categories: Past and Future

In December 2014, the US Federal Drug Administration (FDA) published the final version of the "Pregnancy and Lactation Labeling Rule" mandating changes to the content and format of prescription drug labeling as they pertain to use during pregnancy and lactation. The labeling changes went into effect on June 30, 2015—immediately for products submitted for FDA approval after that date and to be phased in for all other medications and products. The new labeling will contain Pregnancy and Lactation subsections, each of which will have three principal components: a risk summary, clinical considerations, and a data section. There will also be a new subsection entitled "Females and Males of Reproductive Potential." The goal is to provide relevant information that will help providers make prescribing decisions and counsel women regarding the use of the medication during pregnancy and lactation. This system attempts to include all currently available information to help the clinician weigh the risks and benefits of prescribing a particular drug during pregnancy.

Because the "Rule" will be phased in over time, we will provide a brief summary of the former FDA categories here. Categories include A, B, C, D, and X (as well as N for Not Rated), and classification is based on the amount of evidence for safety in animal and human studies (see Table 15.1). The system uses evidence from animal studies as part of the definitions of three out of the five categories. Many clinicians assume that there is an increasing level of risk from category A to X, which is inaccurate. For example, category B medications simply do not have adequate studies in humans to place them in category A as safe or in categories C, D, or X depending on the level of risk in humans. For instance, oral contraceptives are in category X because there is no reason to use them in pregnancy, not because there is evidence of associated birth defects. Further, the level of investigation used to categorize individual medications varies from medication to medication as does the level of risk actually imposed by a particular drug. As a result, medications may be placed in the same category but have vastly different levels of risk and/or different

Table 15.1 Psychotropic medication used for bipolar disorder in pregnancy

Medication	FDA category	Potential complications	Comments and recommendations
Antidepressants			
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram = C Escitalopram = C Fluoxetine = C Fluvoxamine = C Paroxetine = D Sertraline = C Vilazodone = C	– Modest increased risk of spontaneous abortion – Modest increased risk of preterm birth and low birth weight – No confirmed risk of birth defects except for small absolute increased risk of cardiac defects (2/1000 births) with *paroxetine* with first trimester exposure – Poor Neonatal Adaptation Syndrome with third trimester exposure – Conflicting evidence for small increased risk of Persistent Pulmonary Hypertension with third trimester exposure	– Best studied class of antidepressants – Most studies confounded by indication (i.e., not controlled for the underlying psychiatric illness). – Behaviors and risk factors associated with the psychiatric illness might influence some of the associations – Large studies that attempt to control for the underlying psychiatric illness generally suggest no increased risks – High relapse rate in women who stop their antidepressants for pregnancy – Avoid use of paroxetine during pregnancy if possible
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Duloxetine = C Desvenlafaxine = C Venlafaxine = C	– Fewer data available – Modest increased risk of spontaneous abortion – Modest increased risk of preterm birth and low birth weight – No confirmed risk of birth defects – Poor neonatal adaptation syndrome with third trimester exposure – Conflicting evidence for small absolute increased risk of persistent pulmonary hypertension with third trimester exposure	– Most studies are confounded by not controlling for the underlying psychiatric illness

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Medication	FDA category	Potential complications	Comments and recommendations
Other antidepressants	Bupropion = C Mirtazapine = C Trazodone = C	– Fewer data available	– Most studies are confounded by not controlling for the underlying psychiatric illness
Tricyclic antidepressants	Amitriptyline = C Clomipramine = C Desipramine = N Doxepin = N Imipramine = N Nortriptyline = N	– Fewer data available	– Therapeutic drug monitoring allows monitoring of serum levels and appropriate dose adjustments during pregnancy
Monoamine oxidase inhibitors	Selegiline Transdermal = C Phenelzine = C Tranylcypromine = N	– Significantly fewer data available	– Orthostatic hypotension may be pronounced in pregnancy
Mood stabilizers			
Lamotrigine	C	– No increased risk of major congenital malformations – One early and small study found an association with cleft palate that has not been replicated	– Serum levels should be monitored and maintained during pregnancy as levels usually decrease as pregnancy progresses
Valproic acid	D	– Associated with up to 10 % rate of malformations. Neural tube defects, effects on cognition and brain volume, craniofacial anomalies, cardiac defects, cleft palate, and hypospadias have been described – Recently linked to autism	– Generally should not be used during pregnancy. – High dose folate (4 mg) supplementation is recommended.
Carbamazepine	D	– Increased risk of malformations including spina bifida, other neural tube defects, facial abnormalities, skeletal abnormalities, hypospadias, and diaphragmatic hernia – Increased risk of neonatal hemorrhage	– Generally should not be used during pregnancy – High dose folate (4 mg) supplementation is recommended

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Medication	FDA category	Potential complications	Comments and recommendations
Oxcarbamazepine	C		
Lithium	D	– 1/1000 develop Ebstein's anomaly – No cognitive or behavioral effects in exposed children	– Lithium levels should be followed closely during pregnancy – The dose should be held or reduced with the initiation of labor – Postpartum, the dose should be reduced to pre-pregnancy levels (if it was increased during pregnancy) – Fetal echocardiagram in the first trimester is recommended
Antipsychotic medications			
First generation antipsychotics	Chlorpromazine = N Fluphenazine = N Haloperidol = C Loxapine = N Perphenazine = C Trifluoperazine = C Thiothixene = N Fluphenazine = N	– No major congenital malformations have been demonstrated – Associated with low birth weight and preterm delivery – No difference in IQ or behavior in exposed children – Exposure in third trimester associated with transient extrapyramidal and withdrawal symptoms in the infant	– Most studies are confounded by not controlling for the underlying psychiatric illness – High potency antipsychotics are preferred over low potency due to anticholinergic, hypotensive, and antihistaminergic side effects
Second generation antipsychotics	Aripiprazole = C Asenapine = C Clozapine = B Lurasadone = B Olanzapine = C Paliperidone = C Quetiapine = C Risperidone = C Ziprasidone = C	– No major congenital malformations have been demonstrated – May increase maternal weight gain – May increase risk of gestational diabetes – May increase size of the baby – Neurodevelopmental delays found at six months but resolved by 12 months	– Most studies are confounded by indication (i.e., not controlled for the underlying psychiatric illness). – There are fewer data available for clozapine and lurasadone – Glucose monitoring recommended – Routine ultrasound monitoring of fetal size in late pregnancy should be obtained – Clozapine has been associated with floppy baby syndrome, and

