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Psychiatric Disorders and Psychotropic Treatment in the Postpartum Period

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KEYWORDS: Postpartum Depression • Postpartum Psychosis • Psychotropics • Lactation • Pharmacokinetics

LEARNING OBJECTIVES: This lesson will enable clinicians to: (1) understand the prevalence and risk factors of psychiatric disorders in the postpartum period, (2) consider the negative effects of psychiatric illness on mothers and infants, (3) recall the recent implementation of the *U.S. Food and Drug Administration* (FDA) *pregnancy and lactation labeling rule* (PLLR), (4) recognize the general principles of psychotropic use during lactation, and (5) review literature on the safety of psychotropic use during lactation.

LESSON ABSTRACT: The prevalence of psychiatric disorders during the postpartum period is at least comparable to that of the general population, with some indication that the first five weeks after childbirth are a vulnerable period for the onset of psychiatric illness. Additionally, there are significant detrimental effects of psychiatric illness on the mother and infant and of factors specific to the postpartum period that influence management. All psychotropic medications are secreted in breast milk, but the majority are present only in low concentrations and can be used safely in lactating mothers. Psychiatrists are often hesitant to prescribe psychotropics to lactating mothers. In this continuing medical education lesson, we will review the prevalence and risk factors of psychiatric disorders in the postpartum period, the adverse effects of psychiatric illness on mothers and infants, the recent implementation of the FDA's PLLR, the general principles of psychotropic use during lactation, and the safety of psychotropic use during lactation, with an emphasis on the medications that are associated with significant side effects.

COMPETENCY AREAS: This lesson addresses the gaps in learning in the area of knowledge and patient care with regard to the special patient population of postpartum and lactating women. Many psychiatrists lack knowledge and an appreciation of the burden of psychiatric illness in the postpartum period, the risks of untreated psychiatric illness for mothers and infants, and how to safely prescribe psychotropic medications to a lactating mother. After reading this lesson, readers will have a better understanding of the prevalence of psychiatric disorders in postpartum mothers, the negative effects of psychiatric illness on mothers and infants, and safety concerns regarding the use of psychotropic medication during lactation.

Psychiatric Disorders in the Postpartum Period

The presence of various psychiatric disorders in the postpartum period has been recognized for centuries. Evidence strongly indicates that the prevalence of psychiatric disorders during pregnancy and the postpartum period is at least comparable to that in the general population and that pregnancy and the postpartum state are not protective against the emergence or recurrence of psychiatric illness. Additionally, there are significant, detrimental effects of psychiatric illness on the mother and infant. For example, a depressed mood during pregnancy is reported to be associated with poor attendance at antenatal clinics, substance misuse, low birth weight, and preterm delivery.[1] In a 2013 meta-analytic review, it was found that overall, depressed mothers provide less responsive caregiving; are more likely to discontinue breastfeeding early or have problems breastfeeding; are less likely to comply with recommended safety practices, such as the use of car seats; and their children have lower rates of preventive healthcare utilization and vaccination.[2] These significant consequences of peripartum mental illness indicate a need for practitioners to know the risks of developing these disorders to properly counsel their patients.

Postpartum Blues:

Postpartum blues, often called "baby blues," is typically defined as a transient state of heightened emotional reactivity.[3] Women most often report mild symptoms of depression, insomnia, and decreased concentration. Depressive symptoms at this time can include irritability, anxiety, and tearfulness.[4] In 40%–80% of women, symptoms of postpartum blues develop in two to three days after delivery and usually resolve within two weeks.[5] Among women who experience postpartum blues, 20% will go on to experience a major depressive episode in the first postnatal year.[3]

Postpartum Depression:

Approximately 50% of major depressive episodes presenting in the postpartum period actually have onset prior to delivery, and they are best referred to as peripartum episodes.[6] According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), the specifier "with peripartum onset" is applied to depressive disorders when the most recent episode of depression occurs during pregnancy or in the first four weeks following delivery.[7] This same specifier is also applied to bipolar disorder and brief psychotic disorder. However, clinically and for research purposes, various cut-off marks, such as up to three months, six months, or one year following childbirth, have been utilized. Approximately 30% of women with postpartum depression still report depression beyond the first year after delivery.[8]

Some of the best data on the epidemiology of unipolar major depression during pregnancy and the postpartum period comes from a quantitative review commissioned by the Agency for Healthcare Research and Quality. In the study, Gaynes et al. reported the point prevalence of major depressive disorder at three months postpartum to be 4.7% (95% *confidence interval* [CI], 3.6–6.1), the period prevalence from birth to three months postpartum to be 7.1% (95% CI, 4.1–11.7), and the incidence from birth to three months postpartum to be 6.5% (95% CI, 4.2%–9.6%).[9] The values for depressive disorder (both major and minor depression) were considerably higher than for major depressive disorder alone at 12.9%, 19.2%, and 14.5% for point prevalence, period prevalence, and incidence, respectively.[9] The data reveals just how widely prevalent depression is in the postpartum period.

Studies reviewed by Gaynes et al. in which postnatal subjects were compared with a control group revealed similar prevalence rates of depression among women of similar ages, except for one study by Cox et al.[10] in which a threefold higher rate of the onset of depression was found within five weeks of childbirth. However, no difference was found in the six-month point and period prevalence.

