*Key Words: paroxetine, pregnancy, placental passage, major depression, postpartum depression, infant exposure*

# Clinical Management of Perinatal Depression: Focus on Paroxetine

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***ABSTRACT*** *~ The literature on antidepressant use during pregnancy and lactation is replete with review articles and clinical decision algorithms. Remarkably, a limited number of such articles include the methodological advances that have served to define the extent of fetal and neonatal exposure to antidepressants. For this review, MEDLINE search for original research articles focusing on obstetrical, neonatal, and infant outcomes associated with antidepressant use was conducted. These articles were scrutinized to include those with data on the selective serotonin reuptake inhibitors (SSRIs) and limited to breast-feeding studies that included infant serum concentrations. Sixty-seven articles were identified that included a total of 3,050 cases of SSRI use during pregnancy and 240 cases of use during lactation. The amount of obstetrical outcome data available for each SSRI was proportional to the duration of time each medication has been available. In contrast, the lactation data were heavily weighted toward sertraline and paroxetine relative to other antidepressants. The myriad of confounds, failure to control for maternal depression, lack of prospective documentation of other medications, and environmental exposures preclude any definitive conclusions. There was no clear association between SSRI exposure and obstetrical complications or poor outcome. In contrast, the amniotic fluid, umbilical cord, and nursing infant sera literature demonstrated significantly different exposures to individual medications.*
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## INTRODUCTION

Given the high prevalence of depression among women of reproductive age, the growing proportion of women planning to nurse, and the well-established use of paroxetine and other selective serotonin reuptake inhibitors (SSRIs) as first-line therapies for depression, clinicians frequently face decisions regarding the use of SSRI antidepressants during pregnancy and lactation. The most common clinical

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presentations include: (1) a preconception consultation with a patient who wishes to conceive but has a history of depression and is being treated with an SSRI; (2) an urgent consultation in the early weeks of an unplanned pregnancy with a patient who has been taking an SSRI; (3) providing treatment recommendations to a patient who is experiencing a perinatal depressive relapse after discontinuing SSRI therapy; and (4) offering treatment to a patient who is experiencing her first episode of depression during pregnancy or the postpartum.

These clinical scenarios are complicated by the tandem concern for the welfare of 2 patients, namely mother and child, as well as the complex interplay between depressive illness and the course of perinatal reproductive physiology. The formulation of rational treatment recommendations must ultimately be informed by the data regarding the reproductive safety of available treatments and the potential consequences of perinatal depressive illness. The therapeutic strategy is further modified by the patient's treatment history.

In this article, we review the data regarding perinatal depression and the perinatal use of SSRI antidepressants, with a particular emphasis on findings regarding the role of paroxetine during pregnancy and the postpartum. Finally, we offer guidelines for incorporating these data into a rational approach for managing perinatal depression.



## OVERVIEW OF CLINICAL ISSUES

The magnitude of this dilemma is best appreciated when we first recognize that perinatal depression is a commonplace problem. Despite traditional lore that pregnancy is a time of well-being, the prevalence of major depression during pregnancy rivals that of nonpuerperal episodes.[1-4] Furthermore, women with bipolar disorders who discontinue treatment during gestation are especially vulnerable to depressive relapse,[5] and pregnancy affords no reliable protection from SSRI-responsive anxiety disorders such as obsessive-compulsive disorder[6-8] or panic disorder.[9,10] The postpartum picture is even more grave. There is a dramatic rise in psychiatric hospitalizations during the first month after delivery.[11] Postpartum depression affects between 10% and 22% of adult women, and up to 26% of adolescent mothers,[12,13] and the postpartum is also a time of heightened risk for women with bipolar disorder.[14,15]