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Medication	FDA category	Potential complications	Comments and recommendations
			exposed infants should be monitored for agranulocytosis weekly for six months
Antianxiety medications			
Benzodiazepines	Alprazolam = D Chlordiazepoxide = D Clonazepam = D Diazepam = D Lorazepam = D Oxazepam = D	– May induce perinatal toxicity: temperature dysregulation, apnea, lower APGAR scores, hypotonia, and poor feeding – Use just before delivery associated with floppy baby syndrome – Some studies suggest oral cleft palate defects; others are negative	– Consider tapering benzodiazepines prior to delivery – Intermittent use is unlikely to induce withdrawal symptoms in the newborn
Gabapentin	C	– No increased risk of major congenital malformations – One study found increased risk of preterm birth, low birth weight, and NICU admission	
Pregabalin	C	– Evidence of congenital malformations and growth restriction in animals; no evidence of congenital malformations in humans, but there are few studies	
Buspirone	B	– No evidence of congenital malformations in animals – No data in humans	
Adjunctive psychotropic medications			
Antihistamines	Diphenhyrdramine = B Doxylamine = A Hydroxyzine = C Pheniramines = C	– Limited data – Commonly used – Conflicting data on pregnancy outcomes	– There are few data on chronic versus intermittent use
Sleep agents	Eszopiclone = C Ramelteon = C Zolpidem = C	– No evidence of major congenital malformations – May increase risk of low birth weight and preterm delivery	– There are few data on chronic versus intermittent use.

levels of evidence supporting their categorization. The FDA Pregnancy Categories therefore can provide a "quick and dirty" assessment but often do not provide enough information that is useful in planning clinical care. It is hoped that by providing all available information about a particular medication on the label itself rather than grossly classifying the information into a categorical system, clinicians and patients will make more informed decisions based on the literature as a whole.

15.4 Changes in Metabolism and Drug Clearance During Pregnancy

In pregnancy, major adaptive physiologic changes occur in a woman's gastrointestinal, cardiovascular, renal, and hepatic systems. These changes have a significant impact on the pharmacokinetic processes of drug absorption, distribution, metabolism, and excretion. Because of the impact of pregnancy on these basic physiologic and pharmacokinetic processes, adjustments in medication dosing are often required in pregnancy.

Physiological changes throughout pregnancy ultimately result in approximately a 50 % increase in plasma volume, increased body fat, and increased medication distribution volume. Renal blood flow, glomerular filtration rate, and medication elimination also increase (Seeman 2004) and changes in liver enzyme activation occur (e.g., CYP1A2 activity decreases; the activity of CYP2D6 and CYP3A increases) (Tracy et al. 2005). These liver enzyme changes, which are mostly hormone-dependent, can result in either increased or decreased medication clearance and are highly relevant to many psychiatric medications (Pavek et al. 2009; DeVane et al. 2006).

All psychotropic medications are able to move freely between the maternal and placental systems. The rate and extent of exchange between the maternal and placental systems is variable and poorly defined, and genetic factors that may play a role in variations in distribution are poorly understood. There are few data to help guide clinicians make decisions regarding medication dosing in pregnancy. The scant evidence that does exist is based primarily on observational studies and, given the reported high interindividual variability, should be cautiously interpreted (Pavek et al. 2009).

When available, therapeutic monitoring of serum levels can help guide decisions regarding medication dosing. Otherwise, clinicians must rely on what is generally known regarding pharmacokinetic changes in pregnancy and some basic principles. These principles include making sure a woman is taking the lowest beneficial dose of medication (i.e., the dose that provides sufficient maternal benefit while minimizing fetal exposure) during her pregnancy (DeVane et al. 2006). Because many of the changes in pharmacokinetics evolve over the duration of the pregnancy, this means that clinicians will need to monitor the woman's mental state more

frequently and adjust the dose of psychiatric medication(s) accordingly and perhaps repeatedly (DeVane et al. 2006; Tracy et al. 2005).

15.5 Managing Medications for Bipolar Disorder During and After Pregnancy

The ideal situation is to begin planning for pregnancy prior to pregnancy. It is important to assume that every woman of childbearing age will get pregnant and to discuss medication use during pregnancy and use of birth control measures as part of their ongoing treatment. If a woman is taking a medication that should not be used during pregnancy, such as valproic acid, a discussion should be held with the woman and, if possible, her partner to discuss this fact and to plan what should be done in case of accidental pregnancy. As many as 50 % of pregnancies are still unplanned in the USA (Mosher and Bachrach 1996); thus, discussing ideal and contingency plans ahead of time would minimize the chance that psychiatric medications will be abruptly discontinued and the patient will relapse.

The patient's past psychiatric history, severity of symptoms, and history of medication response all play a role in designing the course of clinical care during pregnancy. For example, while fluoxetine and sertraline are considered appropriate antidepressant choices during pregnancy, if a woman has a history of not responding to either of these medications they cannot be part of the treatment plan. Severity of illness is important to take into account: a case in which the psychiatric symptoms were mild, responded well to medication, and had not recurred could be considered for discontinuation of the medication prior to pregnancy. In contrast, a patient whose psychiatric symptoms were severe, dangerous, and required hospitalization several times would not be a candidate for medication discontinuation. Similarly, a woman's reproductive age should play a role in deciding when and if to attempt to change medications prior to pregnancy; an older woman may not have the reproductive time to experiment with a different medication prior to pregnancy.

