Review: The Use of Antidepressants in Pregnant and Breastfeeding Women: A Review of Recent Studies

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Review

The Use of Antidepressants in Pregnant and Breastfeeding Women: A Review of Recent Studies

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Abstract

Antidepressants are one of the most commonly prescribed medications for pregnant and lactating women. However, there have been some recent concerns about their safety. This article summarizes recent research on the impact of untreated depression on the baby, the effects of antidepressants on the baby when prescribed during pregnancy, the short- and longer-term effects of prenatal exposure on infants and children, and the passage of medications into breast milk. Recommendations are made on providing mothers and their health care providers with information so they can make accurate risk/benefit analyses about using these medications while pregnant or breastfeeding. *J Hum Lact*. 26(2):187-195

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Depression is one of the most commonly occurring conditions occurring among pregnant and postpartum women. Treatments for depression include antidepressants and a wide-range of nonpharmacologic treatments, such as psychotherapy, social support, exercise, and St. John's wort. We have described alternative treatments for depression in detail elsewhere and will not be describing them here.[1,2] Rather, the focus of this article is antidepressant medication.

In some cases of depression, medications are the most appropriate treatment choice. But decisions about using medications with pregnant and lactating women always require balancing various forms of risk. Medication exposure involves risk, but so does untreated depression. Newport and colleagues note that "maternal depression and/or its treatment results in some degree of exposure, be it illness or treatment. Exposure cannot be eliminated; it can only be reduced. Therefore, no clinical decision in the context of PPD [postpartum depression] is ever risk free."[3]

With recent concerns about antidepressant use, it can be difficult for clinicians to know whether they are safe. Existing studies can be contradictory. For example, in 2005, GlaxoSmithKline published findings that infants exposed in utero to paroxetine (Paxil) may have a higher risk for congenital cardiovascular defects.[4] A subsequent report refutes this study and suggests that the incidence of cardiovascular defects is the same as in unexposed pregnancies.[5] Along these same lines, although there are extensive data that suggest that the transfer of antidepressants into human milk is minimal,[6] other recent articles have raised concerns about whether mothers taking antidepressants should be encouraged to breastfeed because of possible long-term effects of antidepressants transferred via the milk.[7]

Medications present challenges when used in pregnant and breastfeeding women. These challenges include: (1) what are the complications to the pregnancy if the mother goes untreated? (2) What are the complications to the fetus, if the mother is treated with medications? (3) What are the complications to the newborn infant from untreated maternal depression? and finally, (4) What are the complications from maternal transfer of medications into her milk, and absorption by the infant?

In this paper, we summarize recent research on how antidepressants affect the developing fetus and whether these effects persist into childhood. To identify articles, we searched PubMed and PsychInfo for articles

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on antidepressants, pregnancy, and breastfeeding with a focus on infant outcomes from 1990 to the present. We also searched by specific medication names (eg, sertraline [Zoloft], fluoxetine [Prozac], paroxetine). We also summarize research on the transfer of medications to the infant via breastfeeding. Although we are mainly concerned with the impact of medication exposure via breastfeeding, the studies of in utero exposure are helpful because they allow us to understand the longer-term effects of much higher levels of exposure than would be seen with exposure via breast milk only. Finally, we make recommendations regarding how to counsel mothers.

Risks Associated with Untreated Depression

One challenge associated with medicating pregnant and breastfeeding women is making accurate risk/benefit analyses.[8] Are the risks of using medication less than the risks of untreated depression? In many cases, the answer is likely to be yes. Discontinuing medications during pregnancy can lead to relapse of symptoms for up to 68% of women.[9] And the effects of untreated depression are not trivial.

Untreated Depression and Preterm Birth

A number of recent studies have demonstrated that depression is a strong risk factor for preterm birth and low birth weight.[10] In a prospective cohort study of 681 women from France, the rate of spontaneous preterm birth for depressed women was more than double that of nondepressed women (9.7% vs 4%; odds ratio [OR] = 3.3, confidence interval [CI] = 1.2-9.2).[11] A study in Goa, India (N = 270) found that maternal psychological morbidity was independently associated with low birth weight (OR = 1.44, CI = 1.0-2.07). Babies with mothers with high scores on the General Health Questionnaire (GHQ) were significantly more likely to be of low birth weight. These findings were true even after controlling for other factors that influence birth weight, such as maternal age, maternal and paternal education, and paternal income.[12]

