Breastfeeding During Maternal Antidepressant Treatment With Serotonin Reuptake Inhibitors: Infant Exposure, Clinical Symptoms, and Cytochrome P450 Genotypes

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Background: The aims of the study were to quantify the drug exposure in breastfed infants of antidepressant-treated mothers, to identify possible adverse events, and to correlate these variables to maternal and infant drug metabolism–relevant genotypes and milk triglyceride content.

Method: The study included 25 lactating women treated with citalopram (N = 9), sertraline (N = 6), paroxetine (N = 6), fluoxetine (N = 1), or venlafaxine (N = 3) and their 26 breastfed infants. Drug concentrations in maternal and infant serum and milk were analyzed using liquid chromotography mass spectrometry methods; milk triglyceride levels were measured with a commercial kit. Cytochrome P450 (CYP) 2D6 and CYP2C19 activity was determined by polymerase chain reaction–based genotyping of the mothers and infants. An infant adverse event questionnaire was completed by the medication-treated mothers as well as by a control group of medication-free breastfeeding mothers of 68 infants.

Results: Sertraline and paroxetine were not detected in any of the drug-exposed infants. The infant serum level of citalopram was either undetectable (N = 4) or low (N = 6). All venlafaxine-exposed infants had measurable drug concentrations. We identified a paroxetine-treated mother and her infant who were both CYP2D6 poor metabolizers, as well as a citalopram-treated mother with CYP2C19 poor metabolizer status, but the serum drug levels of their infants were still either undetectable (paroxetine) or low (citalopram). There was no evidence of adverse events in the drug-exposed infants.

Conclusion: Serum drug levels in breastfed infants of antidepressant-treated mothers were undetectable or low. This study adds further evidence to previously published data indicating that breastfeeding should not be generally discouraged in women using serotonin reuptake inhibitor antidepressants.

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Maternal depression in the postpartum period is common; a prevalence rate of 13% has been indicated in a meta-analysis.[1] Due to the harmful effects of depression in general and the many challenges related to caretaking of the newborn in particular, it is very important to initiate effective, rapid-onset therapies. Treatment with antidepressant drugs of the selective serotonin reuptake inhibitor (SSRI) type has been recommended as first-line therapy in postpartum depression,[2] and the SSRIs are also the treatment of choice for postpartum dysthymia, panic disorder, and obsessive-compulsive disorder.[3] In addition to the SSRIs, the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine may also be effective in the treatment of postpartum depression.[4]

However, treatment guidelines specific to postpartum depression are not yet available,[2] and therapy is often complicated by the mother's desire to breast-feed and uncertainty about drug exposure and subsequent potential adverse events in the infant. Relapse of postpartum major depression after treatment discontinuation has been reported,[5] supporting the need for ongoing treatment for women with this condition.[6] Human milk is the ideal food during infancy[7]; it gives the best source of nutrients and provides both defense factors for the growing infant and better antioxidant protection than do maternal milk substitutes.[8,9] Breastfeeding is therefore important from a nutritional and immunologic point of view.[10] It also has possible positive effects on cognitive development[11] and may

enhance psychological bonding between the mother and infant, which is particularly important for depressed mothers. Therefore, women are strongly encouraged to breast-feed when possible.[12] As a large number of women would be expected to receive treatment with serotonin reuptake inhibitors in the postpartum period in the future, safety considerations with regard to infant exposure are of crucial importance.[13]

In reviews based on published case reports and case series, Spigset and Hägg[14] and Dodd et al.[15] stated that treatment with SSRIs is generally compatible with breastfeeding. Although the number of well-documented cases is still limited, the accumulating data on the use of antidepressant drugs by lactating women indicate that the benefits of using medication to treat depression in nursing mothers may well outweigh the theoretical risk of concomitant drug exposure in the infants.[2,6] In another review, Burt et al.[16] recommended that pediatricians be involved in monitoring infants when psychotropic medications are used during breastfeeding. In line with this view, a policy statement of the American Academy of Pediatrics expressed concern about psychotropic drugs and their possible effects through breast milk exposure of the nursing infant, stating that these drugs affect neurotransmitter function in the developing central nervous system and that it may not be possible to predict long-term neurodevelopmental effects.[17]