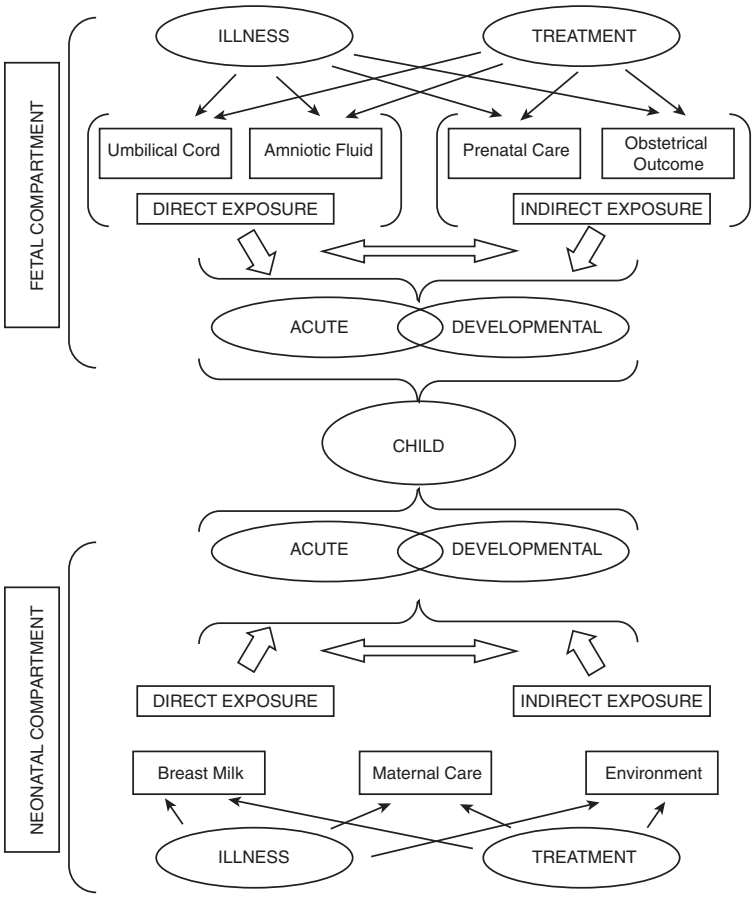
Facing the specter of perinatal depression, the driving force behind the decision-making of the new or expectant mother is invariably the welfare of her child. This understandably raises concerns regarding the effect on the child of antidepressant exposure during pregnancy or lactation. A risk-benefit assessment predicated solely upon antidepressant exposure not only ignores the potentially deleterious impact of untreated maternal depression but erroneously implies that perinatal SSRI treatment selfishly

sacrifices the child's safety for maternal comfort. Such misguided thinking places an unnecessary burden of guilt on women who may already be struggling against the psychological toll of depression.

As noted by our group previously, some degree of exposure always occurs in the arena of perinatal psychiatry (Figure 1).[16] Each facet of the exposures is further modulated by individual fetal and neonatal metabolic capacity and by any inherent genetic vulnerability that may exist. The potential risks arising from such exposure to either maternal depression or SSRI therapy can be classified as acute or developmental for the offspring. *Acute effects* are usually evident immediately and are independent of the developmental window of exposure. Examples of the potential adverse acute effects of exposure include preterm delivery, slowed growth, medical

**FIGURE 1**

PATHWAYS OF POTENTIAL EXPOSURE

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compromise, or medication toxicity or withdrawal. *Developmental effects* are by definition dependent on the timing of exposure and often are not fully evident until later. For example, exposure during early gestation may result in somatic teratogenesis producing structural malformations. Because organogenesis is virtually complete by the conclusion of the first trimester, somatic teratogenesis is not a significant concern of later exposure. However, central nervous system (CNS) development continues throughout prenatal life and indeed throughout childhood. Consequently, the potential developmental effect of later exposure includes so-called neurobehavioral teratogenesis, in which alterations in CNS programming can have persistent effects on the child's cognitive ability, emotional regulation, and adaptability to stress. In the following sections, we review data regarding the effects of exposure to untreated maternal depression and exposure to SSRIs.