A study of 70 depressed and 70 nondepressed women found that women with depressive symptoms had higher prenatal cortisol and norepinephrine levels, and lower levels of dopamine and serotonin. A higher percentage of depressed mothers (34%) had babies who were low birth weight compared with the nondepressed mothers (14%). The newborns' plasma cortisol and norepinephrine levels were similarly elevated (40% of maternal cortisol crosses the placenta). The infants also had lower levels of dopamine and serotonin, and less optimal habituation, orientation, motor skills, range of state, and autonomic stability on the Brazelton Scale.[13] The women were recruited and assessed for depression during their second trimester of pregnancy, and again during the neonatal period. None of the women were being treated for depression or taking psychotropic medications.

Another study found that elevated maternal cortisol was related to preterm birth. In this study of 300 pregnant women in their last trimester of pregnancy, mothers with high prenatal levels of urinary cortisol were significantly more likely to have premature babies.[14] These babies had smaller head circumferences, abdominal circumference, biparietal diameter, and fetal weight. The neonates with high cortisol levels had a shorter gestational age and lower birth weight. They also had lower habituation and higher reflex scores on the Brazelton Assessment Scale. Using discriminate function analysis, the researchers found that maternal cortisol levels more accurately predicted short gestation and low birth weight than did scores on the depression inventory. Mothers with elevated cortisol levels are not necessarily depressed, as stress alone has this same physiological profile. But elevated levels of cortisol are seen in some patients with depression.

High anxiety, another condition associated with high cortisol levels, during pregnancy can also increase the risk of preterm birth. A study of 1820 women from Baltimore found that women with high levels of anxiety about their pregnancies were significantly more likely to have infants prematurely.[15] Indeed, women with the highest levels of pregnancy-related anxiety had 3 times the risk of preterm birth compared to women with low anxiety. These findings were true even after controlling for traditional risk factors for preterm birth, including first- or second-trimester bleeding, illicit drug use, unemployment, previous preterm or stillbirth, smoking, low body mass index, maternal education, age, and race.

Effects of Maternal Depression on Child Development

Depression also has a negative effect once the baby is born. Moreover, depression that is chronic and/or severe has a more detrimental effect than depression that is periodic or mild. A study of 80 mothers in their second trimester of pregnancy included 4 groups:

nondepressed women, women depressed only during pregnancy, women depressed only postpartum, and women who were depressed during pregnancy and postpartum. The authors found that babies born to mothers with prenatal depression spent significantly more time fussing and crying, and they demonstrated more stress behaviors than babies whose mothers were not depressed or who were depressed only postpartum.[16] Infants of mothers who were depressed at both time points had poorer Brazelton Neurobehavioral Assessment scores than infants of mothers who had only prenatal or postpartum depression. Based on these findings, the authors concluded that infants are not only influenced by the mere presence of depression, but by the timing and duration as well.

In a study of 112 mother–infant dyads, chronic maternal depression in the first postpartum year was related to delayed psychomotor development at 15 months.[17] Twenty-five percent of infants whose mothers were chronically depressed scored in the mildly to significantly delayed range in psychomotor development compared with infants of nondepressed mothers. These scores were higher than the normal distribution on which the test is based. Infants of chronically depressed mothers were also less likely to be walking competently by 15 months. Contrary to expectation, chronic maternal depression was not associated with a delay in infant language development. Brief maternal depression did not negatively influence infant performance at either 12 or 15 months. The effects were similar for boys and girls.

Children who were premature may be more susceptible to the negative effects of maternal depression. In a series of 2 studies, researchers compared cortisol levels in children, aged 14-16 months, following interacting with their depressed or nondepressed mothers.[18] Preterm infants were found to be more reactive to their mothers' depression than infants who were full term. In the second study, neonatal cortisol levels were also higher in preterm infants of depressed mothers compared to infants of nondepressed mothers. The authors concluded that premature infants were more sensitive to the emotional environment of their homes, and that there were possible implications for their developmental outcomes as a function of depression in the mother.

In summary, untreated maternal depression influences infants during pregnancy by increasing the risk of preterm birth. It also has effects long after pregnancy by affecting the cognitive, psychomotor, and emotional development of infants and young children. The severity and chronicity of maternal depression influence its impact on children. The effects appear to be compounded for premature babies.