Despite the similar prevalence, childbirth is associated with an increased risk of psychiatric readmission for mothers during the first postpartum month compared to non-mothers, with the highest risk at 10–19 days postpartum.[11]

There are several risk factors for postpartum depression. The greatest risk is a prior history of postpartum depression. The relapse rate is about 40% if there has been a previous episode of postpartum depression.[8] Other risk factors include domestic violence or prior abuse, negative life events, low social support, low

partner support, marital difficulties, low socioeconomic status, depression and anxiety in pregnancy, prior history of depression, neuroticism, substance abuse, increased parity, and chronic illness.[8]

Bipolar Disorder in the Postpartum Period:

Women with bipolar disorder have at least a 20% risk of experiencing a severe recurrence after childbirth, and the risk of any mood episode in the postpartum period approaches 50%.[12] A population-based cohort study conducted over 30 years showed that in the first month following birth, the risk of readmission is increased in women with a history of bipolar disorder, with a relative risk of 37%. Women who have their first psychiatric admission in the first postpartum month are more likely to be meet the criteria for bipolar disorder in the future.[11]

As there are significant concerns about some mood stabilizers with regard to teratogenicity, treatment is frequently discontinued during pregnancy. The recurrence risk of bipolar disorder during pregnancy is 2.3 times higher with the discontinuation of mood stabilizers.[13] The majority of these episodes are depressive or mixed episodes. Viguera et al. reported that with lithium discontinuation during pregnancy, rates of recurrence are similar for pregnant women during pregnancy and for non-pregnant women (the first 40 weeks after discontinuation); however, recurrences are almost threefold higher in postpartum women compared to controls during equivalent period (weeks 41–60 after lithium discontinuation).[14]

Postpartum Psychosis:

Most cases of postpartum psychosis are believed to be cases of bipolar disorder rather than a primary psychotic disorder. These episodes generally consist of psychotic mania or severe psychotic depression. The status of postpartum psychosis is subject to nosological debate, as it is a heterogenous entity encompassing psychotic mania, psychotic depression, brief psychotic disorder, and psychotic exacerbations of underlying schizophrenia or schizoaffective disorder. However, the term remains in widespread clinical use.

The actual rates of postpartum psychosis are not known, but a reported psychiatric admission rate of 1–2 per 1000 births is often used as a rough estimate for postpartum psychosis.[12] Postpartum psychosis is most common in the first two weeks following delivery, usually between the first one to three days. Sudden onset and rapid deterioration are typical features of postpartum psychosis.[12] It is important to exclude medical causes of psychosis specific to the postpartum period, such as eclampsia, delirium, thyroid disorder, and infection, because these conditions are potentially fatal if not properly diagnosed and treated.

A prior history of postpartum psychosis places women at a very high risk for developing postpartum psychosis. Risk is similarly elevated for women with bipolar disorder who have a family history of postpartum psychosis. **Primiparity is the only strongly associated obstetric risk factor for developing postpartum psychosis, which is theorized to result from medication discontinuation due to concerns about teratogenicity.[12]**

Postpartum Anxiety Disorders, Obsessive-Compulsive Disorder and Posttraumatic Stress Disorder:

There is very little information in the literature on anxiety during pregnancy and the postpartum period, with much of the literature dedicated to depression and psychosis. In published reports, the prevalence of anxiety during depression ranges from 13%–21% and 11%–17% in the postpartum period.[15]

Obsessive-compulsive disorder (OCD) during pregnancy and the postpartum period is significant as pregnancy is a known risk factor for developing OCD compared to the general population and for exacerbating existing OCD symptoms[8]. An estimated prevalence of OCD ranges from 0.3%–29% during pregnancy and from 1.7%–9.0% during the postpartum period, but pre-existing OCD was exacerbated equally during pregnancy and the postpartum period in the range of 20%–50%. Specific symptoms during pregnancy and the postpartum period include obsessions about contamination or aggression toward the child, leading to compulsive cleaning, avoidance of the infant, and/or excessive checking on the well-being of the infant.[16] The literature is also recognizing that woman can develop *posttraumatic stress disorder* (PTSD) from trauma experienced during pregnancy or childbirth, and the prevalence is estimated at 1%–2%, which may be higher in low-income countries.

A Brief Treatment Overview of Psychiatric Disorders in the Postpartum Period

In general, psychiatric disorders during the postpartum period require the same standard treatments as during the non-postpartum period, except that consideration must be given to the safety of these medications during lactation. Sleep deprivation needs to be prevented in postpartum mothers with psychiatric disorders, and this may require either the suspension of breastfeeding if the nursing intervals are too frequent or the supplementation of breastfeeding with formula or pumped breast milk with the assistance of other caregivers.

"Postpartum blues" typically do not require treatment beyond psychosocial support and reassurance. Treatment of postpartum major depression should be comprehensive, utilizing both psychotherapy and psychopharmacology. Interpersonal and cognitive behavior therapies have been shown to be effective forms of treatment.[17] Antidepressants can be prescribed for postpartum depression, and overall, the same general principles apply as with other types of major depressive disorder. Nursing should not be discouraged unless a complicating factor, such as psychosis, suicidality, or infanticide risk, is present. Patients should also be reminded that *electroconvulsive therapy* (ECT) is always an option and that it has the highest rates of response and remission of any antidepressant treatment at 70%–90%. This is consistent with the 2010 American Psychiatric Association guidelines on the treatment of major depressive disorder.[18]

Regarding the treatment of postpartum bipolar disorder, standard treatments for bipolar disorder (mood stabilizers and atypical antipsychotics) should be utilized, with consideration given to their safety during lactation. Additionally, women should be educated on optimizing sleep during the postpartum period to avoid precipitating an episode of mania. The use of prophylactic mood stabilizers should be continued in the postpartum period, as bipolar disorder has a high risk of relapse when medication is discontinued. If the mood stabilizer had been stopped during pregnancy, it must be restarted immediately after birth, as manic symptoms can recur within three to four days postpartum.