At the same time, the patient and her partner's wishes regarding medication use during pregnancy should be taken into account when designing a treatment plan. If one or the other is strongly against medication use during pregnancy, it is best for the treatment provider to make sure they understand the risks of no treatment to both the mother and the baby, the rates of relapse, and to outline a course of close follow-up during and after pregnancy rather than insist on the use of medication during pregnancy. It is important to maintain a partnership characterized by good communication with the patient and her partner so that if there is a relapse the patient will remain safe and is more likely to seek care and treatment.

While each case should be considered individually and there are no hard and fast rules, there are some "rules of thumb" that can be used when designing a treatment strategy (modified from Payne and Meltzer-Brody (2009)):

1. All medication changes should be done prior to pregnancy if possible. This minimizes the number of exposures to the baby and promotes mood stability for the mother.
2. Ideally the patient should be stable psychiatrically for at least three months before attempting pregnancy. This is not always practical but should provide some evidence and reassurance that the patient's mood is stable prior to entering pregnancy.
3. Use medications that we know something about; older medications are usually better. If a medication has been available for a long period of time, there will be more evidence to support its safety or teratogenicity in the literature.
4. Use medications that have been tried in larger, nonpsychiatric populations. For instance, antiseizure medications have been tested in the larger population of women with seizure disorders. While many antiseizure medications are teratogenic, some with psychiatric indications have been shown to be safer during pregnancy (e.g., gabapentin and lamotrigine).
5. Minimize the number of exposures for the baby. Try to minimize the number of medications used but consider exposure to psychiatric illness as well. One common scenario is for a woman on a newer antidepressant to become pregnant and receive the recommendation to switch antidepressants to an older medication that has more evidence for safety during pregnancy. While this might have made sense prior to pregnancy, this plan would actually increase the exposures for the baby significantly. First, the baby has already been exposed to the newer antidepressant and switching to a second medication would be another exposure. In addition, the likelihood that the patient would relapse while switching is high, thus exposure to the mood disorder would be a third exposure for the child. Changing medications for breastfeeding also increases the number of exposures.
6. Monitor blood levels of medications when possible. As noted, changes in drug metabolism and weight gain during pregnancy may alter blood levels of psychiatric medications as pregnancy progresses. Medications that can be monitored by blood levels offer an advantage in this situation as changes in dosing can be made prophylactically. Medications for which laboratory monitoring is not available must be managed based on clinical response. Many women need adjustment of doses during the late second and third trimesters and should be evaluated more often during this time period.
7. Consider breastfeeding when planning for pregnancy. Consider whether the medication should be used during breastfeeding and what the plan would be for monitoring the medication during breastfeeding.
8. If a baby was exposed to a medication during pregnancy, it may not make sense to discontinue the medication (or, alternatively, not breastfeed) for breastfeeding. The baby was exposed to a larger concentration of the drug in utero compared to the concentration found in breast milk. That being said there are certain medications that might be difficult to justify the use of drug during breastfeeding. For example, clozapine, with its risk of neutropenia, should not be used during breastfeeding. Overall, the benefits of breastfeeding are

considered to be large; thus, recommending to a woman whose infant was already exposed to a medication in utero that she not breastfeed rarely makes sense, with the obvious exception of when the mother does not feel comfortable breastfeeding while taking a medication, or if the baby appears to be having side effects (e.g., sedation) from the medication.

9. Use a team approach. This rule of thumb applies to two groups: (1) family and (2) other doctors involved in the patient's care. Educating the family regarding the risks and benefits of treatment and no treatment, as well as signs and symptoms to be aware of for relapse is essential to providing good care for both mother and child. Similarly, communicating directly with the patient's other treatment providers will minimize miscommunication and differences of opinion and maximize treatment outcomes for the patient.
10. Be supportive if your patient doesn't accept your recommendations. There are many reasons why a particular patient may choose to go against her treatment provider's advice, particularly regarding medication use during pregnancy. Many women will feel guilty if they take any medication during pregnancy and underestimate the risks of untreated mood disorder during pregnancy. Many women are also under pressure from significant others, friends, and family members, or even other doctors, to discontinue medication during pregnancy. It is important as the treatment provider to continue to provide support to the patient despite disagreements regarding treatment during pregnancy. Again, using a team approach will often help avoid disagreements, and providing as much information as possible regarding the risks of untreated mood disorder during pregnancy can also help. In addition to talking directly to family and other treatment providers, in this situation it is often most appropriate to offer close follow-up care so that if a relapse occurs it is caught early and treatment can be offered. It is also important to keep in mind that the patient and her family must feel comfortable with the treatment used during pregnancy so they do not look back and regret decisions made during this critical time.
11. If a woman has stopped her medications during pregnancy, encourage restarting them postpartum. Several studies have shown that restarting psychiatric medications, particularly lithium, postpartum reduces the risk for psychiatric relapse (Stewart et al. 1991; Cohen et al. 1995; Austin 1992; van Gent and Verhoeven 1992; Bergink et al. 2012), particularly in BD. Emphasizing the increased risk for relapse during the postpartum time period can be helpful for this discussion.
12. Monitor women during the postpartum period closely. Because the postpartum period has an elevated risk for relapse, women should be seen frequently during this time period in order to promote early intervention.
13. Promote healthy sleep habits during the postpartum time period. Studies indicate that decreased sleep for women with BD is associated with relapse during the postpartum time period (Sharma et al. 2004; Sharma 2003). Emphasizing the need for regular sleep with the patient and the family may help minimize this trigger for relapse.