It is therefore still controversial as to whether breastfeeding should be encouraged during antidepressant treatment. To add more evidence and knowledge to this important issue, we conducted a study involving 25 antidepressant-treated breastfeeding mothers and their infants, measuring maternal serum and milk drug concentrations as well as infant serum drug levels. We also clinically evaluated the infants by means of a maternally reported questionnaire, with comparison to a control group. Moreover, we elucidated whether genetically determined variation in the maternal and infant activity of the cytochrome P450 (CYP) isozymes CYP2C19 and CYP2D6, which are involved in the metabolism of the SSRI and SNRI antidepressants, may affect infant drug levels and clinical status. No previous studies have included *CYP2D6* and *CYP2C19* genotyping to identify poor, extensive, and ultrarapid metabolizers among lactating mothers and their infants. In brief, CYP2D6 is the major enzyme involved in the metabolism of fluoxetine (to the active metabolite norfluoxetine), paroxetine, and venlafaxine (to the active metabolite *O*-desmethylvenlafaxine), and CYP2C19 is the major enzyme involved in the metabolism of citalopram and one of the major enzymes involved in the metabolism of sertraline.[18] The frequency of poor metabolizers for CYP2D6 and CYP2C19 in white populations is about 7% to 8% and 3%, respectively.[19–23] Finally, milk triglyceride concentrations were measured in order to study whether variations in infant drug exposure could be explained by alterations in milk triglyceride content.

METHOD

Subjects

We performed a study in lactating women with DSM-IV major depressive disorder treated with one of the serotonin reuptake inhibitors citalopram, fluoxetine, paroxetine, sertraline, or venlafaxine in monotherapy. Patients were recruited via communication of general information about the project to psychiatrists and general practitioners throughout Norway. In total, 25 white women and their 26 infants (1 pair of dizygotic twins) were enrolled in the study. The women participated on a voluntary basis after the procedures had been fully explained. They provided written informed consent on a form before inclusion in the study, which was approved by the Board of Research Ethics in Health Region III of Norway.

Symptom Rating in Infants

To further explore the potentially undesirable effects of infant drug exposure during breastfeeding, antidepressant-treated nursing mothers and a control group of nursing mothers not treated with any medication were asked to complete an infant symptom score form (form is available from the authors on request). The symptom scores were rated from 0 to 3 on each item (0 = absent, 3 = severe). The items were chosen to include symptoms that are the most commonly known adverse events for the drugs included in the study.[24] In addition, the symptoms were chosen as representative of those that had been previously suspected in breastfed infants whose mothers had been treated with these drugs.[25–27]

Collection of Serum and Milk Samples

The concentrations of the antidepressants were measured in breast milk as well as in maternal and infant serum. All samples were obtained after the drug concentrations had attained steady state, i.e., after the patients had used the drug at the same dose for 14 days or more (85 days for fluoxetine). The mothers were asked to obtain ten 5-mL milk portions during a period of 24 hours. The mothers were instructed to sample milk from both breasts, collect foremilk and hindmilk, and distribute the sampling as equally as possible throughout the 24-hour period. The samples were stored at –80ºC until the day of analysis. The serum drug concentrations were analyzed in 1 blood sample from the mother and 1 sample from the infant. In the mothers, the samples were collected in the morning immediately before administration of the next dose.