Prenatal Exposure to Antidepressants

Risk/benefit analyses also need to weigh the risk of antidepressants taken during pregnancy. Medications have several ways of transferring to babies in utero. They transfer via the placental blood supply[19,20] and via the amniotic fluid.[21] The amount transferred via the placenta is significant and can produce neonatal plasma levels equal to or higher than that of the mothers. In a study of 38 pregnant women who were taking selective serotonin reuptake inhibitors (SSRIs), antidepressant and metabolite concentrations were found in 87% of umbilical cord samples. The mean maternal:fetal serum ratios ranged from 0.29 to 0.89. The lowest ratios were for sertraline and paroxetine, and the highest were for citalopram and fluoxetine. Unfortunately, prenatal exposure to antidepressants is associated with an increased risk of preterm birth and other neonatal complications. These effects can also be significant.[19]

The Effects of Prenatal Exposure on Neonates

In a large population study in British Columbia, Canada (N = 119 547), prenatal exposure to SSRIs was assessed in Canadian mothers.[22] The percentage of SSRI exposure ranged from 2.3% to 5% over the 39-month recruitment period. Birth weight and gestational age were significantly less for the SSRI-exposed infants than for the infants of depressed mothers who were not treated. The most commonly used medications were paroxetine (44.7%), fluoxetine (27.2%), sertraline (25.6%), fluvoxamine (4.6%), and citalopram (3.3%). The rates of complications for SSRI-exposed (vs nonexposed) were as follows: 13.9% for neonatal respiratory distress (vs 7.8%), 9.4% for jaundice (vs 7.5%), and 3.9% for feeding problems (vs 2.4%). The most common complication was respiratory distress, but it was not significantly higher in the infants of depressed, nonmedicated mothers. In addition, the length of hospital stay was significantly longer for exposed infants. The authors concluded that exposure to prenatal SSRIs was associated with increased risk of low birth weight and respiratory distress, even when maternal illness severity was accounted for. They noted that these findings were contrary to what they expected in that they predicted that reducing depression

would lessen adverse neonatal complications associated with maternal depression. They also noted that both exposure to SSRIs and depressed maternal mood had an additive negative effect of exposure to depression alone for these outcomes.

A large, prospective US study (N = 997 infants, 987 mothers) sought to investigate the neonatal effects of exposure to antidepressants during the third trimester.[23] The medications used included tricylic antidepressants, such as clomipramine and amitriptyline, and SSRIs, including citalopram, paroxetine, fluoxetine, and sertraline. Following exposure, there was an increased risk for preterm birth (OR = 1.96, CI = 1.6-2.4) and low birth weight (OR = 1.98, CI = 1.55-2.52). After exposure to antidepressants, especially tricyclic medications, there was an increased risk for lower Apgar scores (OR = 2.33, CI = 1.49-3.64), respiratory distress (OR = 2.21, CI = 1.71-2.86), neonatal convulsions (OR = 4.7, CI = 2.2-9.0), and hypoglycemia (OR = 1.62, CI = 1.22-2.16). Infant outcomes after exposure to paroxetine were no worse than exposure to other SSRIs. Conclusions were that there were neonatal effects of antidepressants consumed late in pregnancy, and that SSRIs (because of their overall better profile) may still be the medications of choice during pregnancy.

A prospective study collected data from women whose babies were born between 1995 and 2003.[24] There were 200 neonates exposed to antidepressants in utero and 1200 nonexposed neonate controls. The purpose of this study was to assess the impact of antidepressants on newborns exposed during pregnancy. The antidepressant users were classified into 3 groups: before conception and during the first trimester; during the second and third trimesters; and before conception and during the entire pregnancy. The most commonly used medications were paroxetine (58 cases), fluoxetine (32 cases), and amitriptyline (26 cases). As with previous studies, there was a significantly increased risk of preterm birth for exposed vs nonexposed infants. This finding was particularly true for the chronically exposed group.

Of the 200 infants exposed to antidepressants,[24] 14 experienced adverse events and 3 required NICU/SCN admission. There was no significant difference in adverse events after adjusting for prematurity, birth weight, and sex of the neonate between the exposed and nonexposed groups. Moreover, there were no significant effects found by medication type. Three cases (5%) of neonatal complications were reported with paroxetine exposure, one of which required admission to the NICU. In contrast, in the nonexposed group, there were 17 complications (5%), 6 of which required NICU admission. One case of cardiac malformation was reported following paroxetine exposure in the first trimester, and a total of 2% of the control group had malformations, none of which were cardiac malformations. A major limitation of these findings is that data were collected via maternal interview and therefore may have underreported findings, especially minor effects.

