REVIEW ARTICLE

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The Safety of Newer Antidepressants in Pregnancy and Breastfeeding

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Contents

Abstract

The pregnancy and postpartum periods are considered to be relatively high risk times for depressive episodes in women, particularly for those with pre-existing psychiatric illnesses. Therefore, it may be necessary to start or continue the pharmacological treatment of depression during these two timeframes. Hence, the aim of this review is to examine the effects on the fetus and infant of exposure, through the placenta and maternal milk, to the following drugs: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram, mirtazapine, venlafaxine, reboxetine and bupropion.

The teratogenic risks, perinatal toxicity and effects on the neurobehavioural development of newborns associated with exposure through the placenta or maternal milk to these medications need to be carefully assessed before starting psychopharmacological treatment in pregnant or lactating women. In spite of the limitations of some of the studies reviewed, the older selective serotonin-reuptake inhibitors (SSRIs) [as we await further data regarding escitalopram] and venlafaxine seem to be devoid of teratogenic risks. By contrast, the data concerning possible consequences related to exposure to SSRIs via the placenta and breastmilk on neonatal adaptation and long-term neurocognitive infant's development are still controversial. Nevertheless, a number of reports have shown that an association between placental exposure to SSRIs and adverse but self-limiting effects on neonatal adaptation may exist. In addition, the information on both teratogenic and functional teratogenic risks associated with exposure to bupropion, mirtazapine and reboxetine is incomplete or absent; at present, these compounds should not be used as first-line agents in the pharmacological treatment of depression in pregnancy and breastfeeding.

Untreated depression is not without its own risks since mothers affected by depression have a negative impact on the emotional development of their children and major depression, especially when complicated by a delusional component, may lead to the mother attempting suicide and infanticide. Consequently, clinicians need to help mothers weigh the risks of prenatal exposure to drugs for their babies against the potential risks of untreated depression and abrupt discontinuation of pharmacological treatment. Given these situations, we suggest that choosing to administer psychopharmacological treatment in pregnant or breastfeeding women with depression will result primarily from a careful evaluation of their psychopathological condition; currently, the degree of severity of maternal disease appears to represent the most relevant parameter to take this clinical decision.

Pregnancy and the postpartum period are thought to be relatively high risk times for depressive episodes in women, particularly for those with pre-existing psychiatric illnesses.[1,2] In the latest epidemiological study,[3] psychiatric disorders were present in 14.1% of pregnant women. Major and minor depression were prevalent in 3.3% and 6.9% of patients, respectively. In specific populations, the rate of affective disorders may be as high as 51% of pregnant w omen.[4] Higher rates were observed in

women from poorer minorities in the US (i.e. African American and Hispanic populations) and in unmarried teenagers.[4] The first 3 postpartum months are a high-risk period for psychiatric illnesses. An estimated 5–20% of women experience postpartum depression within 6 months of the birth of their child.[5-7] The negative effects of depressed mothers on their infants are well documented,[6-9] so treating these women would appear to be an obvious solution if it were not that the majority of the patients with depressive or affective disorders in pregnancy and/or during breastfeeding are often undiagnosed and untreated.[1-4]

An increasing number of new antidepressants have been introduced onto the market in the last 5 years. The data available in the literature seem to be quite reassuring as to their safety profile during pregnancy and breastfeeding,[10,11] since several pharmacological treatments appear to be safe and well tolerated by mother and infant alike. Nevertheless, the teratogenic risks, perinatal toxicity and effect on the newborn's neurobehavioural development as a result of exposure to medication throughout lactation should be carefully evaluated before starting a psychopharmacological treatment during pregnancy or breastfeeding.[12,13]

The purpose of this review is to analyse and summarise the data available in the literature regarding the safety of the second and third generations of antidepressants in pregnancy and breastfeeding and to identify the best strategies for administering psychopharmacological treatment of depressive and mood disorders during these two periods, in order to reduce the risks associated with prenatal and postnatal exposure to antidepressants.

1. Literature Search Methodology

A computerised Medline/PubMed/TOXNET search was carried out between January 1993 and 20 December 2004, using the following key words: 'antidepressant in pregnancy' and/or 'breastfeeding' and/or 'lactation'. No language restrictions were placed on the search. A separate search was also run to complete the safety profile of the ten antidepressants most widely used in clinical practice: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, mirtazapine, reboxetine, venlafaxine and bupropion. The resulting articles were cross-referenced for other relevant articles not identified through the electronic search. Hence, this review examines the newer antidepressants most widely used in the treatment of depression (except for nefazodone because although it was used as an antidepressant in the US, in Italy, as well as in other European countries, the marketing of the compound has been suspended by the manufacturer). A summary of the reviewed studies is available from URL: http://www.adisonline.com/drs/extras/28.2.gentile.