14. If a woman required an increased dose of mood stabilizer during pregnancy, consider decreasing it postpartum. For example, many women require increased doses of lamotrigine during pregnancy (Clark et al. 2013). Postpartum, lamotrigine concentrations have been shown to increase rapidly, possibly resulting in toxicity (Clark et al. 2013). Blood levels should be monitored closely during the postpartum time period in order to prevent toxicity. No studies have demonstrated whether psychiatric medications that do not have blood levels available should be decreased postpartum. For example, it is unclear whether an antidepressant increased during the third trimester should be decreased postpartum. In general, given the high risk of relapse postpartum, most treatment providers continue a woman on the higher dosage that was required during pregnancy. Patients should be followed closely, however, for the emergence of side effects, which would indicate a need to decrease the dosage to the previously effective dose.

We turn now to a discussion of the use of specific psychiatric medications during and after pregnancy (see Table 15.1).

15.6 Mood Stabilizers

15.6.1 Lithium

Lithium use during the first trimester has been associated with an increased risk of a serious congenital heart defect known as Ebstein's anomaly, which occurs in approximately one out of 1000 live births. The risk for Ebstein's anomaly with first trimester exposure was originally thought to be much higher (400 times higher than baseline), but a pooled analysis of lithium-exposed pregnancies found that this defect only occurs in one out of 1000–2000 exposed children (Cohen et al. 1994). This translates to less than 1 % of exposed children developing the anomaly. Lithium has also been associated with perinatal toxicity, including case reports of hypotonia, cyanosis, neonatal goiter, and neonatal diabetes insipidus. For women with severe BD, the risk of recurrence during pregnancy may overshadow the relatively small risk of Ebstein's anomaly. For such women, maintenance lithium therapy during pregnancy may be the most appropriate course. On the other hand, for women with significant periods of euthymia and few past mood episodes, slowly tapering off lithium and reintroducing lithium after the first trimester may help reduce the risk of relapse during the postpartum period. There are limited data on the long-term outcomes of children exposed in utero, but a follow-up of children up to age five demonstrated no evidence of cognitive or behavioral issues in a small sample of children (Jacobson et al. 1992). Lithium levels should be followed closely during pregnancy and the dose should be held or reduced with the initiation of labor. Hydration during delivery should be adequate and the dosage should be

reduced to pre-pregnancy levels (if it was increased during pregnancy) with close monitoring of serum levels postpartum (Pearlstein 2013).

15.6.2 Valproic Acid

Valproic acid is associated with a high rate of malformations with first trimester exposure (Pearlstein 2013). As many as 10 % of exposed children are born with neural tube defects, effects on cognition and brain volume, craniofacial anomalies, cardiac defects, cleft palate, and/or hypospadias (Pearlstein 2013). Valproic acid exposure has also been recently linked to autism (Bromley et al. 2013; Christensen et al. 2013). Providers should encourage pregnant women who elect to continue any anticonvulsant to take high-dose folate (4 mg per day) for the theoretical benefit of reducing the risk of neural tube defects and to undergo a second trimester ultrasound to screen for major congenital anomalies. Blood levels of valproic acid should also be followed carefully. In general, when prescribing valproic acid to a woman of childbearing age, a discussion of the risks of valproic acid exposure during pregnancy should be conducted.

15.6.3 Carbamazepine

Carbamazepine also carries an increased risk of malformations, primarily of spina bifida as well as other neural tube defects, facial abnormalities, skeletal abnormalities, hypospadias, and diaphragmatic hernia (Pearlstein 2013). Carbamazepine is also a competitive inhibitor of prothrombin precursors and may increase the risk of neonatal hemorrhage. As with valproic acid, high-dose folate should be taken and screening for malformations as well as therapeutic blood monitoring should be done.

15.6.4 Lamotrigine

According to the manufacturer-sponsored Lamotrigine Pregnancy Registry and other published studies (Cunnington and Tennis 2005), there appeared to be no increased risk of congenital defects above the baseline risk with lamotrigine monotherapy; however, when combined with valproic acid in pregnancy, the risk estimate was found to be elevated to above 10 %. While these initial findings seemed to offer women a relatively safe alternative to other anticonvulsants in pregnancy, the North American Antiepileptic Drug Pregnancy Registry found that infants exposed to lamotrigine monotherapy during pregnancy had a much higher risk of oral cleft defects (Holmes et al. 2008). However, a more recent and larger

study failed to find an association (Dolk et al. 2008). Dolk and colleagues assessed the association between oral cleft palate and exposure to lamotrigine using a population-based case-control design using data from the EUROCAT congenital malformation registries. The study population included 3.9 million births from 19 registries between 1995 and 2005. The authors identified 5511 cases of non-syndromic oral cleft. The control group consisted of 80,052 cases of non-chromosomal, non-oral cleft malformations. In this study, there was no evidence of an increased risk of isolated oral clefts relative to other malformations. Lamictal levels may decrease over the course of pregnancy and thus should be followed and adjusted if needed (Clark et al. 2013).

15.7 Antipsychotics

A 2004 Cochrane report (Webb et al. 2004) on the use of antipsychotics for primary (non-affective) psychosis in pregnancy found no trials meeting their inclusion criteria and concluded "continued use of antipsychotic drugs in these women in pregnancy and lactation without sound evidence raises serious clinical and ethical concerns." This report led many clinicians to recommend the discontinuation of antipsychotic medications during pregnancy. However, as more evidence has accumulated in the past decade, it appears that antipsychotics are—for the most part—relatively safe to use in pregnancy. Furthermore, *not* using these medications when indicated for serious mental illness poses a much greater risk to both mother and child, including the risks of suicide and infanticide (Robinson 2012).