The results of the Sloane Epidemiology Center Birth Defects Study recently confirmed that SSRIs do not significantly increase the risk of birth defects overall. They included 3 birth defects in their study: craniosynostosis, omphalocele, and heart defects.[25] Sertraline increased the risk of omphalocele (OR = 5.7, CI = 1.6-20.7) and septal defects (OR = 2.0, CI = 1.2-4.0), and paroxetine increased the risk of the heart defect right ventricular outflow tract obstruction (OR = 3.3, CI = 1.3-8.8). It should be noted that even with these odds ratios, only 1.7% to 4.7% of infants with these defects were exposed to SSRIs in the first trimester. The authors concluded that the overall risk of having a child affected by SSRI use was only 0.2%.

Discontinuation Syndrome

There are a number of reports of neonatal withdrawal symptoms in newborn infants exposed during gestation to one of the SSRIs. Discontinuation syndrome is characterized by poor adaptation, jitteriness, irritability, and poor gaze control after gestational exposure to selective SSRIs, and has been reported for fluoxetine,[26] sertraline, and paroxetine.[27]

In a prospective study of neonates, newborn behavior was compared between babies exposed to medication in the second and third trimesters of pregnancy (N = 46), and nonexposed babies (N = 23). Among babies exposed to medications, some were exposed to SSRIs alone. The second group was exposed to an SSRI and clonazepam.[28] Maternal drug levels were assessed during pregnancy and at delivery. Infant drug levels were assessed via cord blood and at day 2 postpartum. All but 1 of the babies were born healthy and at full term. Thirty percent of the exposed infants had symptoms of poor transient neonatal adaptation. These symptoms were significantly more common in the SSRI/clonazepam group (39%) than in the SSRI group alone (25%). The most common symptoms were mild respiratory distress, and in some rare cases, hypotonia. Indeed, all the infants with symptoms had respiratory distress, frequently described as TTN (transient

tachypnea of the neonate). The symptoms were self limited, and when these infants were assessed at 2 and 8 months on the Bayley Scales of Infant Development, there were no significant differences between the exposed and nonexposed groups. These effects were especially likely when paroxetine was combined with clonazepam, as clonazepam appeared to change metabolism of paroxetine. The SSRIs used in the study included fluoxetine, sertraline, and paroxetine. Interestingly, the infants without symptoms had had longer exposure to the medications than infants with symptoms, but these differences were not significant.[28]

In a recent review,[29] the authors noted that exposure to SSRIs late in pregnancy increased the risk of neonatal discontinuation syndrome (OR = 3.0, CI = 2.0-4.4) compared with early exposure or no exposure. This finding suggests a typical withdrawal syndrome, indicating that tapering these medications in the third trimester may be advisable. Most of these studies reported on the effects of fluoxetine and paroxetine. These symptoms are generally mild and self-limiting, and they can be managed with supportive care. Severe symptoms are rare, and no reported neonatal deaths have occurred that are attributable to SSRI exposure. Paroxetine seems to be the SSRI that produces the majority of withdrawal symptoms in neonates. Compared with other SSRIs, it is the medication with the greatest pharmacologic affinity for the 5-HT transporter. In addition, it has the most anti-muscarinic activity of the SSRIs and is biologically similar to the tricyclic antidepressants. It has the shortest half-life of all SSRIs. And lastly, it does not have active metabolites (such as fluoxetine), which could ease or delay withdrawal symptoms.

In summary, discontinuation syndrome generally occurs 24-48 hours postpartum (longer for fluoxetine) and typically lasts only a day or 2. Minimal or no treatment is suggested, and breastfeeding should continue in these situations.

Do Effects of In Utero Exposure Persist into Childhood?