Analysis of Antidepressant Drugs and Triglycerides

Serum and breast milk levels of citalopram, desmethylcitalopram, fluoxetine, norfluoxetine, paroxetine, ser-

traline, desmethylsertraline, venlafaxine, and *O*-desmethylvenlafaxine were measured using liquid chromatography mass spectrometry. Serum and milk samples of 1 mL were extracted with organic solvents after alkalinization with sodium bicarbonate. The evaporated and concentrated extracts were analyzed on an Agilent 1100 Series LC/MSD system (Agilent Technologies, Palo Alto, Calif.). In serum, the limits of detection for citalopram and desmethylcitalopram were 1 nmol/L; for the other analytes, the limits of detection were all below 5 nmol/L. In milk, the limits of detection were as follows: citalopram, 1 nmol/L; desmethylcitalopram, fluoxetine, norfluoxetine, paroxetine, sertraline, desmethylsertraline, and *O*-desmethylvenlafaxine, 5 nmol/L; and venlafaxine, 10 nmol/L. The milk triglyceride concentrations were measured by enzymatic hydrolysis with subsequent determination of glycerol, using a commercial kit (Triglycerides GPO-PAP, Boehringer Mannheim; Mannheim, Germany).

CYP2C19 and *CYP2D6* Genotyping

EDTA-anticoagulated blood samples were obtained from 24 of 25 participating mothers and their 25 corresponding infants (including 1 pair of twins). Genomic DNA was extracted from leukocytes by the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). *CYP2C19* genotyping for the poor metabolizer–related *CYP2C19*2*, *CYP2C19*3*, and *CYP2C19*4* variants was performed as 3 separate restriction enzyme digestion assays of *CYP2C19*-specific polymerase chain reaction (PCR) products according to standard methods described by others.[28,29] *CYP2D6* genotyping for the poor metabolizer–related *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*6*, and *CYP2D6*7* variants was performed by a multiplex PCR reaction, as described by Stüven et al.,[30] with the following modifications of the oligonucleotides: primers G1 and G2 for detection of the rare *CYP2D6*8* allele were not included in the assay, the sequence of the common multiplex forward primer M was altered to 5'-GGATGGTGGGGCTAAT-3', and the reverse T2 primer for detection of the **6* allele was shortened to 5'-TCCTCGGTCACCCC-3'. The poor metabolizer–associated *CYP2D6*5* gene deletion allele and the ultrarapid metabolizer–associated *CYP2D6*2×2* duplication variant were identified by 2 separate long PCR assays.[31,32] For all of the PCR assays, we included pretyped positive and negative control DNA. *CYP2C19* and *CYP2D6* alleles with none of the mutations tested were classified as *CYP2C19*1* and *CYP2D6*1*, respectively. Detailed information about the PCR conditions is available from the authors on request. The genotyping procedure was conducted with no prior information about demographic or pharmacologic data related to the samples.

Statistics

The mean drug concentration in breast milk for each subject was calculated as the area under the time-concentration curve (AUC) divided by the sampling time, which most often was 23 to 25 hours. AUC was calculated by means of the trapezoidal rule, using the pharmacokinetic program package Kinetica, version 2.0.1 (InnaPhase Sarl, Champs-sur-Marne, France).

The relationship between the infant antidepressant dose per kilogram of body weight (D_{infant}) and the maternal antidepressant dose per kilogram of body weight was shown using the equation $D_{infant} = C_{milk} \times V_{milk}/D_{mother}$, where C_{milk} = antidepressant concentration in milk, V_{milk} = daily volume ingested by the infant (assumed to be 150 mL/kg body weight), and D_{mother} = maternal daily antidepressant dose per kilogram of body weight. For the drugs with active metabolites, fluoxetine and venlafaxine, the sum of the concentrations of the parent substance and the metabolite (norfluoxetine and *O*-desmethylvenlafaxine, respectively) on a molar basis was converted to mass units of the parent substance and used as C_{milk}.

For the comparison of infants in the antidepressant group and the control group, χ^2 tests were used for dichotomous demographic variables, Student t tests were used for continuous demographic variables, and Mann-Whitney U tests were used for the comparison of symptom scores. Student t tests were used for the comparison of triglyceride and drug concentrations in prefeed and postfeed milk. The correlation coefficients between milk triglyceride levels and drug concentrations were determined using analysis of covariance with subject as a categorical predictor variable. P values < .05 were considered statistically significant.