## REPRODUCTIVE DATABASE: EXPOSURE TO MATERNAL DEPRESSION



Growing evidence indicates that maternal depression during pregnancy may bear numerous untoward effects on unborn children. The acute effects of prenatal maternal depression include a doubling of the rate of preterm delivery,[17,18] slowed fetal growth resulting in lower birth weights[17,19] and smaller head circumferences[20] at delivery. These effects of maternal depression may be mediated directly by alterations in fetomaternal physiology[21] or indirectly by depression-associated changes in maternal behavior. Specifically, depressed gravidas are more likely to neglect prenatal care, use tobacco, alcohol, or cocaine, engage in suicidal behavior, and receive poor nutrition.[22] Prenatal depression may also be associated with adverse neurobehavioral developmental effects. A vast preclinical literature indicating that prenatal stress programs aberrant neuroendocrine stress responses in offspring that persist into adulthood[23] is now accompanied by similar findings of exaggerated glucocorticoid stress responses in the infants of women who were depressed during pregnancy (P. Brennan et al, unpublished data). In addition, prenatal maternal stress and depression are associated with lower cognitive abilities in children up to 6 years of age[24] and a variety of other neurobehavioral alterations.[25,26] Although clinical research regarding the developmental sequelae of prenatal depression is limited, there is a wealth of clinical data regarding the untoward consequences of postpartum depression. The children of depressed mothers exhibit ineffective emotional regulation,[27,28] greater anxiety,[29] poor social interactions,[30] aberrant attachment behaviors,[31] and delays in both cognitive[32] and language development.[24] These children are ultimately more likely to experience emotional instability, suicidal behavior, and conduct problems, and to require psychiatric

treatment.[29,33] It is noteworthy that a significant portion of so-called postpartum depression may actually begin prior to parturition[1] (Z.N. Stowe, unpublished data), and some of these findings may be mediated by depression during pregnancy.

## REPRODUCTIVE DATABASE: EFFECTS OF SSRI EXPOSURE

Administering antidepressants during pregnancy or lactation entails complicated clinical, ethical, and potentially legal ramifications. These complexities have exerted a tremendous pressure to identify safe treatment alternatives for perinatal depression. Consequently, the reproductive safety database regarding SSRIs has accumulated so rapidly during the past decade that these drugs are already among the most extensively studied medications in pregnancy and the single best-studied class of medicines in lactation. The current database comprises information gleaned from myriad sources including birth registries, retrospective surveys, case reports, case series, reports from poison control and teratology centers, and a handful of controlled observational studies. Although voluminous in comparison to the reproductive safety data for other classes of medications, the absolute numbers are small, and it is difficult to draw definitive conclusions given the heterogeneity of the sources and the paucity of adequately controlled studies. Nevertheless, the existing data do provide helpful information regarding the *quantitative* and *qualitative* effects of perinatal SSRI exposure.



## QUANTITATIVE MEASUREMENTS OF FETAL/INFANT EXPOSURE

The quantitative analyses assess the amount of fetal and infant SSRI exposure by measuring rates of placental passage and breast milk excretion.

### *Prenatal Exposure*

Fetal medication exposure is dictated by placental passage, which is in turn determined by placental tissue perfusion and certain physicochemical properties of the particular compound, including molecular weight, lipid solubility, protein binding, and ionization.[34-36] Although ex vivo placental perfusion studies afford a crude index of placental transfer, these limited data have not been consistent with the more direct quantitative assessment of fetal exposure that is obtained by calculating the fetal-maternal ratio of medication concentrations from maternal and umbilical cord plasma samples collected at delivery. In an extensive assessment of placental passage of SSRIs, a forthcoming publication reports the lowest fetal-maternal ratio for paroxetine (36%, n=22), with increasingly higher ratios for sertraline (48%, n=32), desmethylsertraline (59%, n=32), fluvoxamine (78%, n=4), norfluoxetine (80%, n=33), fluoxetine (82%, n=33),

OD-desmethylvenlafaxine (141%, n=9), and venlafaxine (690%, n=9) (Z.N. Stowe et al, unpublished data). Similar results were demonstrated in collaboration with another group.[37] The surprisingly high placental transfer of venlafaxine and its principal metabolite might be attributable to their low molecular weight and especially low protein binding. Placental passage of citalopram was not assessed in this study (Z.N. Stowe et al, unpublished data) but a recent case series (n=11) reported fetal-maternal ratios of 64%, 66%, and 68%, respectively, for citalopram, desmethylcitalopram, and didesmethylcitalopram.[38]

Of note and potential concern are the umbilical cord concentrations of norfluoxetine and OD-desmethylvenlafaxine, which were less than those of the parent compound, raising the question of fetal metabolic capacity for these compounds. The placental passage data and concern for the fetal metabolism of fluoxetine are paralleled in the amniotic fluid data from our group,[39,40] which failed to find detectable amniotic fluid concentrations of paroxetine and sertraline.