2. Selective Serotonin-Reuptake Inhibitors

2.1 Fluoxetine

2.1.1 Pregnancy Outcomes

Chambers et al.[14] prospectively identified 228 pregnant women taking fluoxetine in their medical record review. The rate of spontaneous pregnancy loss did not differ significantly between the women treated with fluoxetine (table I) and the control patients, nor was the rate of major structural abnormalities significantly different (5.5% vs 4.0%, respectively). The incidence of three or more abnormalities was significantly higher among the 97 infants exposed to fluoxetine who were evaluated for minor abnormalities, than among 153 control infants (15.5% vs 6.5%). However, in the Chambers et al.[14] study the women in the fluoxetine group were significantly older than the women in the control group (32.0 ± 5 vs 30.0 ± 5 years of age, respectively). This difference may explain the greater number of minor abnormalities encountered in the drug-exposed group. In contrast, several meta-analyses and prospective studies have recently confirmed the lack of drug-related teratogenic effects associated with fluoxetine.[15-19]

2.1.2 Perinatal Adverse Events

Chambers et al.[14] found that the 73 infants exposed to fluoxetine during the third trimester of pregnancy, when compared with 101 infants ex-

Table I. Rates of spontaneous abortions in women exposed to the second and third generations of antidepressant during pregnancy[20]

Drug	Sample size	Rate of spontaneous abortion (%)	Reference
Fluoxetine	128	13.5	16
	228	10.5	14
	796	13.8	18
	118	14.4	19
Paroxetine	97	11.2[a]	21
	118	10.2	19
Fluvoxamine	56	9.0	22
	26	11.2[a]	21
Sertraline	147	11.2[a]	21
	112	16.7	23
Citalopram	357	Not analysed	24
Venlafaxine	39	17.9	20
	150	12.0	25

a Extracted rate from pooled data comes from a whole analysis of 270 women exposed to these three specific selective serotonin-reuptake inhibitors.

posed to the medication during the first and the second trimesters, showed higher rates of:

- premature delivery (relative risk 4.8) that is not explained by a direct effect of the drug on uterine contractility;[26]
- admission to special-care nurseries (relative risk 2.6);
- poor neonatal adaptation (relative risk 8.7).

Birth weight was also lower, but this finding is still controversial.[17,27,28] Several case reports described perinatal complications that were associated with intrauterine exposure to fluoxetine; the onset of cardiac arrhythmia was described in the child of a mother treated with fluoxetine 30 mg/day during the third trimester of pregnancy.[29] Campino[29] suggests that there may be a relationship between atrial and ventricular premature contractions and maternal fluoxetine therapy because the onset of cardiac disorders has been occasionally described following administration of fluoxetine in healthy adults,[30] although the drug is thought to have minimal cardiovascular effects.[31] Two reports described CNS adverse effects in neonates whose mothers had taken fluoxetine 20 mg/day for most of their pregnancy.[32,33] Another four studies (including 25 infants overall) reported subtle perinatal effects of intrauterine exposure to fluoxetine consisting of:

- mild transient respiratory distress not associated with other conditions;[34]
- reduced proportion of T-helper cells that may be correlated with an interference of the serotonin reuptake blockade on the fetal immune system;[35]
- reduced behavioural pain responses and increased parasympathetic cardiac modulation following acute neonatal noxious events, probably because of an interference of fluoxetine on serotonin activity in pain modulation;[36]
- neonatal withdrawal symptoms.[37]

In contrast to these studies, Suri et al.[38] recently demonstrated that there were no adverse effects of fluoxetine exposure on obstetric outcomes, such as infant gestational age, birth weight, Apgar score and admission to neonatal intensive care units.

In addition, two studies involving a total of 95 mother-child pairs exposed to fluoxetine throughout gestation confirmed that drug exposure *in utero* had no long-term adverse effect on the neurocognitive development (IQ, language and behaviour) of infants.[39,40] Finally, in a very recent study involving 11 mother-infant pairs, Heikkinen et al.[41] concluded that common clinical dosages of fluoxetine (20–40 mg/day) resulted in relatively low maternal plasma concentrations of fluoxetine and norfluoxetine (317–850 nmol/L) during the pregnancy. The relatively low fluoxetine concentrations in pregnancy may be partly explained by a physiological increase in the demethylation of fluoxetine by cyto-

chrome P450 (CYP) 2D6. No effects were observed on either pregnancy outcome or fetal growth.