Given the number of studies that have found effects in the newborn period, it is important to know whether these effects persist into childhood. Two studies examined the long-term effects of prenatal and postnatal exposure to SSRIs. Both studies included the same cohort of patients and were designed to assess "behavioral teratogenicity" at age 4 that may have occurred in the wake of SSRI exposure in utero, and via breast milk exposure. Behavioral teratogenicity included internalizing and externalizing behaviors. Internalizing behaviors include emotional reactivity, depression, anxiety, irritability, and withdrawal.[30] Externalizing includes levels of activity, impulsiveness, noncompliance, verbal and physical aggression, lowered task persistence, lowered problem solving, disruptive acts, and emotional outbursts.[31]

In these studies, 22 mother–infant dyads exposed to SSRIs were compared to 14 healthy mother–infant dyads. Of the 22 depressed mothers, 5 were taking fluoxetine, 14 taking paroxetine, and 3 taking sertraline. Nine of these women were also taking olanzapine. The exposure to the medication was substantial, averaging 181 days of prenatal exposure and 60 days postnatal for SSRIs and 41 days postnatal for olanzapine.[30,31]

Not surprisingly, the mothers in the medication groups had significantly more depression and anxiety at baseline. Interestingly, mothers in this study remained symptomatic even after treatment for depression: 64% still had anxiety symptoms and 73% had symptoms of depression. At the 4-year visit, 59% of mothers had anxiety symptoms and 50% had depressive symptoms.[30] These infants were exposed to both the effects of medications and ongoing maternal depression. It is surprising—and shocking—that such a high percentage of these mothers had ongoing depression that was neither detected by their care providers nor adequately addressed.

With regard to medication exposure, there were no significant differences in either parent or caregiver ratings of internalizing behaviors that were measured via the Child Behavior Check List. Independent raters also rated the child's behavior in a laboratory setting where they were blind to their medication status. There were no significant differences between exposed and nonexposed groups. When the entire cohort was measured, increased parental reports of internalizing correlated with mothers' symptoms of depression and anxiety. This finding was not true for teacher ratings. The relationship remained even after prenatal exposure was added to the model. Maternal mood was more predictive of internalizing behaviors than prenatal medication exposure.[30]

Similarly, in the study of externalizing behaviors, there was no difference at age 4 between the exposed and nonexposed groups.[31] Current maternal depression and anxiety were more predictive of externalizing at age 4 than prenatal medication exposure. Umbilical cord

blood levels were associated with externalizing behaviors at 4 years, but once current maternal depression was added to the model, it accounted for only 11.2% of the behavioral outcome. When the children were observed in a laboratory setting, those who were exposed to medication demonstrated significantly less persistence in completing tasks compared to children with no exposure. And poor neonatal adaptation predicted increased aggressiveness. When comparing the independent effects of prenatal medication exposure versus current maternal mood, the authors concluded that current maternal stress and mood were better predictors of externalizing behaviors, even after controlling for prenatal depressed mood or medication exposure. This study was the first to consider the dual role of prenatal SSRI exposure and current maternal mood.

Summary of the Effects of In Utero Exposure

The effects of in utero medication exposure are not trivial and include increased risk of preterm birth. There is an increased risk of neonatal complications, but the overall rate appears to be low. It is reassuring that, although a substantial number of medication-exposed infants are symptomatic in the newborn period, by age 4 most of the differences have disappeared, and that maternal depression accounts for more symptomatology than medication exposure. It should also be noted that in utero exposure is substantially greater than exposure via breastfeeding. Medications that enter the central nervous system, particularly SSRIs, transfer readily into fetal circulation, which means that the fetus attains levels of medication comparable to those in the mother's plasma. Although many principles of drug entry into the fetus are somewhat similar to the transfer of medications to breastfeeding infants, the systems are different.

Breastfeeding and Medications

Possible antidepressant use is an issue for hundreds of thousands of breastfeeding women each year.[3] Indeed, antidepressants are among the most frequently used medications used by lactating women.[32] Many breastfeeding women presenting with depressive symptoms may not require pharmacotherapy.[1] Early postpartum, sleep deprivation and stress are clearly normal, and general support may be all that is required. But in some patients with severe depression, medications are clearly indicated. For these reasons, it is important that major depression in breastfeeding women be closely monitored, and if necessary, treated.

As with decisions about antidepressant use during pregnancy, clinicians must help breastfeeding women weigh the risks of treatment with medications versus no treatment.[7,33,34] To date, most adverse effects have been reported in case studies, not larger, randomized trials. In addition, any risk/benefit analysis must also weigh the risks of infant exposure to mothers' medications versus the risks of not breastfeeding, which can be considerable. Still, some urge caution.[7,35,36] This can become a dilemma for mothers. Mothers may opt to not breastfeed because they are on medications. Conversely, mothers may refuse treatment for depression because they fear that they will be forced to wean.