### *SSRI Exposure During Lactation*



Quantitative analyses of infant SSRI exposure during lactation are hindered by inconsistent milk-collection methods that complicate efforts to compare rates of breast milk excretion between compounds. Because of these difficulties in breast milk sampling, infant plasma monitoring has emerged as the research standard over milk-plasma ratio. Easily representing the largest lactation database for any class of medications,[41,42] the current SSRI literature incorporates plasma measures of 88 nursing infants exposed to sertraline,[43-51] 59 paroxetine-exposed infants,[49,51-53] 58 fluoxetine-exposed infants,[49,54-58] 20 citalopram-exposed infants,[38,59-61] 16 venlafaxine-exposed infants,[62-64] and 8 fluvoxamine-exposed infants.[51,65,66] It is noteworthy that detectable concentrations of paroxetine and fluvoxamine have not been observed in nursing infants despite using highly sensitive assay techniques.[52] Collectively, these findings indicate that infant SSRI exposure during lactation is considerably lower than transplacental exposure.

Considerable effort has been invested in the development of models to forecast SSRI exposure via lactation without performing invasive procedures on the child. Most such models calculate the infant's daily SSRI dose from the milk-plasma ratio, which is derived from the collection of single random samples of breast milk and maternal plasma. Such simplistic approaches may unfortunately provide unreliable estimates of infant exposure because they ignore the pharmacokinetic profiles of SSRI breast milk excretion. Accurately forecasting lactation exposure requires the consideration of 2 breast milk excretion gradients: *distribution gradient* and *time gradient*. The distribution gradient occurs over the course of a

single feeding. Because SSRI antidepressants, like most psychotropic agents, are highly lipophilic compounds, they are present in higher concentrations in the fatty hindmilk. Considerable variation can be found between the SSRI concentrations of a foremilk sample and a hindmilk sample collected during the same feeding. The time gradient of excretion occurs from one dose to the next. Because most SSRIs are administered once per day, the time gradient is typically mapped on a 24-hour chart. The pharmacokinetic profiles of breast milk excretion, including delineation of both the distribution gradient and time gradient, have been best defined for sertraline[46] and paroxetine.[53] The latter study found that the distribution gradient of paroxetine breast milk excretion followed third-order kinetics, with hindmilk paroxetine concentrations ranging from 3 to 6 times higher than foremilk concentrations. Interestingly, there was no significant time gradient for paroxetine excretion as had been observed in the earlier sertraline study. Other studies have assessed the time gradient of excretion for citalopram,[61] fluoxetine,[55,57,58] fluvoxamine,[66] paroxetine,[67] and sertraline[47] without controlling for the distribution gradient of the respective compounds. The detailed mathematical modeling of lactation exposure to fluoxetine and sertraline utilizing both gradient and time course data has demonstrated superiority in predicting infant serum concentrations over previous techniques employing the milk-plasma ratio.[68,69]



## QUALITATIVE MEASUREMENTS OF FETAL/INFANT EXPOSURE

The reproductive database also consists of qualitative assessments of fetal and infant SSRI exposure. These include studies of both the developmental and acute effects of perinatal SSRI exposure. As previously mentioned, the potential developmental effects of SSRI exposure include somatic and neurobehavioral teratogenicity. Five investigations, including 3 prospective cohort studies[70-72] and 2 birth registries[73,74] encompassing 932 live-born infants with first-trimester exposures to fluoxetine, 368 with first-trimester exposures to citalopram, 220 with first-trimester exposures to paroxetine, 184 with first-trimester exposures to sertraline, and 26 with first-trimester exposures to fluvoxamine, have failed to demonstrate that exposure to any SSRI is associated with an increased risk of major congenital malformations. However, one group did report a significantly higher incidence of 3 or more minor anomalies among 97 infants with first-trimester fluoxetine exposure compared with 153 nonexposed control infants.[71] This finding has not been replicated. Two meta-analyses[75,76] concluded that there is no increased risk of major malformations associated with prenatal SSRI exposure.