2.1.3 Breastfeeding

In addition to the report by Taddio et al,[42] fluoxetine and norfluoxetine excretion in human milk and the relative infant dose have been evaluated in four studies, including a total of 94 mother-infant pairs, and no detrimental effects were noted.[43-46] Nineteen nursing mothers (one with a pair of dyzygotic twins) participated in another study by Hendrick et al.[47] The women were receiving a stable dosage of fluoxetine (10–60 mg/day) and all but two took the medication during the last trimester of pregnancy. Fluoxetine was detectable in 30% of the nursing infant sera (1–84 ng/mL), whereas norfluoxetine was found in 85% (1–265 ng/mL). Peak breast milk concentrations occurred approximately 8 hours after maternal administration. A maternal fluoxetine dosage of ≤20 mg/day was significantly less likely to produce detectable concentrations of either fluoxetine or norfluoxetine in infants compared than higher daily dosages. Table II summarises the available data on the fluoxetine/norfluoxetine milk/plasma ratio and the relative infant dose. None of the infants examined in the study experienced adverse events. Moreover, the neurological development of 11 children born from mothers taking fluoxetine during pregnancy and breastfeeding at fixed dosages (20–40 mg/day), and followed up for 1 year, was normal.[41] Only two reports actually suggested short-term neonatal complications that could not be definitely associated with fluoxetine exposure during breastfeeding. Lester et al.[48] described the onset of colic and associated symptoms (increased crying and vomiting, decreased sleep) in a neonate whose mother was taking fluoxetine. Hale et al.[49] described the case of an infant born to a mother who ingested fluoxetine while she was pregnant. Eleven days after the start of breastfeeding (while the mother continued taking fluoxetine) the infant became increasingly somnolent, lethargic, feverish and virtually unresponsive. The infant was switched to formula feeding on day 11 postpartum. On the third day of hospitalisation, the baby was able to consume enough formula and was discharged home. The infant slowly returned to normal over the ensuing 3 weeks. The fluoxetine concentration in the mother's breast milk was 114 ng/mL. Reduced postnatal growth has been observed in infants breastfed by mothers receiving fluoxetine and this may be of clinical relevance in cases where the infant's weight gain is already of concern.[50]

Table II. Selective serotonin-reuptake inhibitors (SSRIs), their principal metabolites and breastfeeding: milk/plasma ratio, relative infant dose,[a] and report of adverse events

SSRI/metabolites	Milk/plasma ratio	Relative infant dose (%)	Infant plasma concentrations (ng/mL)	Total sample size of evaluated infants	Adverse events reported
Fluoxetine	0.68	6.5–11 NA	28–340	68[39,44-47,51]	Yes
Norfluoxetine	0.56		38–250		
Fluvoxamine	1.34–1.31	1.34–1.38	Both fluvoxamine and its metabolite were below the detection limits in all samples	8[52-55]	No
Paroxetine	0.96	1.13–1.25	Paroxetine was below the detection limits in all samples	104[23,51,55-58]	No
Sertraline	1.93	0.2	<0.5–67.5	101[51,55,59-64]	No[b]
N-desmethylsertraline	1.64	0.3	2–6		
Citalopram	1.8	4.4–5.1[c]	2.0–2.3	28[51,65-67]	Yes
Demethylcitalopram	1.8	N/A	2.2		

a On mg/kg maternal dose weight-adjusted basis.

b Unusually high serum concentrations were observed in one infant, without clinical consequences.

c Mean combined dose of citalopram and demethylcitalopram (as citalopram equivalent).

NA = not applicable.

2.2 Fluvoxamine

2.2.1 Pregnancy Outcomes and Perinatal Adverse Events

The teratogenic effects and the perinatal complications associated with fluvoxamine exposure *in utero* were evaluated in 92 pregnant women.[21,22] Thirty-seven of these patients received fluvoxamine in combination with other drugs. The incidence of adverse events was not significantly different between the examined group and the control group (see table I for the rate of spontaneous abortions).

2.2.2 Breastfeeding

Kristensen et al.[52] evaluated two infants whose mothers were receiving fluvoxamine while breastfeeding. Table II summarises the available data on the fluvoxamine milk/plasma ratio and the relative infant dose. Two case reports calculated the excretion of fluvoxamine in human milk.[53,54] The daily maternal dosage of the drug was 200mg and 100mg and the maternal plasma and milk concentrations were 170 ng/mL and 310 ng/mL in the first report and 50 ng/mL and 90 ng/mL in the second, where the neurobehavioural development of the infant up to 21 months of age was normal. Two other infants were also reported to be healthy 2–3 years after fluvoxamine exposure.[68] No detectable medication was present in another four infants exposed to fluvoxamine (detection limit: 1 ng/mL) and the authors concluded that the use of fluvoxamine is safe during breastfeeding.[55]

2.3 Paroxetine

2.3.1 Pregnancy Outcomes

Four studies (including 434 pregnant women overall) did not show any increase in teratogenic risks or other adverse effects (see table I for the rate of spontaneous abortions), when paroxetine was used at the recommended doses.[19,21,24,69]