Although antipsychotic use in pregnancy has not been definitively associated with an increased risk of congenital anomalies or any other adverse outcomes (Einarson and Einarson 2009; Einarson and Boskovic 2009), very few rigorously designed prospective studies that control for the underlying psychiatric illness have examined their safety in pregnancy. Although studies that control for potential confounders—including smoking—indicate persistent risks for adverse pregnancy outcomes (particularly low birth weight and preterm delivery) among women with an episode of schizophrenia in pregnancy compared to controls, it cannot be determined whether these outcomes are due to antipsychotic use (Nilsson et al. 2002), genetic vulnerabilities, or associated behaviors. However, a recent study examined birth outcomes in a matched cohort of women who used antipsychotics in pregnancy ($n = 1021$) and those who did not ($n = 1021$) and an unmatched cohort of women who used antipsychotics in pregnancy ($n = 1200$) and those who did not ($n = 40{,}000$). The analysis revealed no increased risk of adverse outcomes (preterm birth, gestational diabetes, hypertension, and large for gestational age infants) in the matched cohorts that controlled for the underlying illness and risk factors (Khalifeh et al. 2015).

When prescribing antipsychotics in pregnancy, pharmacokinetics must also be considered. Because CYP1A2 enzymes are downregulated with advancing pregnancy, doses of olanzapine and clozapine may need to be decreased, while doses of

medications that are metabolized by upregulated enzymes may need to be increased (Seeman 2013). Of note, quetiapine, risperidone, haloperidol, and olanzapine have been shown to exhibit the lowest placental transfer from mother to fetus (Newport et al. 2007).

Normal metabolic changes associated with pregnancy may increase the risk for gestational diabetes in conjunction with the use of antipsychotics. In fact, many antipsychotics, particularly second generation antipsychotics (SGAs), are associated with excessive maternal weight gain, increased infant birth weight, increased risk of gestational diabetes, and infants being born large for gestational age (Seeman 2013; Newham et al. 2008). Several cases of gestational diabetes associated with the use of antipsychotics, including clozapine and olanzapine, have been reported (Barnes 2011; Gentile 2010; Reis and Kallen 2008). This suggests that routine ultrasound monitoring of fetal size in late pregnancy might be beneficial for women taking these medications in pregnancy or for women who gain substantial weight (Newham et al. 2008; Paton 2008).

There is also a lack of evidence regarding late pregnancy exposure to antipsychotics, including little on longer-term developmental outcomes, and so the risks remain unclear. Behaviors observed in infants exposed to antipsychotics in utero include motor restlessness, dystonia, hypertonia, and tremor (Gentile 2010; Coppola et al. 2007). The few studies examining the relationship between in utero exposure to First Generation Antipsychotics (FGAs) and neurodevelopment have shown no difference in IQ or behavioral functioning at five years (Barnes 2011; Altshuler et al. 1996; Thiels 1987). Studies of SGAs have shown associated neurodevelopmental delays at six months of age (Peng et al. 2013; Johnson et al. 2012). However, in a case-control prospective study, these delays were no longer evident at 12 months (Pearlstein 2013; Peng et al. 2013). The American College of Obstetricians and Gynecologists states that "no significant teratogenic effect has been documented with chlorpromazine, haloperidol, and perphenazine" and suggests that the "use of piperazine phenothiazines (e.g., trifluoperazine, perphenazine) may have especially limited teratogenic potential" (ACOG Practice Bulletin: Clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007). Use of psychiatric medications during pregnancy and lactation 2008).

More recently, in utero exposure to FGAs has been associated with an increased risk of premature delivery (Habermann et al. 2013), and exposure specifically in the third trimester has been associated with transient extrapyramidal and withdrawal symptoms. The FDA issued a drug safety communication in 2011 for all antipsychotics noting the potential risks of abnormal muscle movements and withdrawal symptoms (Communication 2011). However, given that these extrapyramidal/withdrawal reactions are usually self-limited, the American Academy of Pediatrics Committee on Drugs guidelines recommend the preferential use of high-potency FGAs in order to minimize maternal anticholinergic, hypotensive, and antihistaminergic effects of the low-potency antipsychotics (Use of psychoactive medication during pregnancy and possible effects on the fetus and newborn. Committee on Drugs. American Academy of Pediatrics 2000). These 2000

guidelines also recommended against the use of any depot preparations of antipsychotics due to lack of flexibility in dosing and in order to limit exposure to the neonate of prolonged potential toxic effects.

SGAs have no evidence of being safer to use in pregnancy than FGAs. The best studied is olanzapine, which has global safety pregnancy surveillance data suggesting no difference in outcomes with fetal exposure to olanzapine compared to the general population (Brunner et al. 2013). However, there is concern that fetal exposure to these newer medications may increase infant birth weight and the risk of being born large for gestational age (Newham et al. 2008). Several studies suggest increased risk of hypoglycemia associated with the use of SGAs in pregnancy (Gentile 2004). However, this may be due to higher baseline rates of diabetes in women prescribed antipsychotics (Vigod et al. 2015; Khalifeh et al. 2015), reinforcing the need for a thorough evaluation and appropriate glucose monitoring for women prescribed these medications.

Clozapine has been associated with floppy baby syndrome. In addition, infants with in utero exposure to clozapine should be monitored for agranulocytosis weekly for the first six months of life (Gentile 2010).

15.8 Antidepressants

Antidepressants are the most commonly prescribed psychotropic medication during pregnancy (Hanley and Oberlander 2014). Although they are not consistently used in BD, many patients with BD require the use of antidepressants, and one study demonstrated that as many as 80 % of patients with BD have taken an antidepressant at some point during their treatment (Ghaemi et al. 2000). The literature examining antidepressant use during pregnancy and pregnancy outcomes is large and exemplifies the problems outlined previously: a number of possible negative outcomes have been identified over the past 10 years by studies that did not control for the underlying psychiatric illness; subsequent, more properly controlled studies have either shown no increased risk of adverse outcomes or yielded conflicting data. Much of the work examining the association between antidepressant medications and outcomes of exposed pregnancies has focused on the selective serotonin reuptake inhibitors (SSRI) class of antidepressants. The term "antidepressant" indicates that a mixture of antidepressant classes was examined in the study.