### *Prenatal Exposure to SSRIs*

The only published reports regarding the neurobehavioral impact of prenatal SSRI exposure are from 2 prospective cohort studies published by the same group comparing the outcomes of fluoxetine-exposed children, tricyclic antidepressant (TCA)-exposed children, and nonexposed children.[24,77] Using standard rating instruments administered by an investigator who was blinded to child exposure status to assess global intelligence quotient (IQ), language development, temperament, mood, activity level, and behavior in children between 16 months and 7 years of age, the investigators found no significant differences with respect to any neurodevelopmental measure among the 3 groups of children in the earlier study, which included 55 children exposed to fluoxetine at some time during gestation.[77]

In the recent follow-up study, which included 40 children exposed to fluoxetine throughout gestation, the investigators again observed no neurobehavioral differences associated with antidepressant exposure, but did find that the duration of maternal depression during pregnancy was a significant negative predictor for global cognition and that the number of maternal postnatal depressive episodes was associated with diminished language development.[24] There are no published data regarding the neurodevelopmental impact of prenatal exposure to other SSRIs or exposure to any SSRI during lactation. The data on pregnancy and lactation are summarized in Table 1.



**TABLE 1**

**DATA ON FETAL AND INFANT ANTIDEPRESSANT EXPORUSRE DURING PREGNANCY AND LACTATION**

| MEDICATION | METABOLITE | CASES IN PREGNANCY | PLACENTAL PASSAGE | NEUROBEHAVIORAL FOLLOW-UP | NURSING INFANT SERUM |
|---|---|---|---|---|---|
| Fluoxetine | | 1269 | 82% | 95 | 58 |
| | Norfluoxetine | | 80% | | 58 |
| TCAs | | 761 | Variable* | | |
| Citalopram | | 375 | 64%-68% | NA | 20 |
| | Desmcit | | NA | | |
| Paroxetine | | 223 | 36% | NA | 58 |
| Sertraline | | 184 | 48% | NA | 88 |
| | Desmsert | | 59% | | 88 |
| Venlafaxine | | 150 | 690% | NA | 16 |
| | OD-venla | | 141% | | 16 |
| Fluvoxamine | | 88 | 78% | NA | 6 |

*Determined via placental perfusion.
SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

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### *Perinatal Exposure to SSRIs*

Overall, studies of the developmental effects of SSRI exposure have been reassuring, particularly when compared with data regarding the untoward developmental effects of exposure to maternal depression. However, studies regarding the acute effects of perinatal SSRI exposure have generated greater concern and more controversy. The potential acute adverse effects of SSRI exposure during pregnancy include miscarriage and preterm delivery, delayed fetal growth, neonatal toxicity, and neonatal withdrawal syndromes. One early cohort study reported a nonsignificant trend toward higher rates of spontaneous abortion among 128 women treated with fluoxetine or 74 women treated with a TCA when compared with matched control subjects.[70] This is accompanied by another cohort study reporting an odds ratio for preterm delivery (<37 weeks) of 1.30 when comparing women who used any of a number of SSRIs in early pregnancy against control subjects,[74] and yet 2 others reporting higher rates of preterm delivery among 55 women who were taking paroxetine during the third trimester[78] and among 73 women who were taking fluoxetine during the third trimester.[71] In addition, a recent retrospective study of a health maintenance organization (HMO) database observed a higher rate of preterm deliveries among 185 women who had been prescribed an SSRI during pregnancy than among 185 control subjects.[79] However, other groups have failed to find an association between prenatal SSRI exposure and preterm delivery or miscarriage.[24,72] Because none of the studies reporting an



**TABLE 2**

**PUBLISHED STUDIES OF ANTIDEPRESSANT USE DURING PREGNANCY**

| DRUG | REPORTS (N) | PATIENTS (N) | REFERENCES |
|---|---|---|---|
| Fluoxetine | 8 | 1269 | Pastuszak 1993[70]; Goldstein 1995[97]; Chambers et al 1996[71]; McElhatton 1996[98]; Goldstein 1997[73]; Ericson et al 1999[74]; Cohen 2000.[99] |
| TCAs | 17 | 761 | Altshuler et al, 1996[100]; Nulman 1997[77]; Kulin 1998.[72] |
| Citalopram | 2 | 375 | Ericson et al 1996[74]; Heikkinen 2002.[38] |
| Paroxetine | 3 | 223 | Kulin et al 1998[72]; Ericson et al 1999[74]; Hendrick et al 2003.[37] |
| Sertraline | 3 | 184 | Kulin et al 1998[72]; Ericson et al 1999[74]; Hendrick et al 2003.[37] |
| Venlafaxine | 1 | 150 | Einarson 2001.[101] |
| Fluvoxamine | 3 | 88 | McElhatton 1996[98]; Kulin et al 1998[72]; Hendrick et al 2003.[37] |

TCA=tricyclic antidepressant.