2.3.2 Perinatal Adverse Events

In a prospective, controlled cohort study, 12 of 55 newborns exposed to paroxetine during the third trimester of pregnancy experienced complications necessitating intensive treatment and prolonged hospitalisation.[70] The main complaints were respiratory distress (n = 9), hypoglycaemia (n = 2), and jaundice (n = 1). The authors stated that the high rate of complications emerging from the study might have been related to the withdrawal syndrome commonly caused by the drug. Two reports also described a suspected withdrawal syndrome in four infants whose mothers had been treated with paroxetine during pregnancy.[33,71] Another two cases presented with perinatal complications; one was an infant with a respiratory distress syndrome who had to be hospitalised in a special nursery unit for 48 hours and the other was a newborn exhibiting a transitory increase in breathing rate whose mother had taken paroxetine 40 mg/day from week 25 of gestation until delivery.[70] A third neonate showed lethargy, no crying and no response to tactile stimulation, as well as abnormal EEG findings.[72] One case of neonatal convulsions and subarachnoid haemorrhage after intrauterine exposure to paroxetine has also been described.[73] In addition, paroxetine has been associated with other perinatal effects, such as poor neonatal adaptation (n = 16),[34] decreased CD4+ cell count (n = 11)[35] and abnormal neonatal pain response (n = 11).[36] Finally, severe clinical symptoms related to serotoninergic overstimulation have been described in a newborn; plasma drug concentrations were low in this infant after birth, but she was genotyped to be a poor metaboliser of CYP2D6, the enzyme catalysing the metabolism of paroxetine.[74] Nevertheless, four infants whose mothers had taken paroxetine during pregnancy and who were monitored up to 8 months of age showed no signs of behavioural teratogenicity.[75]

2.3.3 Breastfeeding

Paroxetine levels in maternal milk are extremely variable, fluctuating between 5.3 ng/mL and 145.0 ng/mL.[58] The milk drug concentration is higher in fore milk than in hind milk. In 38 infants whose mothers were treated with a fixed dose of paroxetine, the serum level of the drug was below the detectable limit (2 ng/mL).[51,68,76] Twenty-five infants whose mothers met DSM IV (4th Edition of the Diagnostic and Statistical Manual of Mental

Disorders)[77] criteria for major depressive disorders were included in a study investigating paroxetine concentration in infant serum.[56] The maternal fixed dosage of paroxetine was 10, 20 or 40 mg/day; in all the infant serum samples, paroxetine concentrations were below the lower limit of quantification (0.1 ng/mL). No unusual adverse events were reported in any of the infants. The lack of adverse events or abnormal behaviour had already been indicated in two previous studies; however, these studies involved a limited number of patients.[57,58] The good safety profile of paroxetine for breastfed infants has also been confirmed by a recent prospective cohort study.[78] Table II shows the relative dose of paroxetine received by the infants[57] with peak breast milk concentrations occurring approximately 4–7 hours after maternal administration.[58]

2.4 Sertraline

2.4.1 Pregnancy Outcomes

One prospective investigation evaluated the use of sertraline during pregnancy in 147 pregnant women who had received a mean daily dosage of 50mg (25–200 mg/day).[21] Another investigation prospectively compared the outcomes of 112 pregnant women taking sertraline and those of 191 women exposed to nonteratogenic agents.[23] The rates of major or minor fetal malformations did not differ from those expected in the general population (table I shows the rate of spontaneous abortions in women exposed to sertraline during pregnancy).

2.4.2 Perinatal Adverse Events

Several cases of perinatal complications have been reported by Hendrick et al.;[79] one case presented a nuchal cord associated with transient tachypnoea, another case presented with transient tachypnoea with no concomitant complications and one case presented with an oesophageal perforation. In two of these cases, the infants required hospitalisation in an intensive nursery unit. However, the authors highlighted that there was no certain correlation between the onset of these adverse events and drug exposure *in utero*. Sertraline (as with fluoxetine and paroxetine) seems to be associated with abnormal neonatal findings, as shown by self-limited poor neonatal adaptation (n = 4),[34] selective abnormalities in white blood cell counts (n = 4),[35] jitteriness and enhanced startle response (n = 1)[59] and reduced behavioural pain response (n = 4).[36] In contrast, four infants whose mothers had taken sertraline during pregnancy showed a normal social behaviour and development when monitored up to 8 months of age.[71]