Mothers with postpartum psychosis should be hospitalized, given the high risk of infant neglect, infanticide, and suicide. Antipsychotics and mood stabilizers should be utilized as clinically indicated. In general, mothers with postpartum psychosis should not breastfeed given the clinical severity of affective and psychotic symptoms that usually necessitate inpatient care and given the possibility of the risk of self-harm. Breastfeeding may be resumed after clinical stabilization.

Bergink et al.[19] introduced a four-step algorithm to be used in patients with first-onset postpartum psychosis or mania. By using this treatment method, the authors found that 98.4% of their patients achieved complete remission in the first three steps. At nine months postpartum, the sustained remission was 79.7%. The four steps are as follows: (1) begin treatment with lorazepam at bedtime for three days, (2) begin antipsychotic medication (haloperidol [Haldol] at 2–6 mg per day is recommended) on day four if symptoms continue, (3) add lithium for those who do not have a significant clinical response with a target plasma level of 0.8–1.2 mmol/l after two weeks of treatment with both a benzodiazepine and an antipsychotic, and (4) administer ECT to those who do not respond after 12 weeks to the above triple therapy.

The Effects of Psychiatric Illness on Mothers and Infants:

There has long been a general consensus among both psychiatrists and obstetricians that perinatal and postnatal mental illness has detrimental effects on the fetus and the child. Interaction difficulties between depressed mothers and their children are universal across all cultures and socioeconomic status groups.[20] Meta-analysis data has shown that there is a correlation between perinatal mental illness and obstetrical complications, such as pre-eclampsia, low Apgar scores, and *neonatal intensive care unit* (NICU) admissions; there is, however, no known causation. It is hypothesized that hyper- or hypoactivity of the *hypothalamic–pituitary–adrenal* (HPA) axis may affect uterine artery blood flow, fetal developmental growth, and parturition.[21] **Both antenatal and postpartum depression have been linked with insecure attachment of the disorganized type.** There is an increased risk of poor cognitive outcomes

with postpartum depression when compared to antenatal depression, including a very small decrease in IQ scores.[22]

A meta-analysis of studies on early interactions between mothers and infants shows that mothers with postpartum mental illness were more irritable, hostile, and less engaged with their infants and displayed overall decreased emotions and warmth toward their infants. They even showed decreased rates of play, which can delay the development of social and motor skills in infants. Non-depressed mothers engage in face-to-face play and smiling such that infants learn healthy communication skills, and these behaviors are fewer in depressed mothers. These infants later show less expressive language skills and decreased performance on measures of cognitive-linguistic functioning.[20]

Longitudinal studies have shown that in the children of mothers experiencing antenatal depression, there is an increased risk of emotional problems during childhood and an increased incidence of depressive episodes during adolescence. Some studies have even shown that male infants of mothers with depression are more vulnerable than female infants to high levels of maternal depressive symptoms.[20] Postpartum depression has been shown to increase the risk of depression and *attention-deficit hyperactivity disorder* (ADHD) in children up to 16 years old. Unfortunately, maternal education and support have only been shown to improve associations between postpartum depression and poor childhood outcomes, but have not been shown to improve antenatal depression.[22]

Infanticide is perhaps the most drastic consequence of postpartum psychiatric illness and is most often associated with postpartum psychosis. More than half of mothers with postpartum depression reported thoughts of wanting to harm their infant, fear of being alone with their infant, and fear of their inability to care for their infant.[20]

Table 1:
Negative Effects of Peripartum Psychiatric Illness on the Mother–Child Dyad

- Irritability in the mother and decreased emotional bonding with the infant
- Problems with breastfeeding
- Reduced use of safety practices, such as car seats
- Lower rates of preventive healthcare utilization and vaccination
- Insecure attachment of the disorganized type in the infant
- Negative impact on cognition and language development
- Decreased rates of play in the infant
- Delayed development
- Increased risk of emotional problems in childhood
- Increased risk of depression in adolescence
- Infanticide
- Suicide

The Pregnancy and Lactation Labeling Rule (PLLR)

In December 2014, the FDA published the new PLLR, which took effect on June 30, 2015. This changes the current prescription drug labeling system (A, B, C, D, and X) to a new system that is intended to help healthcare providers better understand the risks and benefits of medication use during pregnancy and lactation and communicate this to their patients more appropriately. New medications approved after June 2015 no longer have the old safety categories, and there is a minimum of three years to submit updated information to meet the requirements of the PLLR for all drugs approved after June 30, 2001.[23] The first regulations were introduced in the US in 1962 in response to the use of thalidomide during pregnancy, which led to at least 17 cases of fetal limb abnormalities. Critics of the ABCDX labeling system have long pointed out that not all drugs within the same category have the same risk, and the categories are often misleading, especially for medications for which no human data exists.