Current research allows us to consider 2 key questions with regard to antidepressant use in breastfeeding mothers: do medications pass into breast milk? And do the medications affect the infants? Research that addresses these questions is summarized below.

Does Antidepressant Medication Enter into Breast Milk?

The most commonly prescribed antidepressants for breastfeeding women are the SSRIs. In general, the SSRIs are well tolerated and highly effective. Further, we have a large number of studies showing they are relatively safe in breastfeeding mothers. Clinical studies of sertraline and paroxetine clearly suggest that transfer of these agents into milk is quite minimal, and virtually no side effects have been reported in numerous breastfed infants.[37-40] In a number of studies, paroxetine and sertraline usually produce undetectable levels in the infants.[41]

Sertraline has been studied in at least 37 mother–infant dyads. Studies of this product consistently report that levels are virtually undetectable in the vast majority of infants. In general, the mean relative infant dose is very low, ranging in various studies from 0.2 to 0.9 with a similar percentage contribution from its metabolite demethylsertraline.[37,38,42] In a report of the 5-HT transporter platelet function in 14 infants exposed to sertraline via milk, no change was noted in platelet function, thus suggesting the amount of sertraline, and it major metabolite desmethylsertraline, transferred to the infants was negligible.[43] This finding was true even in young, exclusively breastfed infants. Clinically, the vast majority of breastfeeding mothers who use an SSRI use sertraline because of its documented safety profile with breastfed infants.

Paroxetine has been studied in more than 57 mother–infant dyads. Again, transmission of paroxetine to infants is extraordinarily low. In most cases, the infant serum levels of paroxetine were below the level of detection. The estimated infant dose via milk is approximately 15 ug/kg/day, or 2.1% of maternal dose. But these estimates vary significantly with maternal dose.[40,44,45] Nevertheless, no untoward effects have been reported in breastfed infants exposed to paroxetine via breastmilk.

At least 3 case reports of colic, prolonged crying, vomiting, tremulousness, and other symptoms have been reported following the use of fluoxetine in breastfeeding women,[26,46,47] although these numbers are probably quite small compared to the thousands of infants who have breastfed without side effect. Recent data suggest that fluoxetine may reduce weight gain in some breastfed infants,[48] and in adolescent children may reduce growth and development.[49] In a recent review of antidepressants in breastfed infants, fluoxetine produced the highest proportion (22%) of infant levels that are elevated above 10% of the average maternal level.[41] Therefore, fluoxetine should be viewed as a less-preferred SSRI for breastfeeding mothers, particularly with newborn infants, and in those mothers who consumed fluoxetine during gestation. Because the metabolic capacity of infants at 12 months approaches that of an adult, the use of fluoxetine in mothers with in older infants is probably less risky.[50]

The mixed serotonin and norepinephrine reuptake inhibitor venlafaxine has now been studied in 9 breastfeeding women.[51,52] In the 9 infants, the relative infant doses for venlafaxine averaged 3.5%, and for its active metabolite (o-desmethylvenlafaxine), the relative infant dose was 6.8%. Moreover, no adverse effects were noted in the infants despite clinical doses of up to 8.2 mg/kg/d.

Another recent study examined the transfer of escitalopram and its metabolite into breast milk.[32] This study included blood and milk samples from 8 women who were taking escitalopram for postpartum depression. The relative infant dose for the combination of escitalopram and its metabolite was 5.3% of the maternal weight-adjusted dose (3.9% for escitalopram; 1.7% for demethylescitalopram). Levels of escitalopram were undetectable in 4 infants and at very low levels in 2 others. The authors concluded that escitalopram is preferred to rac-citalopram for treatment of depression during breastfeeding and is safe for breastfeeding women. The relative infant dose for citalopram is 3.7%.

A meta-analysis of 67 studies of antidepressant levels in breastfeeding infants pooled data from 337 research cases, with 238 infants.[53] This study reported on data with 15 different antidepressants and their major metabolites. The authors found that antidepressants were detectable in the breast milk for all the antidepressants they studied. There were significant Pearson correlations between maternal plasma and breast milk levels for 4 medications: citalopram, dothiepin, fluvoxamine, and paroxetine. But the correlation between maternal level and the level in breast milk was not significant for fluoxetine and sertraline, despite large sample sizes.