2.4.3 Breastfeeding

The sertraline concentrations in breast milk vary substantially over the course of a 24 hour period, with a peak probably occurring between 1 and 9 hours post-ingestion.[80] There is a gradient of drug concentration from fore milk to hind milk,[81] and the mean plasma concentration is linearly related to the dose.[60] A significant negative correlation has been demonstrated to exist between infant age and serum concentrations.[55] For a maternal sertraline dosage in the range of 50–100 mg/day, low levels of either sertraline and norsertraline or norsertraline alone were detected in three infant plasma samples.[61] In another two studies, including 37 nursing infants, detectable concentrations of medication were found in seven serum samples, while desmethylsertraline was found in 17 samples.[51,62,81] Table II summarises the available data on the milk/plasma ratios of sertraline and its metabolite and the relative infant dose.[63] None of the 78 neonates included in the studies reviewed exhibited signs of neurodevelopmental impairment during short-term observation.[55,61-63,81] One report, however, described the case of an infant with abnormally high serum concentrations of both sertraline and N-desmethylsertraline, without clinical relevance.[64] To determine the degree of transporter blockade in infants exposed to the drug through maternal breast milk, the extent of maternal and infant transporters was assessed by measuring platelet levels of serotonin in 14 breastfeeding mother-infant pairs before and after 16 weeks of maternal treatment with sertraline for major depression with postpartum onset.[82] Marked declines in platelet serotonin levels, of as much as 70–96%, were observed in mothers after treatment with sertraline 25–200 mg/day. In

contrast, infants showed little or no change in platelet serotonin levels after exposure through breastfeeding. These observations suggest that mothers taking sertraline can breastfeed without appreciably affecting peripheral or central serotonin transport in their infants.

2.5 Citalopram

2.5.1 Pregnancy Outcomes

One prospective controlled investigation evaluating the use of citalopram during pregnancy examined 357 pregnant women. The rates of congenital birth defects did not vary from those expected in the general population.[24]

2.5.2 Perinatal Adverse Events

Only sporadic case reports have tentatively suggested an association between prenatal exposure to citalopram and perinatal complications; one infant developed generalised hypotonia, transient tachypnoea and left brachial plexus lesion, while a second infant showed signs of neonatal withdrawal syndrome.[33,79] A recent prospective controlled study followed ten pregnant women taking citalopram (20–40 mg/day) and ten women taking fluoxetine (20–40 mg/day), for depressive or panic disorders.[83] The newborns exhibited a greater risk of developing serotoninergic CNS symptoms; the degree of severity of these symptoms was significantly associated with cord blood 5-hydroxyindoleacetic acid levels, but the implications of these findings for long-term infant well-being remain unclear. Citalopram (as well as fluoxetine, sertraline, and paroxetine) has also been associated with Sleep State disorganisation, a sensitive index of neonatal neurodevelopmental integrity following prenatal drug exposure.[65] However, this study was limited by its small sample size and the lack of data about the maternal dosage and timing of drug exposure.[65] In another study, delivery outcome and the neurodevelopment of 11 infants (whose mothers had been taking citalopram 20–40 mg/day during pregnancy) up to the age of 1 year appeared to be normal.[84] These mothers displayed relatively low serum concentrations of citalopram and its metabolites (46–214 nmol/L) during pregnancy and only one patient required an increase in her daily dose.

2.5.3 Breastfeeding

Table II summarises available data on the milk/plasma ratio of citalopram and demethylcitalopram, and the relative infant dose.[51,65-67] The relative dose of the compound for a suckling infant is close to that reported for fluoxetine, and higher than the figure reported for fluvoxamine, paroxetine, and sertraline.[67] Peak milk concentration of citalopram occurs 3–9 hours after intake by the mother.[85] Detectable serum concentrations of citalopram and its metabolite were found in two of three infants exposed to the drug throughout the breastfeeding period, without adverse events. However, in ten breastfed infants citalopram levels were recently found to be undetectable (n = 4) or low (n = 6).[51] A prospective, observational study evaluated the frequency of infantile adverse events from exposure to maternal citalopram therapy via breast milk. Breastfeeding women were subdivided into three groups: the first group consisted of 31 depressed women undergoing citalopram therapy (medium dose: 25.3 ± 11.4 mg/day, 10–60 mg/day); the second group comprised 12 depressed women not pharmacologically-treated; the third group was formed by 31 healthy women who were comparable with the women in group 1 in terms of age and parity. No statistically significant differences were found in the rate of adverse events in the three groups.[86] Conversely, somnolence, weight loss, and decreased feedings have been reported in one suckling infant exposed to the compound via maternal milk.[87]

2.6 Escitalopram

Human data are unavailable for escitalopram.[88] Although one must account for the fact that animal data cannot accurately reflect human situations, very high doses of escitalopram have been associated with decreased fetal body weight and delayed ossification in rats and slight maternal toxicity was also seen at the dosage of 48 mg/kg/day, with a small increase in offspring mortality.[88] Racemic citalopram is excreted in human breast milk, but there is

no data on the serum concentrations of the drug in infants exposed to it throughout breastfeeding.[88]