The new labeling includes three updated categories: "pregnancy" (information regarding pregnancy exposure), "lactation" (the amount of a drug that is transferred in breast milk and potential effects on the infant), and "females and males of reproductive potential" (contraception recommendations and information about infertility). The lactation section includes information on how much of a drug is secreted in breast milk and how this amount compares to blood concentrations. This information will be used to determine how much of the drug is consumed by the infant. Under each of these categories, there is a general outline for each drug that includes whether or not a registry for the drug exists, a general background risk statement, clinical considerations (with prescribing

decision-making suggestions for providers), and a summary of the available data from trials (human and animal data will be presented separately).[24]

General Principles of Psychotropic Use During Lactation:

- Use the lowest effective dose and avoid polypharmacy where possible.
- Where practical, breastfeeding can be timed to avoid peak drug levels in the milk, or the milk can be expressed for subsequent feeding.
- The benefits of breastfeeding for the mother–infant dyad must be weighed against the risks of harm to the infant from medication exposure on a case-by-case basis. The infant is at risk of exposure to medication side effects and the effects of untreated psychiatric illness of the mother. Clinical decision making should take both these exposures into account.
- All infants of lactating mothers receiving psychotropic medications should be monitored for any general and specific adverse effects. Most psychotropic medications can cause sedation.
- Breastfeeding should be stopped if any adverse effects secondary to medication use are suspected.
- Extra caution should be exercised with premature infants and infants with renal, hepatic, cardiac, or neurological impairments, as they are at a greater risk of side effects, even from low levels of medication exposure.
- In general, treatment for psychiatric illness in the mother, especially when the risk of relapse is high, takes precedence over the benefits of lactation. It may be preferable to cease breastfeeding, rather than cease the medication if the two are determined to be incompatible.
- If the mother has taken psychiatric medication during pregnancy up to the time of delivery, her continuation of the medication during lactation will minimize withdrawal/discontinuation symptoms in the infant.
- Take into consideration how the effects of a medication could affect the mother's ability to care for her baby.
- Psychiatric medications for which there is more published data regarding safety should be preferred over recently marketed medications, unless clinically indicated otherwise.
- Where possible, medications with short half-lives, high protein binding, low oral bioavailability, and high molecular weight should be preferred.
- Psychotropics with long pediatric half-lives should be used very cautiously, given the risk of build-up in an infant's plasma over time.
- Acknowledge the maternal caregiver role and respect the mother's preferences with regard to lactation without judgment.
- Offer psychological interventions to all patients who choose not to continue psychotropic medication during lactation.
- Measuring serum levels of the psychotropic medications in the infant is not routinely recommended.

Pharmacokinetics in Lactation

Drugs generally enter a mother's milk through a process of passive diffusion due to the concentration difference between the maternal plasma compartment and the milk compartment. The maternal plasma concentration of the medication therefore becomes a crucial determinant of drug penetration. To diffuse into the milk compartment, drugs have to pass through bilayer lipid membranes of the lactocytes. Lipid-soluble drug molecules are better able to move across these membranes. (In the first three days postpartum there are large gaps between lactocytes facilitating the transfer of maternal immunoglobulins and other proteins, which also allows the transfer of most drugs. Nonetheless, the absolute dose of the medications during this period is still low as the rate of milk production is lower in the first few days.[25]) Some cellular pumps that actively transfer drug molecules into the milk have been identified, most important of which is iodine.

However, transfer by cellular pumps is not a significant mechanism for the lactational transfer of psychiatric medications.

Weakly basic drugs with high pKa (e.g., barbiturates) can become trapped in the milk compartment after diffusion because the relatively lower pH of human milk changes the ionic state of the drugs. Drug molecules in the maternal plasma circulate either bound to albumin or circulate freely. It is the unbound fraction of the circulating drug molecules that is transferred into the milk; therefore, medications with low protein binding are present in higher concentrations in the milk.

Medications transfer easily into human milk if there is a high concentration in the maternal plasma, if they have a low molecular weight, if their protein binding is low, and if they are lipid-soluble.[25]

Once medication is present in the milk, several other pharmacokinetic considerations come into play. The primary consideration is the oral bioavailability (the percentage of a drug that reaches the systemic circulation after oral administration) of the medication to the infant. The medication may be poorly absorbed or may be metabolized by the neonatal liver. The glucuronidation and oxidation systems are immature at birth (they can be functioning at a level as low as 20% of adult levels). Additionally, rates of glomerular filtration and tubular secretion are also significantly lower, which could potentially result in higher-than-anticipated psychotropic exposure for the newborn.[26]