With a standardized infant plasma level of 0.06, fluoxetine produced the highest proportion of detectable infant levels and the highest mean infant level.[53] Citalopram was also relatively high, with a standardized infant plasma level of 0.03. Only 1 infant across studies had an elevated paroxetine level, and that infant had also been exposed prenatally. All other plasma paroxetine levels in infants were undetectable, including 3 infants with prenatal exposure. Maternal dose was highly correlated with infant plasma level for citalopram. The correlation was weak for sertraline. Maternal dose did not predict infant plasma levels for fluoxetine, nortriptyline, or paroxetine.

The authors noted that there are many factors that influence transfer of medication to infants via breast milk. They found that there was a negative relationship between antidepressant protein binding and potential transmission to the fetus. They noted that some potentially serious short-term effects have been noted in case reports of infants exposed to antidepressants via breastfeeding, but that the infant's symptoms correlated with withdrawal and re-exposure to the mother's breast milk. Compared with other antidepressants, fluoxetine was more likely to accumulate in breastfeeding infants. There was also a case report of an infant with no prenatal exposure having symptoms following exposure to citalopram via nursing. This infant's relative infant dose was 13% of the average maternal plasma level.[53]

With regard to long-term effects, the authors noted that low or undetectable infant plasma concentrations alone cannot reassure us that the antidepressant will have no effect on the rapidly developing brain, and whether chronic, low-dose exposure poses a risk. However, the studies with asymptomatic infants are reassuring. Moreover, the authors noted that although antenatal exposure differs from exposure via breastfeeding, the

antenatal data suggest little or no long-term effects on developmental outcomes, and that we must factor in whether there was prenatal exposure, as that provides a "loading dose" that far exceeds any exposure from breast milk and can thus distort findings regarding exposure via breast milk. In addition, studies often fail to account for other confounding factors, such as maternal smoking, which can affect both maternal and infant metabolism. Similarly, mothers' use of alcohol is also often not included in most studies.[53]

In summary, the exposure of breastfeeding infants to paroxetine, sertraline and nortriptyline is unlikely to produce detectable or elevated plasma drug levels. In contrast, infants exposed to fluoxetine may have higher levels of exposure, especially if they had been exposed prenatally. Citalopram may lead to elevated levels in some infants, whereas escitalopram produces a lower relative infant dose. Although these medications appear safe for the majority of babies, only rare side effects have been noted. Therefore, breastfeeding mothers should be advised to observe for any possible signs of adverse reactions including irritability, poor feeding, or major changes in sleep patterns. Premature babies or other unstable infants should be closely monitored for adverse effects.[53]

Summary

Given the data on the adverse effects of depression and psychosis on the neurobehavioral outcome and development of the infant, there is increasing support for the treatment of these disorders, even while the mother continues to breastfeed. It is generally concluded that the risk of not treating depression in formula feeding or breastfeeding mothers is vastly more dangerous than the risk from a small amount of antidepressant in human milk.

Women with postpartum psychiatric disorders and their physicians frequently face the dilemma of whether to continue breastfeeding while taking various psychotropic medications. It is important to remember that breastfeeding contributes significantly to a healthier infant, and it inevitably has a major impact on bonding between mother and infant. Although it is true that all psychotropic medications pass into milk to some degree, most of them do so in levels that are far subclinical and in most instances thus far published, they fail to produce untoward effects in the breastfed infant.

According to the currently available data, infants exposed to various antidepressants, such as sertraline, paroxetine, and perhaps escitalopram, are unlikely to develop detectable plasma levels of these medications. Infants exposed to fluoxetine, venlafaxine, and citalopram appear to be at slightly higher risk of developing elevated levels and complications, especially following prenatal exposure. Clinically, we know that fluoxetine has been prescribed for more than 20 years. If approximately 10% of breastfeeding mothers take antidepressants while breastfeeding, and fluoxetine is second only to sertraline in the number of prescriptions for breastfeeding mothers, then we can estimate that the number of women who have taken fluoxetine while breastfeeding likely numbers in the millions. Even with this high number of mothers who have taken this product while breastfeeding, only a few have reported complications.

Although our understanding of the long-term outcome in infants is rudimentary, all studies thus far suggest that their neurobehavioral outcome is normal. Nevertheless, it is still essential to advise the mother that our understanding of long-term effects of these medications is still evolving and that most of these medications are probably quite safe.

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