3. Noradrenergic and Specific Serotoninergic Antidepressants

3.1 Mirtazapine

3.1.1 Pregnancy Outcomes and Perinatal Adverse Events

One of the first reports on the effect of mirtazapine on pregnancy outcomes and perinatal adverse events described the case of a 28-year-old woman who had taken mirtazapine 45 mg/day during the first trimester with no consequences on delivery outcome and the infant's well-being.[89] Kesim et al.[90] followed two pregnant women who had used mirtazapine in combination with trifluoperazine. The first woman had been exposed to the drugs for a longer time (mirtazapine 60 mg/day and trifluoperazine 8 mg/day from week 1 to week 5 of gestation) than the second (mirtazapine 30 mg/day for 3 consecutive days and trifluoperazine 4 mg/day for 2 consecutive days during week 4 of gestation). The first woman had an uncomplicated vaginal delivery of a female infant at week 40 of gestation. The second woman delivered a male infant by caesarean section because of premature rupture of the membranes at week 39 of gestation. The babies were followed for 6 months and no major abnormalities or minor malformations were observed. The second woman's baby developed neonatal hyperbilirubinaemia that decreased spontaneously without phototherapy (although in several studies[91-93] mirtazapine appeared to have an incidence of interference with liver function in adults, which was not different from that of placebo). The baby also had mild gastro-oesophageal reflux disease (GORD) with vomiting once a day. When he was re-examined at 5 weeks of age, the GORD symptoms had decreased. The authors had no data that could confirm that GORD and hyperbilirubinaemia could be attributed to prenatal exposure to mirtazapine. By contrast, Sacks[94] described seven cases in which mirtazapine (dosage ranging from 7.5 to 45 mg/day) was given in pregnancy for depression and hyperemesis gravidarum. All babies were born healthy at term, and each with normal Apgar scores at 1 and 5 minutes. However, one case of severe weight gain (approximately 19kg), which was followed by the development of gestational diabetes, was reported.[94] Mirtazapine therapy (oral/intravenously, at a dosage from 6 to 30 mg/day) was successfully started in another four patients who were affected by treatment-resistant hyperemesis resulting in severe weight loss;[95,96] no adverse events were recorded in their infants. In addition, Yaris et al.[97] described nine pregnant women who took mirtazapine alone or in combination with other drugs; one spontaneous abortion was observed in one woman exposed to mirtazapine, alprazolam, diazepam and trifluoperazine. Conversely, no congenital abnormalities or developmental impairments were observed in the other eight babies, who were followed up for 12 months. Recently, the case of a schizophrenic patient treated with several psychotropic agents (including mirtazapine) who experienced an unplanned pregnancy has been described; delivery, at week 37 of gestation, was uncomplicated and the baby was healthy.[98]

Saks[94] has described one case of persistent fetal circulation and pulmonary hypertension with mirtazapine therapy in an infant exposed *in utero* to mirtazapine. The infant was transferred to an intensive care unit and was healthy when discharged 3 days later. Nonetheless, there was no evidence that this event was associated with intrauterine exposure to the medication.

3.1.2 Breastfeeding

In animal studies, mirtazapine appears to be excreted in small amounts in milk.[99] Recently, the first data on mirtazapine treatment in breastfeeding women were described.[100] The study demonstrated that mirtazapine is excreted in human milk (maternal milk concentrations ranged from 7 ng/mL to 34 ng/mL); however, the drug concentration in an examined infant was below the therapeutic concentration (0.2 ng/mL). Furthermore, no adverse events associated with the mother's mirtazapine intake were detected.

4. Serotonin-Noradrenaline (Norepinephrine) Reuptake Inhibitors

4.1 Venlafaxine

4.1.1 Pregnancy Outcomes

Data obtained by the UK Drug Safety Research Unit revealed the known outcomes of 39 women who took venlafaxine during pregnancy.[20] There were 26 live births and 6 therapeutic abortions in this group and no reports of malformation. In another prospective controlled study, the outcomes of 150 pregnancies were evaluated after exposure to venlafaxine (dosage ranged from 37.5mg to 300 mg/day).[101] This group was matched with two control groups, the first one exposed to SSRIs and the second to nonteratogenic agents; there were 125 live births and 7 therapeutic abortions in the women who received venlafaxine. There were no differences in pregnancy outcome in the three groups, with the exception that more spontaneous abortions were reported in the venlafaxine group, although this difference did not attain statistical significance (see table I for the rate of spontaneous abortions emerging from the reviewed studies). There were two major malformations (hypospadias and neural tube defect with club foot) in the venlafaxine group, three (ventricular septal defect, pyloric stenosis and absent corpus callosum) in the SSRIs group and one (congenital heart defect) in the nonteratogenic group. A prospective study recently described the outcome of ten infants exposed to venlafaxine monotherapy; all the obstetrical findings were normal in each case and the babies showed no congenital malformation or developmental delay at follow-up at 12 months of age.[97]