The baseline rate of major birth defects or malformations is approximately 3 % in the general population and less than 1 % of these are thought to be secondary to an exposure to a medication (Cunningham et al. 2010). The literature examining the rate of major birth defects and antidepressant use in pregnancy is complicated by small samples, surveillance bias, and lack of controls for the underlying psychiatric illness and associated risk factors (Byatt et al. 2013); overall they have been conflicting and inconsistent. A small increase in the absolute risk of rare defects with SSRI exposure has been reported (Alwan et al. 2007), but four meta-analyses examining the risk of major malformation with first trimester SSRI exposure found

no statistically significant increased risk (Rahimi et al. 2006; Addis and Koren 2000; Einarson and Einarson 2005; O'Brien et al. 2008). Compared with the SSRIs, there are limited data on major organ malformations for other types of antidepressants. Most studies examining the risk of congenital malformations with tricyclic antidepressant (TCA) exposure found no increased risk of malformations (Davis et al. 2007; Nulman et al. 1997; Pastuszak et al. 1993; Simon et al. 2002; Ramos et al. 2008) though one large epidemiological study found a significant increase in severe malformations (OR 1.36, 1.07–1.72) (Reis and Kallen 2010). With the possible exception of heart defects (see below), bupropion has not been associated with major malformations in several studies (Chun-Fai-Chan et al. 2005; Cole et al. 2007; Alwan et al. 2010). The data available for other types of antidepressants are small but reassuring (reviewed in Byatt et al. (2013) and Yonkers et al. (2014)).

The literature has not consistently identified an association between the use of antidepressants during pregnancy and cardiovascular malformations. Paroxetine use during the first trimester has been associated with a higher risk of cardiac malformations by some studies (Kallen and Otterblad Olausson 2006, 2007) but not others (Alwan et al. 2007; Louik et al. 2007) and remains the most controversial antidepressant in terms of recommendations for pregnancy (Byatt et al. 2013; Yonkers et al. 2014). Studies of bupropion have also yielded conflicting results. The GlaxoSmithKline Pregnancy Registry found increased risk of cardiovascular malformations in both retrospective and prospective reports, and a second retrospective case-control study found a higher rate of left outflow tract heart defects (Alwan and Friedman 2009; Alwan et al. 2010). However, other studies are reassuring (Chun-Fai-Chan et al. 2005; Cole et al. 2007) and the risk, if real, is quite small (<1 % of exposed infants) (Alwan and Friedman 2009). Importantly, one study (Reis and Kallen 2013) found that the combination of a benzodiazepine and an SSRI, but not an SSRI alone, increased the incidence of congenital heart defects, and much of the literature has not controlled for other medication exposures (Byatt et al. 2013; Yonkers et al. 2014). The overall consensus in the field is that the risk of major organ malformations, if it exists, is small in the setting of antidepressant monotherapy (Yonkers et al. 2009).

15.8.1 Spontaneous Abortion

Although the studies in this area are also plagued by lack of controlling for the underlying psychiatric illness and associated risk factors, the overall results suggest that the use of antidepressants in early pregnancy is associated with a modestly elevated risk of spontaneous abortion (Yonkers et al. 2014; Ross et al. 2013; Hemels et al. 2005; Nakhai-Pour et al. 2010). Reported ORs generally range from 1.4 to 1.6 (Pearlstein 2013).

15.8.2 Preterm Birth and Birth Weight

To summarize a large literature, the rate of preterm birth is higher among mothers who take antidepressants. However, most studies did not control for the severity of psychiatric illness and other confounding variables found more commonly in the psychiatric population (Yonkers et al. 2014; Byatt et al. 2013). A recent systematic review and meta-analysis of 41 studies found that the pooled adjusted OR was 1.53 for use of antidepressants at any time and 1.96 for third trimester use (Huybrechts et al. 2014). Controlling for the diagnosis of depression did not eliminate the effect, but residual confounding could not be ruled out (Byatt et al. 2013; Yonkers et al. 2014). Controlling for health habits, depressive disorders, *and* psychiatric illness, one study found greater risk of preterm birth in SSRI users (Yonkers et al. 2012), suggesting some biological role. However, the duration of pregnancy was shortened only by three to five days, and the overall risk was considered modest (Yonkers et al. 2012). The literature examining the role of antidepressant use and low birth weight is similarly complicated by confounding by the underlying illness, and the results have been inconsistent (Yonkers et al. 2014; Byatt et al. 2013; Pearlstein 2013).

15.8.3 Persistent Pulmonary Hypertension of the Newborn

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a failure of the pulmonary vasculature to decrease resistance at birth resulting in breathing difficulties for the infant, leading to hypoxia and often intubation. PPHN has a 10–20 % mortality rate and results in significant morbidity (Walsh-Sukys et al. 2000). It is very rare, affecting one to two infants out of 1000 in the general population (Hageman et al. 1984; Hernandez-Diaz et al. 2007). PPHN has been associated with a number of factors including maternal smoking, diabetes, sepsis, meconium aspiration, and C-section (Hernandez-Diaz et al. 2007).

To date there have been seven studies on the association between SSRIs and PPHN in the newborn with conflicting results. The first was published in 2006 (Chambers et al. 2006) and is the basis for the FDA Alert issued that year regarding the possible association of SSRIs and PPHN. This case-control study compared 377 women who had infants diagnosed with PPHN to 836 matched control women with infants without PPHN. Fourteen of the infants with PPHN had been exposed to an SSRI after the 20th week of gestation compared to six infants who did not have PPHN (Chambers et al. 2006). This generated an adjusted (for maternal diabetes, race, and body-mass index) odds ratio of 6:1. Since this first study, six additional studies have been conducted; three found no association between SSRI exposure and PPHN (Andrade et al. 2009; Wichman et al. 2009; Wilson et al. 2011) and three found an association (Kallen and Olausson 2008; Kieler et al. 2012; Huybrechts et al. 2015), although with lower odds ratios than 6:1. It is also important to keep the

risk in perspective by considering the absolute risk. PPHN is an extremely rare condition, occurring in one to two infants out of 1000 in the general population (Hageman et al. 1984; Hernandez-Diaz et al. 2007). If one assumes that SSRI use increases the odds of developing PPHN at six times the rate in the general population, only six to 12 out of 1000 (0.6–1.2 %) infants exposed to SSRIs would develop PPHN. Thus, 99 % of women who take SSRIs during pregnancy would give birth to a healthy infant who does not develop PPHN.