Some of the pharmacokinetic parameters of importance with respect to lactation include the half-life of the medication, the time interval from the time of medication administration to the time of peak level in the mother's plasma, the percentage of maternal protein binding, oral bioavailability, the *milk-to-plasma* (M/P) ratio, and the *relative infant dose* (RID).[25] The M/P ratio is the concentration of medication in the mother's milk divided by the concentration in the mother's plasma. M/P ratio greater than 1.0 is indicative that the drug is present in breast milk in concentration higher than the concentration in mother's plasma. However, the absolute amount of drug transferred would depend on the concentration in the mother's plasma. Therefore, even a medication with a high M/P ratio would be present in milk in low amounts if the concentration in the mother's plasma is low. Therefore, M/P values by themselves can be misleading. A better indicator is the RID, which is the daily dosage of the drug received by an infant via breast milk (mg/kg/day) expressed as a percentage of the weight-adjusted maternal daily dose (mg/kg/day). A cut-off RID value of 10% is increasingly being accepted to imply that the medication is compatible with breastfeeding. However, values higher than 10% do not necessarily indicate that a medication is incompatible with lactation. Another way of quantifying infant drug exposure is to express the infant serum concentration of the medication as a percentage of the maternal serum concentration. Using this quantifying factor, in a clinical report,[27] the American Academy of Pediatrics provided a list of psychiatric medications with infant serum concentrations exceeding 10% of maternal plasma concentrations during breastfeeding. This list consisted of *citalopram* (Celexa) *clomipramine* (Anafranil), *diazepam* (Diastat, Valium), *doxepin* (Silenor, Zonalon, Prudoxin), *fluoxetine* (Sarafem, Prozac), *fluvoxamine* (Luvox, Faverin, Fevarin, Floxyfral), *lamotrigine* (Lamictal), *lithium* (Lithobid, Lithane), *mirtazapine* (Remeron, Remeronsoltab), *nortriptyline* (Pamelor), *olanzapine* (Zyprexa), *sertraline* (Zoloft), and *venlafaxine* (Effexor). It is pertinent to mention here that majority of these medications are regularly prescribed for use during breastfeeding by clinical experts in this field with no appreciable side effects.

The ideal characteristics of a psychotropic suitable for lactation are a short half-life, high maternal protein binding, a low M/P ratio, low RID, and low infant serum concentration compared to maternal plasma concentration. While helpful in theory, in practice, the lactational risk associated with psychotropics in the existing literature has been determined largely based on reported (and often isolated) adverse events; clinical lactational risk cannot be predicted based on knowledge of pharmacokinetic data alone.[28]

The pharmacokinetics of medication transfer in breast milk involve the two well-recognized excretion gradients of distribution and time.[26] Because psychotropic medications are lipophilic, they are present in greater concentrations in the fatty hindmilk and in lesser concentrations in the foremilk. Owing to the distribution gradient, the M/P ratio calculated from a random breast milk sample can give an inaccurate estimation. The time

gradient gives information about the relationship between medication ingestion by the mother and the time of peak breast milk concentrations for that medication, which depends on the rate of gastrointestinal absorption of the medication. For instance, for sertraline, the peak breast milk concentration occurs approximately eight hours after the most recent dose, while the lowest concentration occurs just prior to the next dose.[26] Knowledge of the time gradient can be utilized to decrease infant medication exposure by timing the breastfeeds at times when the drug concentration in the milk is expected to be low.

Table 2:
Important Pharmacokinetic Parameters in Lactation

Milk-to-Plasma (M/P) Ratio: the ratio of the concentration of medication in mother's milk divided by the concentration in mother's plasma

Relative Infant Dose (RID): the daily dosage of the medication received by an infant via breast milk (mg/kg/day), expressed as a percentage of the weight-adjusted maternal daily dose (mg/kg/day)

The infant serum concentration of medication is expressed as a percentage of the maternal serum concentration.

Psychotropics and Lactation

The discussion below presents a summary of the most pertinent clinical issues related to the use of respective psychotropic medications during lactation. It is not meant to be exhaustive; for a more comprehensive discussion of particular psychotropic medications, consult the Drugs and Lactation Database,[29] which is part of the National Library of Medicine's Toxicology Data Network. It is updated monthly and is peer reviewed for accuracy. It is important to mention that there is a significant dearth of high-quality research in this area, with most of the side effects being reported in isolated case reports, and given the lack of large-scale studies and controlled trials, the rates of the reported side effects are unknown and are expected to be very low. A literature discussion that relies heavily on isolated case reports, as the discussion on the safety of psychotropics in lactation usually is, becomes biased towards the negative because the few cases of adverse events are highlighted, while the millions without adverse events go unrecognized in comparison. Therefore, in this review we have generally chosen not to include adverse events reported in single case studies.

Antidepressants:

Selective-serotonin Reuptake Inhibitors (SSRIs)

Fluoxetine

Fluoxetine (along with its active metabolite norfluoxetine) is present in breast milk in relatively higher amounts compared to other SSRIs. Due to its longer half-life, it is also more likely to accumulate in breastfed infants. Widespread clinical use has established the safety of fluoxetine in lactation colic; decreased sleep, vomiting, watery stools, hyperactivity, and decreased arousal have been reported in isolated case reports, but the rates of these effects are not known and are expected to be clinically very low.[29] Where possible, other antidepressants with lower breast milk excretion should be preferred during lactation, but if required, fluoxetine can be used with caution.

Fluvoxamine

Infant serum levels of fluvoxamine are generally undetectable, although one case of an infant serum level greater than 10% of the mother's has reported.[30] No adverse effects, including effects on neurobehavioral development, have been reported.