4.1.2 Perinatal Adverse Events

One case of neonatal withdrawal syndrome following intrauterine exposure to venlafaxine has recently been described.[102]

4.1.3 Breastfeeding

Table III summarises the available data on the distribution, milk/plasma ratio and relative infant dose breakdown for venlafaxine and O-desmethylvenlafaxine.[103] Detectable serum concentrations of venlafaxine or its metabolite were found in three, two and five infants, respectively, of twelve children followed in three different studies without any adverse events.[51,104,105] Two infants exposed to venlafaxine throughout breastfeeding during the first 6 months of life evidenced a normal neurobehavioural development.[104]

5. Selective Noradrenergic Reuptake Inhibitor

5.1 Reboxetine

There are no data on reboxetine exposure in humans in the literature. In animal studies, reboxetine appears to produce no teratogenic effects.[106] In the rat, the drug is excreted in milk in small amounts but its presence in maternal human milk is still unknown.[107]

6. Other Antidepressants

6.1 Bupropion

6.1.1 Pregnancy Outcomes

The manufacturer's registry of bupropion includes the outcomes of 266 pregnancies of women exposed to the agent during the first trimester of pregnancy. At present, there appears to be no in-

Table III. Serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs), their principal metabolites and breastfeeding: milk/plasma ratio, relative infant dose[a] and report of adverse events

SNRI/metabolites	Milk/plasma ratio	Relative infants dose (%)	Infant plasma concentrations	Total sample size	Report of adverse events
Venlafaxine	2.5–4.8	5.5–7.6	5 μg/L	14[51,103-105]	No
O-desmethylvenlafaxine	2.7–3.8		3–38 μg/L		

a On mg/kg maternal dose weight-adjusted basis.

creased risk for major malformations.[108] In the first trimester, bupropion was taken by 12 other pregnant women for smoking cessation. There were five live births, (no congenital abnormalities reported), two therapeutic terminations and one case of intrauterine death.[109]

6.1.2 Breastfeeding

The excretion of bupropion in breast milk has been evaluated by Briggs et al.[110] and Baab et al.[111] Both bupropion and its metabolites were not detectable in infant sera. In the study by Baab et al.,[111] the levels of reliable quantifiability were relatively high (ranging from 5 to 10 ng/mL for bupropion and from 100 to 200 mg/mL for hydroxybupropion) and the volume of the infant serum sample was strongly related to the thoroughness of the results. However, considering the sum of the compound and its three active metabolites, the average infant exposure in molars may be estimated to be 2% of the standard maternal dosage (150–300 mg/day), corrected for the difference in body weight.[112] However, a case of possible infant seizure following exposure to bupropion through maternal milk has been described.[113]

7. Discussion

7.1 General Considerations

Cohen et al.[114] suggest that there are five areas of psychopharmacological risk assessment during pregnancy and breastfeeding: teratogenesis, behavioural teratogenesis, direct toxicity to the fetus, effects on labour and delivery, and effects through breastfeeding. Nevertheless, the incidence of fetal malformations is influenced by several factors that are difficult to examine and related both to the mother (life style, diet, substance abuse) and to the environment (exposure to potentially teratogenic chemical agents, etc.). These situations expose the fetus to teratogenic risks that are not solely associated with maternal drug ingestion. Untreated depression, on the other hand, is not without its own risks since mothers affected by depression have a negative impact on the emotional development of their children and major depression, especially when complicated by a delusional component, may lead to the mother attempting suicide and infanticide.[115,116] For these reasons, clinicians need to help mothers weigh the risks of prenatal exposure to drugs against the potential risks for themselves and their babies if their psychiatric illness is left untreated.[117]

7.2 Non-Pharmacological Treatments

In the treatment of pregnant and breastfeeding women, cognitive-behavioural therapy (CBT), as well as interpersonal psychotherapy, may be important and effective tools.[118,119] These approaches may be useful for patients with slight or moderate symptoms who refuse medications when they are pregnant or breastfeeding. However, Misri et al.[120] recently found that concurrent treatment with CBT and paroxetine showed no advantage in postpartum depressed or anxious mothers when compared with paroxetine monotherapy.[120] Electroconvulsive therapy (ECT) may be reserved only for inpatients with severe delusional depression or severe neurovegetative symptoms of depression that shows little or no response to psychopharmacological treatment. Although devoid of teratogenic effects, there is actually much less data on ECT than on medications for pregnant or breastfeeding women.[121]

7.3 Antidepressants

Treatment with antidepressants should be strongly considered for all women with moderate to severe depression. In spite of the limitations of some of the studies reviewed, fluoxetine,[122,123] as well as the other older SSRIs (while we await the first available data regarding escitalopram), and venlafaxine, seem to be relatively devoid of structural teratogenic risks.