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association between prenatal SSRI exposure and preterm delivery or miscarriage has controlled for maternal depression, these results are speculative at best. These findings closely parallel the reported rates of preterm delivery among all women who are depressed during pregnancy[17,18] and may thus represent the effect of maternal depression rather than SSRI exposure. Similar conclusions may be drawn regarding those studies reporting an association between prenatal SSRI exposure and lower birth weight[71,79] that have likewise failed to account for impact of maternal depression on fetal growth.[19]

Finally, concerns regarding neonatal toxicity or withdrawal syndromes associated with maternal SSRI use in late gestation have repeatedly been expressed, although few data have been forthcoming. Until recently, this literature was primarily composed of a handful of case reports of presumed neonatal toxicity or withdrawal associated with citalopram,[80] fluoxetine,[80,81] paroxetine,[80,82] and sertraline.[83,84] Although the cohort study by Chambers and colleagues did not mention neonatal toxicity per se, the study outcome, "poor neonatal adaptation," which was defined as "jitteriness, tachypnea, hypoglycemia, hypothermia, poor tone, respiratory distress, weak or absent cry, or desaturation on feeding"[71] has been discussed by at least 1 reviewer under the heading "neonatal toxicity."[85] In the Chambers study, rates of poor neonatal adaptation and admission to a special-care nursery (SCN) were significantly higher among 73 infants exposed to fluoxetine during late gestation than among 101 infants exposed to fluoxetine in early pregnancy or 226 nonexposed infants.[71] A more recent cohort study reported higher rates of similar neonatal complications including bradycardia, respiratory distress, hypoglycemia, suckling problems, and tachycardia among 55 infants exposed to paroxetine in late gestation when compared with a group of 54 infants of whom 50% were exposed to paroxetine early in pregnancy and 50% were not exposed to an antidepressant.[78]

Certainly, these 2 studies raise important concerns regarding SSRI exposure during late pregnancy and remind us that these medicines should not be used indiscriminately during the peripartum. However, because of numerous methodological shortcomings, they fail to provide a definitive picture. First, the assessments of neonatal outcome were not blinded to SSRI exposure status in either study. In the paroxetine study, outcome data were obtained during a telephone interview with the infants' mothers who had previously been counseled by members of the research team regarding the risk or safety of paroxetine. In the fluoxetine study, outcome data were derived from newborn nursery records, which had been recorded by nursery caretakers who were not blinded to exposure status. Consequently, the absence of appropriate blinding may have biased the assessments of neonatal outcome in both studies. Second,

neither study included an assessment of obstetrical complications such as meconium aspiration, maternal fever, or prolonged rupture of membranes that may also explain the relatively nonspecific neonatal symptoms that are being attributed to SSRI exposure. Third, both studies inadequately controlled for the potential effects of maternal depression. Simply including a comparator group composed in part or total of women who were taking an antidepressant earlier in gestation does not control for exposure to maternal depression as the authors of the paroxetine study contend.[78] It seems intuitive that those women whose depressive symptoms were most severe or chronic would be most likely to continue SSRI treatment throughout gestation. If true, the infants of those taking an SSRI in the third trimester may have been exposed to the greatest "dose" of maternal depression. Furthermore, maternal smoking, which is more common among depressed gravidas,[22] has been associated with a constellation of neonatal symptoms remarkably similar to those described in these studies.[86] The fluoxetine study makes no effort to control for the effect of maternal smoking on neonatal complications,[71] and the paroxetine study treats maternal smoking as a dichotomous variable.[78] As such, it affords no opportunity to analyze potential dose effects of maternal smoking, which have been previously reported,[86] on neonatal outcome. Similarly, the paroxetine study appears markedly discordant with the placental passage data suggesting limited exposure.



### *SSRI Exposure During Lactation*

The existing data regarding the acute effects of SSRI exposure during lactation are limited to case reports and case series because no controlled studies have yet been conducted. To date, there have been no adverse events reported in infants exposed to paroxetine, sertraline, or fluvoxamine while nursing. There have been 5 adverse events, including colic, hyperactivity, diarrhea, and emesis, and 2 infants with restlessness, reported among infants exposed to fluoxetine via lactation.[54,57] There is a lone case report of an infant experiencing uneasy sleep during exposure to citalopram via breast feeding,[87] although the citalopram package insert also reports the case of an infant experiencing an apneic episode during breast feeding with that medication.