15.8.4 Poor Neonatal Adaptation Syndrome

The first report of "withdrawal" symptoms in babies exposed to antidepressants occurred in 1973 (Webster 1973). It is unclear if "neonatal withdrawal syndrome" is actually a result of withdrawal from the antidepressant or is due to toxicity. Thus, the alternative "Poor Neonatal Adaptation Syndrome (PNAS)" may be a better description. There are a number of limitations to the studies in the available literature, including inconsistent definitions, no measurement tool, a lack of blinded ratings, and a lack of studies investigating treatment or prevention of the syndrome. Regardless, the FDA instituted a class labeling change in 2004 for both SSRI and SNRI (serotonin–norepinephrine reuptake inhibitors) antidepressants warning that third trimester exposure may be associated with PNAS. According to the label change, "reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying." The subsequent result has been that many practitioners have recommended tapering antidepressants prior to delivery even though it remains unclear if this decreases the risk for PNAS or is safe for the mother. Most cases of PNAS appear to be mild, self-limited, and are not associated with lasting repercussions (Moses-Kolko et al. 2005). Available data suggest that approximately one-third of exposed infants will have at least mild symptoms consistent with the syndrome and that this risk increases when multiple agents, particularly benzodiazepines, are used (Oberlander et al. 2004). Clearly, larger, more rigorous studies of the syndrome as well as strategies to minimize the rate of the syndrome are needed. At this time, there is simply not enough evidence from a safety perspective to recommend tapering antidepressants in the third trimester, particularly in cases of moderate to severe maternal mental illness.

15.8.5 Risk of Autism

Several studies have examined a possible association between SSRI use during pregnancy and autism spectrum disorders (ASD). Croen and colleagues (2011) conducted a case-control study using data extracted from medical records.

Two-hundred ninety eight children with ASD were matched for gender, birth year, and hospital to 1507 controls. Antidepressant use in the year before delivery was found to double the risk of ASD in the offspring (OR = 2.0 [1.2–3.6]) with the strongest effect found with first-trimester exposure (OR = 3.5 [1.5, 7.9]). There was no increased risk for the children of mothers with a history of mental health treatment who did not use antidepressants during pregnancy. Another large, population-based, nested case-control study examined both maternal and paternal depression as well as antidepressant use during early pregnancy and the risk of ASD in a Swedish cohort of over 500,000 children (Rai et al. 2013). Maternal depression was associated with increased risk of ASD (OR = 1.49 [1.08–2.08]) while paternal depression was not (OR = 1.21 [0.75–1.96]). Maternal depression and antidepressant use did not increase the risk of ASD with intellectual disability but did increase the risk of ASD without intellectual disability (OR = 4.95 [1.85–13.23]), although not in the absence of maternal depression (OR = 2.1 [0.97–4.57]). This study was limited by not controlling for the underlying psychiatric illness. The most recent study (Hviid et al. 2013) was a cohort study of 626,875 Danish live births between 1996 and 2005 in which they were able to link information on maternal use of SSRIs before and during pregnancy with ASD diagnoses in the offspring. When compared to women who had never used SSRIs, use of SSRIs during pregnancy was not associated with an increased risk of ASD (OR = 1.20 [0.90–1.61]). In contrast, the OR for women who received SSRIs prior to but not during pregnancy was 1.46 [1.17, 1.81] indicating that the risk is likely due to the underlying illness—depression—not the use of antidepressants.

15.9 Antianxiety Agents

15.9.1 Benzodiazepines

Studies of benzodiazepine use during pregnancy have been contradictory and controversial. Benzodiazepine use during pregnancy has been associated with case reports of perinatal toxicity, including temperature dysregulation, apnea, depressed APGAR scores, hypotonia, and poor feeding. In addition, early studies revealed an elevated risk of oral cleft palate defects compared to the baseline risk in the general population. However, more recent studies have shown that the overall risk of cleft lip and palate with benzodiazepine use in pregnancy is likely quite low (Iqbal et al. 2002; Lin et al. 2004). Infants exposed to an SSRI in combination with a benzodiazepine may have a higher incidence of congenital heart defects even when controlling for maternal illness characteristics (Oberlander et al. 2009). In considering the risks and benefits of benzodiazepines, clinicians should also consider the risks of untreated insomnia and anxiety in pregnancy, which may lead to physiologic effects as well as diminished self-care, worsening mood, and impaired functioning. Given the consequences of untreated psychiatric symptoms and the

limited and controversial risks associated with benzodiazepine use, some women with overwhelming anxiety symptoms or sleep disturbance may find that the benefits outweigh any theoretical risks. Breastfeeding infants should be monitored for sedation, and the lowest effective dose should be used.

15.9.2 Gabapentin

Several studies have indicated that there is no increased risk of major congenital malformations (Holmes and Hernandez-Diaz 2012; Molgaard-Nielsen and Hviid 2011). A recent study again found no increased risk of malformations but found higher rates of preterm birth, low birth weight, and need for neonatal intensive care admission (Fujii et al. 2013). In general, gabapentin is considered a safe alternative for the management of anxiety symptoms during pregnancy.

15.9.3 Pregabalin

Like gabapentin, pregabalin is not approved for the treatment of anxiety but clinically has some utility in decreasing anxiety symptoms. It is less well-studied than gabapentin but, to date, there is no known association with an increased risk of malformations.