Nevertheless, more than a few reports have shown that an association between placental exposure to SSRIs and adverse but self-limited effects on neonatal adaptation cannot definitely be ruled out. In fact, a number of methodologically rigorous studies have recently reported short-term detrimental sequelae on neonatal developmental areas:[34-36,84,124,125] in cases of prenatal exposure to

SSRIs alone, the incidence of transient symptoms of poor neonatal adaptation has actually been estimated to be 29%; however, in cases of prenatal concomitant exposure to SSRIs (particularly paroxetine) plus clonazepam, this percentage reaches 39%.[126] There is also evidence that intrauterine exposure to SSRIs may increase the risks of low Apgar scores, hypoglycaemia and convulsions.[127] Furthermore, in animal studies maternal fluoxetine treatment is associated with increased fetal plasma cortisol levels;[126] fetal exposure to excess amounts of glucocorticoids during critical developmental periods has been related to increased risks of poor mental outcomes later in life.[126] In addition, information regarding the safety of SSRIs on the long-term development of children is still controversial.[40,124,128,129]

By contrast, the number of reports concerning possible problems associated with the intake of SSRIs via maternal milk is relatively low. The variability of the milk concentrations reached by several antidepressants, which are related to many factors (including the mother's individual metabolism, the different composition of the fore and the hind milk and the timing of the milk sample in relation to the dose of the drug that was taken by the mother) compounds interpretation of the results of studies on breastfeeding, but it is not necessarily an indicator of potential damage for the baby. The variability of the antidepressant concentration is appreciable in the suckling infant's serum as well, but this aspect also appears to be devoid of clinical relevance; indeed, paroxetine and sertraline do not usually cause detectable concentrations in breastfed infants, whereas fluoxetine has been found to produce the highest proportion (22%) of infant concentrations that exceed the average maternal concentrations by 10%. Although based on a smaller sample size, the data on citalopram show that it results in elevated drug levels in 17% of infants.[130] In any case, fat-soluble compounds reach concentrations in the cerebrospinal fluid that are generally 10–30 times higher than those found in serum.[131] Therefore, in many cases, it is still unknown whether maternal ingested SSRIs reach the brain of the suckling infant.[132] Data available on both the structural and functional teratogenic risks associated with intrauterine and postnatal exposure to bupropion, mirtazapine and reboxetine are incomplete or lacking; thus, at present, these compounds should not be used as first-line agents in the pharmacological treatment of depression during pregnancy and breastfeeding.

Although several studies on tricyclic antidepressants (TCAs) have reported no fetal abnormalities or adverse effects during labour, delivery and lactation,[34,47,133-136] some transient perinatal effects associated with intrauterine exposure to these medications have been observed, such as mild withdrawal symptoms.[136] Anticholinergic adverse effects as a result of prenatal and postnatal exposure to TCAs, such as symptoms of functional bowel obstruction and urinary retention in newborns, have also been reported.[137,138]

If the clinical conditions of a mother suggest using a psychopharmacological approach, careful evaluation of the patient's compliance is needed; abrupt discontinuation of antidepressants for fear of harming the fetus may actually result in serious physical and psychiatric adverse effects in pregnant patients, such as withdrawal syndromes and/or relapses of depressive symptoms.[25,139] It is also important not to use daily doses lower than the minimum effective dose threshold and clinicians may often be forced to increase the dose (usually around week 27 of gestation) to avoid a decrease in serum concentrations of medications followed by a recurrence of the depressive symptom cluster.[140] Dose reductions may be feasible only when two conditions are present: a prolonged period of clinical remission, and adequate family and psycho-social support. Nevertheless, depressed pregnant women are often pharmacologically undertreated,[140] although partial and ineffective treatment exposes them to an increased risk of adverse pregnancy outcomes.[141] Marcus et al.[142] calculated that the rate of depressive symptoms among the pregnant women who were screened and treated may be as low as 0.8%. For all of these reasons, the adverse effects of untreated or sub-optimally treated maternal depression should be taken into considera-

tion, so that the best treatment option may be identified without any abrupt discontinuation of therapy.[143,144]

8. Conclusion

In conclusion, we suggest that the choice of whether or not to administer psychopharmacological treatment to pregnant or breastfeeding women with mood disorders should result primarily from a careful evaluation of their psychopathological condition; the degree of severity of maternal disease appears to represent the most relevant parameter to take this clinical decision.

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