## EFFICACY OF SSRIS IN PERINATAL/POSTPARTUM DEPRESSION

Although the focus of the SSRI reproductive data has been to delineate the risk of medication exposure, the child may also benefit by being protected from the untoward effects of maternal depression. It follows, therefore, that establishing the efficacy of antidepressants for perinatal depression is a necessary prerequisite to the construction of rational treatment guidelines.

Clinicians commonly assume that data regarding antidepressant efficacy for nonpuerperal depression may be readily applied to the peripartum, but persistent questions as to whether perinatal depressive episodes are neurobiologically distinct from other depressive syndromes[88,89] suggest such assumptions may be premature. Unfortunately, ethical considerations have precluded conducting randomized clinical trials during pregnancy and lactation, and perinatal antidepressant treatment remains largely empirical with limited definitive efficacy data. There are presently no studies examining SSRI efficacy during pregnancy, and the postpartum data are limited. The treatment studies in postpartum depression have recently been reviewed,[42] and notably the criteria for diagnosis of postpartum depression versus major depression during the postpartum period limit conclusions. Pharmacological studies utilizing fluoxetine,[90] sertraline,[91] and venlafaxine[92] have demonstrated efficacy. Despite the paucity of formal efficacy data, considerable clinical experience indicates that conventional antidepressants, including the SSRIs, effectively manage perinatal depression. Furthermore, treatment efficacy can be maximized by carefully reviewing the patient's past psychiatric history to identify those antidepressants that the patient found most effective and well tolerated.



The dual goals of antidepressant treatment during pregnancy and lactation are to eliminate the child's exposure to maternal depression by

**TABLE 3**

**PUBLISHED STUDIES OF ANTIDEPRESSANT USE DURING BREAST FEEDING**

| MEDICATION | INFANT SERA (N) | REFERENCES |
|---|---|---|
| Sertraline | 88 | Altshuler 1995[43]; Mammen 1997[44]; Eppersen 1997[45]; Stowe 1997[46]; Wisner 1998[48]; Kristensen 1998[47]; Birnbaum 1999[49]; Hendrick 2001[51]; Stowe 2003[69]; **Dodd 2000**.[106] |
| Paroxetine | 59 | Spigset 1996[108]; Birnbaum 1999[49]; Ohman 1999[67]; Misri 2000[52]; Stowe 2000[53]; Hendrick 2001.[51] |
| Fluoxetine | 68 | Burch 1992[104]; Taddio 1996[55]; Lester 1993[54]; Yoshida 1998[56]; Birnbaum 1999[49]; Kristensen 1999[57]; Hendrick 2001[58]; Suri 2000.[68] |
| Venlafaxine | 16 | Ilett 1998[63]; Ilett 2002[62]; Hendrick 2001.[64] |
| Citalopram | 13 | Jensen 1997[59]; Schmidt 2000[60]; Rampono 2000[61]; Heikkinen 2002.[38] |
| Fluvoxamine | 6 | Wright 1991[110]; Piontek et al 2001[107]; Hendrick 2001.[51,64] |
| Nefazodone | 3 | Dodd 2000[105]; Yapp 2000[111] |
| Bupropion | 3 | Briggs et al 1993[103]; Baab et al 2002[102] |

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achieving clinical remission while minimizing the child's antidepressant exposure. Achieving these goals requires an understanding of the impact of the physiological changes of the peripartum upon antidepressant pharmacology as well as the factors governing placental passage and breast milk excretion of antidepressants. Dose adjustments during pregnancy present an intriguing clinical question. Clinicians often reduce the dose of the SSRI upon learning that a patient is pregnant in a well-meaning effort to reduce fetal medication exposure. However, indiscriminate dose reduction may increase the patient's vulnerability to relapse and thus the likelihood that the child will be exposed to maternal depression. Citing the studies suggestive of possible SSRI neonatal toxicity or withdrawal syndromes, some reviewers have advocated SSRI discontinuation 1 to 2 weeks before delivery.[85] Maternal dose reduction in response to the limited case reports proximate to a high-risk time for depression seems premature. In fact, the limited data regarding SSRI dose management during pregnancy indicate that upward dose titration, not reduction, may be necessary in the early stages of the third trimester to maintain maternal well-being.[93] The requirement for such dose increases may be a consequence of both pharmacokinetic and pharmacodynamic alterations associated with pregnancy.[94]