Paroxetine and Sertraline

Paroxetine (Pexeva, Paxil) and sertraline have low levels in breast milk and are generally undetectable in infant serum. They can generally be used during lactation without adverse effects, although irritability and feeding problems have been reported with paroxetine, and hypotonia, drowsiness, growth disturbance, and withdrawal symptoms on cessation of feeding have been reported with sertraline.[29] **Paroxetine and sertraline are considered by many reviewers to be two of the preferred antidepressants for use during lactation;** however, clinically, it should be recognized that paroxetine has the worst withdrawal symptoms among the SSRIs. Sertraline is also the only psychotropic with an L1 lactation risk category (extensive data, compatible) as of 2015, according to Hale.[25]

Citalopram

Low infant serum levels of citalopram have been reported to be detectable in some infants. Poor suckle, drowsiness, and sleep disturbance have been reported.[31] However, adverse effects in infants are comparable to controls,[32] and normal neurobehavioral development up to one year has been reported.[33]

Escitalopram

Limited available data indicates that *escitalopram* (Lexapro) should be preferred over citalopram during lactation due to lower levels in breast milk and the lack of reported adverse events.[29]

Serotonin–norepinephrine Reuptake Inhibitors (SNRIs)

No adverse effects have been reported in infants with the use of venlafaxine, *desvenlafaxine* (Pristiq), and duloxetine during lactation. Duloxetine in breast milk is low and infant serum levels are undetectable to low. Both venlafaxine and desvenlafaxine are present in breast milk in relatively higher amounts, with desvenlafaxine exposure of breastfed infants being about half of the total drug exposure of breastfed infants compared to venlafaxine.[29] Infant serum levels are less than 10% for desvenlafaxine but can be higher than 10% for venlafaxine.

Tricyclic Antidepressants (TCAs)

For decades, TCAs have been used during lactation with safe outcomes. In general, the infant serum levels for TCAs are undetectable to low. Side effects in infants have not been reported with the use of *amitriptyline* (Pamelor), clomipramine, *desipramine* (Norpramin), *dosulepin* (Prothiaden, Dothep, Thaden), *imipramine* (Tofranil), *mianserin* (Lumin, Tolvon), and nortriptyline in lactation. Doxepin is an exception among TCAs in this regard due to its sedating effects, long half-life, high infant serum levels, and two reported cases of respiratory depression.[30, 34] There is a universal recommendation among reviewers to avoid doxepin during lactation, especially as other safer alternatives are available.[25,26,28,29,34,35] It carries a Hale's lactation rating of L5 (limited data, hazardous).[20] Of the TCAs, some reviewers prefer nortriptyline for use during lactation.[34, 35]

Monoamine Oxidase Inhibitors (MAOIs)

There is little to no published literature establishing the safety of MAOIs during lactation. Additionally, the clinical use of MAOIs is complicated by significant drug interactions and dietary restrictions. Therefore, MAOIs are not preferred for use during lactation.

Other Antidepressants

Bupropion

Bupropion (Wellbutrin, Buproban, Aplenzin) has low levels in breast milk and side effects have not generally been reported, except for a case of seizure in a six-month-old infant consistent with its seizure- lowering potential.[36]

Mirtazapine

Mirtazapine (Remeron) is generally present in low concentrations in breast milk, and no adverse events with its use have been reported.

Trazodone

Trazodone (Oleptro) drug levels in milk are low, and no adverse effects have been reported.

Mood Stabilizers:

Lithium

Lithium use during the first trimester of pregnancy has been associated with a teratogenic risk of cardiac malformations, characteristically the Ebstein anomaly (a malformation of the tricuspid valve and right ventricle), which occurs in 1 in 1000 births with lithium exposure.[38] Its use during the second and third trimesters can lead to a number of neonatal complications, such as premature labor, polyhydramnios, cardiomegaly, hepatomegaly, nephrogenic diabetes insipidus, goiter and hypothyroidism, and gastrointestinal bleeding.[38] It can also result in "floppy infant syndrome" in neonates secondary to lithium toxicity, manifesting as flaccidity, lethargy, poor suckling, low Apgar scores, shallow breathing, and apnea. Holding lithium 24–48 hours prior to delivery (in case of planned induction) and resuming after delivery when the mother is medically stable can help minimize the infant's serum lithium concentration at birth, decreasing the risk of neonatal toxicity.[39] Treatment with lithium during pregnancy often requires an elevated dose because maternal

renal clearance is increased. After delivery, maternal renal clearance returns to baseline levels, and maternal lithium levels therefore require close monitoring.

Lithium is present in breast milk in relatively higher amounts compared to other psychotropic medications. The M/P ratio varies from 24%–66%. The RID is 12%–30%. Infant serum levels are usually within the range of 10%–50% of maternal serum concentrations,[40, 41] but this range can be as wide as 5%–200%.[34]

Numerous side effects in infants with lithium exposure via lactation have been reported in the literature, including hypotonia, lethargy, hypothermia, cyanosis, and electrocardiogram changes.[41, 42] However, in multiple studies, lithium has been well tolerated by breastfed infants with no signs of toxicity or behavioral and developmental effects.[29,43]

Due to lithium's high concentrations in breast milk and high infant serum levels and the reported adverse effects and potential for serious toxicity, lithium has traditionally been considered to be incompatible with breastfeeding. However, other sources have argued for a cautious rehabilitation of lithium use during lactation based on evidence from multiple studies where breastfed infants did not experience significant adverse effects. This is particularly the case when the infant is healthy and is being regularly monitored.[28] The American Academy of Pediatrics[44] has classified lithium as a medication associated with significant effects on some nursing infants that should be administered to nursing mothers with caution. It has a Hale's lactation category of L4 (significant data—possibly hazardous).[25]

Some authors have recommended monitoring infant serum lithium, serum creatinine, *blood urea nitrogen* (BUN), and *thyroid-stimulating hormone* (TSH) every 4–12 weeks during breastfeeding,[43,45] but other sources have recommended obtaining infant serum lithium levels and utilizing laboratory monitoring only if concerns arise during clinical monitoring.[46]

The hydration status of the infant has dramatic effects on lithium levels, and dehydration can result in significant lithium toxicity. The hydration status of nursing infants should therefore be carefully monitored during maternal lithium therapy.