15.9.4 Buspirone

Animal reproduction studies have found no evidence of teratogenesis, but there is no available evidence one way or the other in humans.

15.10 Sleep Aids

Antihistamines are widely available over-the-counter and are often used in early pregnancy as a treatment for nausea and vomiting and in late pregnancy for insomnia. These medications include diphenhydramine, doxylamine, hydroxyzine, and the pheniramines (latter not available in the USA). A recent systematic review of antihistamines and birth defects (Gilboa et al. 2014) identified two cohort ($N = 31$) and eight case-control ($N = 23$) studies that found an association between prenatal antihistamine exposure and congenital malformations; however, methodological concerns included study population selection, measurement of antihistamine exposure, and identification of malformations (Gilboa et al. 2014). In

addition, potentially confounding factors such as presence of hyperemesis gravidum, a clinical condition for which antihistamines are often used and which is itself associated with an increased risk of adverse fetal outcomes, was not addressed in the analysis (Fejzo et al. 2013).

Although over 90 % of pregnant women report using over-the-counter antihistamines to treat insomnia (Black and Hill 2003), a recent systematic review of sleep-promoting medication use in pregnancy (Okun et al. 2015) identified only two studies on prenatal antihistamine exposure. One found no association between exposure and congenital malformations (Reis and Kallen 2013). The other study is the only randomized control trial of antihistamines in pregnancy, which compared antidepressant, antihistamine, and placebo for insomnia in the third trimester (Khazaie et al. 2013). Although this trial did not measure any neonatal outcomes, it did find that diphenhydramine was associated with significantly longer sleep duration and efficiency and fewer depressive symptoms compared to placebo. Sleep agents including eszopiclone, ramelteon, and zolpidem have not been associated with major organ malformations (Okun et al. 2015), but zolpidem use for greater than 90 days has been associated with increased risk of low birth weight, preterm birth, and cesarean delivery (Cohen et al. 2010). Thus, taken as a whole, the current limited evidence suggests that antihistamine and sleep agent use in pregnancy are not consistently associated with an increased risk of adverse pregnancy outcomes, though larger studies are needed.

15.11 Psychotropic Medications and Breastfeeding

The literature on the use of psychotropic medications during breastfeeding is relatively sparse with few long-term outcome studies and mainly case reports. Overall the data that are available to date are generally reassuring. All psychotropic medications enter breast milk. Any psychotropic medication may be associated with side effects in the breastfeeding infant, and therefore the baby should be monitored closely for adverse effects and either the medication or the breastfeeding stopped if there appear to be ill effects. Premature infants may be more vulnerable to adverse effects due to immature metabolic systems (Berle and Spigset 2011).

There have been limited reports on the use of lithium during breastfeeding and most are reassuring with undetectable or very low blood levels in the exposed children (Bogen et al. 2012). Breastfeeding on lithium, however, requires a very vigilant parent who will have a low threshold for taking the baby for an emergency evaluation in the setting of potential dehydration since lithium levels can rise and become toxic in this setting (Bogen et al. 2012). Monitoring the baby's blood level regularly is recommended.

The anticonvulsants, unlike during pregnancy, appear to be relatively safe during breastfeeding. In fact, a recent study demonstrated that children who were exposed to anticonvulsants in utero had improved developmental and intellectual outcomes if they were breastfed for at least six months compared to exposed

children who were not breastfed (Meador et al. 2014). Blood levels in the exposed infant can be monitored but do not need to be regularly tested due to a low likelihood of toxicity, unlike with lithium (Pearlstein 2013).

Very few studies have examined the use of antipsychotic medications in breastfeeding and many agents have no data at all (Klinger et al. 2013). Olanzapine and quetiapine are generally considered safe for breastfeeding (Klinger et al. 2013), but there are few data to guide the use of other antipsychotic medications. There are sporadic case reports of adverse effects in antipsychotic-exposed breastfed infants, but no clear pattern of effects has emerged (Gentile 2008). Clozapine should not be used during breastfeeding due to the risk of neutropenia (Gentile 2008).

Overall, antidepressant medications are the best-studied class of psychotropic medications in breastfeeding, but again the data are limited. Overall, the data are reassuring, and it appears that only a small percentage (1–10 %) of the mother's dosage is found in breast milk. Long-term developmental studies show no differences in children exposed to antidepressants in breast milk compared to unexposed children. There is one case report of seizure in an infant exposed to bupropion (Pearlstein 2013). There is also a theoretical risk of fluoxetine toxicity due to its long half-life; sertraline, paroxetine, and nortriptyline generate the lowest serum levels in the exposed infant (Pearlstein 2013).

Benzodiazepine use during breastfeeding should be limited to the lowest effective dose and the baby monitored for sedation and lethargy, though this is rare. Long-term studies are not available.

15.12 Conclusions

Interpretation of the literature regarding the association between psychotropic medication use during pregnancy and outcomes for the exposed baby is complicated by the fact that the population of women who require psychotropic medications during pregnancy have other associated risk factors and behaviors that may also influence outcomes. Large, well-designed, and controlled studies have shown that most classes of psychotropic medications appear to be relatively safe for use during pregnancy. Untreated psychiatric disorders, including BD, during pregnancy have associated risks for both mother and child, and these risks need to be considered in the risk-benefit analysis of using psychotropic medication during pregnancy. Women with BD are at risk for relapse if medications are stopped for pregnancy and are at risk for both postpartum depression and postpartum psychosis after delivery. Psychotropic medications should not be precipitously stopped, and a comprehensive evaluation and individualized treatment plan is needed for women with BD who wish to become or are pregnant. Future work should focus on the proper management of psychotropic medications during pregnancy including prophylactic dosing strategies and management before and after delivery. Finally, improved prospective data procurement regarding potential confounders are also needed in order to truly address the question of whether exposure in utero to psychotropic medication affects outcomes for the child.

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