## TREATMENT GUIDELINES AND FUTURE DIRECTIONS

Treatment recommendations for perinatal depression should be the product of a thorough risk-benefit assessment that considers the maternal psychiatric history and the potential deleterious effects of exposure to both untreated maternal illness and antidepressant medications during particular developmental windows. Drawing from the reproductive database, treatment guidelines must be individualized to the patient's personal history and therapeutic goals. The following general recommendations may be helpful when considering perinatal SSRI therapy:

(1) *Informed consent*—Although it is impossible to provide an exhaustive list, evidence regarding possible adverse effects of medicine exposure must be reviewed. Presently, patients considering paroxetine should be informed that it does not appear to increase the risk of birth defects, is well tolerated by nursing infants, and crosses the placenta at lower rates than other SSRIs. Furthermore, they should be informed that there are no data regarding the long-term neurobehavioral effects of paroxetine exposure and that concerns have been raised regarding neonatal withdrawal symptoms, although it is unclear whether such symptoms are truly a consequence of paroxetine withdrawal. It is equally important to discuss the risks of untreated depression and to document that other treatment modalities have been considered.

(2) *Medication selection*—Because the primary goal of treatment is to maximize efficacy so that the child's exposure to maternal depression is eliminated, the most important factor in choosing a medication is treatment history. Novel agents should not be chosen when the patient has a history of a good therapeutic response to a particular antidepressant. Other medication characteristics to guide selection include: previous exposures during pregnancy, overall reproductive safety database, less placental passage or entry into breast milk, fewer metabolites to minimize potential for infant accumulation, and fewer side effects and drug interactions.

(3) *Dose selection*—The goal of treatment is remission. Partial treatment only enhances risk by continuing to expose the child to both illness and medication. The minimum effective dose should be maintained throughout treatment, and the clinician should remain mindful that dosage requirements might change during pregnancy. Investigations of both TCAs and SSRIs have demonstrated a need to increase the dose in later pregnancy for many women.[93,95,96] To minimize the potential for neonatal withdrawal or toxicity after delivery, SSRI discontinuation may be considered for those patients who have infrequent or mild depressive episodes. Because of the high risk of postpartum relapse, SSRI discontinuation during pregnancy is not recommended for those with more severe symptoms. Adjusting the feeding and dose schedule can minimize exposure of nursing infants by discarding breast milk with greater breast milk antidepressant concentrations.

(4) *Communication*—The psychiatrist should discuss the treatment plan with the obstetrician and, if the patient chooses to nurse, the pediatrician. Because clinical status may rapidly change during the peripartum, more frequent visits (ie, monthly) should be considered during pregnancy and the first few postpartum months.

(5) *Monitoring nursing infants*—Because most clinical laboratory assays lack the sensitivity necessary to detect the typical SSRI levels in nursing infants and even detectable concentrations are uninterpretable, infant serum monitoring is not routinely indicated for SSRI exposure. If a nursing child develops symptoms that are reasonably suspected to be an SSRI effect, then breast feeding should be suspended, regardless of infant medication level.

Despite the rapidly expanding reproductive safety database, the use of SSRIs during pregnancy and lactation continues to generate considerable debate. Myriad questions remain unanswered. The principal shortcoming of most existing studies is that they take a myopic view that assesses medication effects or illness effects without controlling for the other. Consequently, purported adverse effects of SSRI exposure may actually

represent either direct or indirect effects of maternal depression and vice versa. The recent study by Nulman and colleagues[24] is the only investigation to date that endeavors to discriminate medication and illness effects and thus has set the standard for future perinatal psychiatric research.

Finally, quantitative analyses indicate that fetal and neonatal antidepressant exposure is significantly less with certain medications, namely paroxetine and sertraline. Yet these medications have yet to undergo the neurodevelopmental follow-up scrutiny established by Nulman and colleagues.[77] Until longitudinal follow-up data is available for these other medications, the clinician confronts the difficult choice between medications with lower quantitative child exposure and medications with more voluminous qualitative outcome data.✤

## DISCLOSURE

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