Valproic Acid

Valproic acid is present in low concentrations in breast milk and infant serum, and no side effects have been reported. Its use during lactation is generally considered safe. Some authors recommend periodic monitoring of serum valproate levels, blood counts, and liver enzymes in nursing infants,[47] but the recommendation is not universal. Although safe during lactation, there are significant fetal risks associated with the use of valproic acid during pregnancy.[38]

Carbamazepine

Carbamazepine (Tegretol, Carbatrol, Equetro) is present in breast milk in relatively high levels with detectable infant serum levels, but its use during lactation is generally considered safe. The vast majority of infants do not experience any adverse effects. Poor suckling, decreased weight gain, sedation, and spasms have been observed after the cessation of breastfeeding; however, the rates of these effects are unknown and likely to clinically very low.[31,34] Infants should be clinically monitored for jaundice and signs of hepatic dysfunction. The monitoring of blood counts, serum liver enzymes, and serum carbamazepine levels in infants has been recommended.[47] Similar to valproic acid, carbamazepine use is safe during lactation, but there are significant fetal risks associated with its use during pregnancy.[38]

Lamotrigine

Lamotrigine (Lamictal) has high infant plasma levels (up to 50% of maternal levels), and neonates have a low ability to metabolize the drug.[29] Benign thrombocytosis, irritability, poor feeding, and respiratory sedation have been reported.[31,34] Lamotrigine can cause a life-threatening rash in adults and children, with a higher risk in the pediatric population.[48] This has not been reported so far in breastfed infants.

Typical Antipsychotics:

Infant exposure to typical antipsychotics via lactation is generally clinically insignificant. Most studies have reported no adverse effects. Three infants exposed to a combination of haloperidol and chlorpromazine were reported to have delayed development,[49] but other

studies have reported no developmental delays with *haloperidol* (Haldol) and *chlorpromazine* (Thorazine).[34,50] Chlorpromazine was associated with lethargy in one infant, but no side effects have been noted for haloperidol, *flupenthixol* (Depixol, Fluanxol), *perphenazine* (Trilafon), *trifluoperazine* (Eskazinyl, Eskazine, Jatroneural), *zuclopenthixol* (Cisordinol, Clopixol, Acuphase), *sulpiride* (Dogmatil), and amisulpride.[34,51]

Atypical Antipsychotics:

As with typical antipsychotics, the transfer of atypical antipsychotics through breast milk to infants is low and clinically insignificant. There is a paucity of published literature on the use of atypical antipsychotics in lactation, but no recurring adverse effects have been reported in infants exposed to olanzapine, aripiprazole, risperidone, quetiapine, and ziprasidone.[34, 51]

Sedation and excessive accumulation of clozapine in breast milk have been reported,[31] but the rates are unknown. Due to clozapine's potential to cause agranulocytosis, some authors are wary of its use during lactation.[29, 51] As clozapine is most often used for treatment-resistant schizophrenia after other antipsychotics have failed, in situations warranting concern, it is more feasible to discontinue breastfeeding than to discontinue clozapine.

Sedatives and Hypnotics:

Benzodiazepines

There is a risk of *central nervous system* (CNS) depression and apnea with lactational exposure to benzodiazepines, although the risk is generally low. In one study of 124 mothers treated with benzodiazepines (mostly *lorazepam* [Ativan], *clonazepam* [Klonopin], and *midazolam* [Dormicum, Hypnovel]), sedation was noted in two infants (1.6%).[52] Sedation has been reported with diazepam use,[31] and sedation and withdrawal symptoms have been reported with alprazolam use.[31]

Neonates metabolize benzodiazepines slowly, and benzodiazepines therefore accumulate in neonates who receive continued exposure through lactation. **Benzodiazepines with longer half-lives, such as diazepam, are not recommended for use during lactation for that reason.** Lorazepam has no active metabolites and is preferable in low doses. When used judiciously, benzodiazepines are safe during lactation, and single doses should not require any limitation on breastfeeding. However, all infants exposed to benzodiazepines should be monitored for signs of CNS depression, and breastfeeding should be discontinued if signs of toxicity, such as sedation, reduced suckling, or respiratory depression, are noted.

Other Hypnotics

Limited published literature appears to indicate that *zaleplon* (Sonata), *zolpidem* (Edluar, Ambien, Zolpimist), and zopiclone are safe to use during lactation.[31,51]

Table 3:
Psychotropic Medications and Lactation: Summary of Concerns

Antidepressants
- Fluoxetine has a longer half-life and is more likely to accumulate.
- Doxepin has been linked to sedation and respiratory depression in infants. Its use is contraindicated during lactation.
- Avoid MAOIs given the significant drug interactions, dietary restrictions, and lack of safety literature.
- Bupropion can lower the seizure threshold.

Mood Stabilizers
- Lithium is present in milk in high amounts and has the potential for toxicity. Administer with caution during lactation, with regular clinical and laboratory monitoring of the infant.
- Lamotrigine has the potential to cause a life-threatening rash. Monitor and immediately discontinue with any appearance of a rash.

Antipsychotics
- There is limited data for antipsychotics in general, but there are no significant safety concerns except for clozapine, which can potentially lead to agranulocytosis.

Benzodiazepines
- Benzodiazepines can accumulate in neonates due to immature hepatic (cytochrome P450) enzymes.
- There is a risk for CNS and respiratory depression. Monitor clinically.
- Avoid benzodiazepines with long half-lives, such as diazepam.

Conclusion

The prevalence of psychiatric disorders during the postpartum period is at least comparable to that of the general population, with some indication that the first five weeks after childbirth are a vulnerable period for the onset of psychiatric illness. Additionally, there are significant detrimental effects of psychiatric illness on the mother and infant. These include a negative impact on bonding with the infant, reduced cognitive and language development, insecure attachment, increased risk of depression for the child in childhood and adolescence, suicide, and infanticide. All psychotropic medications are secreted in breast milk, but the majority are present only in low concentrations and can be used safely in lactating mothers. Medications that warrant further caution include fluoxetine (risk of accumulation), doxepin (respiratory depression), MAOIs (complicated clinical use and lack of safety literature), lithium (high breast milk concentration, potential for toxicity), and benzodiazepines (CNS and respiratory depression).

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Multiple-Choice Questions

57. Which of the following is *true* with regard to the risk of psychiatric illness in the postpartum period?

A. A prior history of depression does not increase the risk of subsequent development of postpartum depression.

B. Primiparity is an obstetric risk factor strongly associated with developing postpartum psychosis.

C. Most cases of postpartum psychosis are believed to be cases of schizophrenia.

D. Pregnancy and the postpartum period have been shown to be "protective periods" for mental health, with lower incidence and prevalence of psychiatric disorders.

58. Which of the following is *false* with regard to the consequences of psychiatric illness in the postpartum period?

A. Infanticide is more often associated with postpartum psychosis, but women with postpartum depression also report thoughts of wanting to harm their infants.

B. Postpartum depression has been shown to increase the risk of emotional problems beyond childhood years and even into adolescence.

C. Both antenatal and postpartum depression can lead to insecure attachment of the disorganized type.

D. Children of depressed mothers have higher rates of preventive healthcare utilization.

59. Which of the following is *true* regarding the use of antidepressants and mood stabilizers during lactation?

A. Paroxetine and sertraline are the preferred antidepressants for use during lactation.

B. Fluoxetine has a short half-life and is less likely to accumulate in infants.

C. There are no reported cases of seizures in infants exposed to bupropion through lactation.

D. The hydration status of the infant does not significantly influence lithium levels in the neonate during breastfeeding.

60. Which of the following is *false* regarding the use of antipsychotics and sedatives/hypnotics during lactation?

A. Infant exposure to typical antipsychotics via lactation is generally low, and most studies report no adverse effects.

B. Clozapine has the potential to cause agranulocytosis in the infant due to exposure via breast milk.

C. There is no significant risk of CNS depression and apnea with exposure to benzodiazepines because they are not found in high concentrations in breast milk.

D. Benzodiazepines with short half-lives are preferred for use during lactation.

Best Practices in CME

Psychiatric Disorders and Psychotropic Treatment in the Postpartum Period

Asim A Shah, MD; Awais Aftab, MD; and Samantha Latorre, MD

ID#: L003358

This valuable take-home reference translates the evidence-based, continuing medical-education research and theory acquired through reading the associated CME lesson into a simple list that reviews key points in for easy assimilation into the clinician's armamentarium knowledge and daily practice.

CME Lesson Overview

The information in this lesson will be helpful to psychiatrists, family physicians, and obstetricians who require information on the prevalence of psychiatric disorders in the postpartum period, the negative effects of psychiatric illness on the mother and infant, and the psychopharmacological treatment of postpartum or lactating patients with psychiatric disorders.

Key Point 1: Risk of Psychiatric Disorders in the Postpartum Period

Evidence strongly indicates that the prevalence of psychiatric disorders during pregnancy and the postpartum period is at least comparable to that in the general population, with some indication that the first month after childbirth is particularly high risk for the onset of depression and psychiatric admission.

Key Point 2: Effects on Psychiatric Illness on Mother and Infant

There are significant detrimental effects of untreated psychiatric illness on the mother and infant. These include the negative impact on bonding with the infant, reduced cognitive and language development, insecure attachment, increased risk of depression for the child in childhood and adolescence, suicide, and infanticide.

Key Point 3: Pharmacokinetics in Lactation

The ideal characteristics of a psychotropic suitable for lactating women are short half-life, high maternal protein binding, low milk-to-plasma ratio, low relative infant dose, and low infant serum concentration compared to maternal plasma concentration.

Key Point 4: Psychotropic Medications and Lactation

All psychotropic medications are secreted in breast milk, but the majority are present only in low concentrations and can be used safely in lactating mothers. Medications that warrant further caution include fluoxetine, doxepin, MAOIs, lithium, and benzodiazepines.

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