RESULTS

The study included 25 lactating mothers and their 26 infants (13 girls and 13 boys; 1 pair of twins). The mean age of the mothers was 31 years (range, 20–42 years). As shown in Table 1, citalopram was the most commonly prescribed drug (N = 9), followed by sertraline (N = 6), paroxetine (N = 6), venlafaxine (N = 3), and fluoxetine (N = 1). Twelve of the 25 women (4 taking citalopram, 3 taking paroxetine, 2 taking sertraline, 1 taking fluoxetine, and 2 taking venlafaxine) also used their medication during pregnancy. The doses used were within the recommended dose ranges for the various drugs, and the maternal serum drug concentrations were within the expected ranges given the doses ingested.

The age of the infants at the time of inclusion varied from 2 to 42 weeks, with a mean age of 18 weeks. As demonstrated by the drug concentrations in the milk, all infants were exposed to an antidepressant drug during breastfeeding. The mean milk/maternal serum drug concentration ratios varied from 0.3 to 2.4 for the various drugs (Table 1). By body weight–adjusted comparison, the mean relative infant doses were calculated to range

Table 1. Data From 25 SRI-Treated Breastfeeding Mothers and Their 26 Infants (1 pair of twins)[a]

Variable	Citalopram	Sertraline	Paroxetine	Fluoxetine	Venlafaxine
Mothers/infants, N	9/10	6/6	6/6	1/1	3/3[b]
Age					
Mothers, y	28.2 (23–35)	32.8 (28–41)	31.8 (20–41)	24	38 (32–42)
Infants, wk	18 (3–42)	15 (5–34)	16 (2–33)	11	16 (8–30)
No. of milk samples per mother, mean	7.0	6.0	8.8	6.0	6.8
Maternal drug dose, mg/d	24 (20–50)	64 (50–100)	20 (10–30)	20	131 (75–225)
Maternal serum drug concentration, nmol/L	221 (57–508)	95 (46–129)	145 (22–210)	734[c]	965 (407–1432)[d]
Milk drug concentration, nmol/L	389 (157–725)	151 (97–230)	88 (18–152)	218[c]	2314 (1012–3203)[d]
Milk/maternal serum drug concentration ratio	2.1 (1.1–4.3)[e]	1.8 (1.2–3.5)[f]	0.7 (0.6–0.9)	0.3[c,g]	2.4 (2.2–2.6)[d,h]
Relative dose to the infant,[i] %	5.2 (2.5–9.4)	0.9 (0.6–1.7)	1.4 (0.5–2.6)	3.3[c]	5.2 (3.8–6.4)[d]
Infant serum drug concentration, nmol/L	1.9 (0–8)[j]	0 (0–0)[k]	0 (0–0)[k]	47[l]	91 (31–128)[d,m]
Infant serum drug concentration as % of maternal serum drug concentration	0.9 (0–4.8)	0 (0–0)	0 (0–0)	6.4[c]	10.2 (5.3–19.0)[d]

[a]Values are shown as mean (range) unless otherwise noted (only 1 mother was taking fluoxetine). The milk concentration calculations are based on mean values distributed over the entire dose interval and including both foremilk and hindmilk samples. In total, 185 milk samples were analyzed. The maternal serum drug concentration measurements are based on trough level sampling.
[b]One pair was studied twice, first with a maternal dose of 150 mg/day, thereafter with a dose of 75 mg/day.
[c]For the sum of fluoxetine and the active metabolite norfluoxetine.
[d]For the sum of venlafaxine and the active metabolite *O*-desmethylvenlafaxine.
[e]Ratio for the metabolite desmethylcitalopram: mean = 2.9; range, 0.9–6.3.
[f]Ratio for the metabolite desmethylsertraline: mean = 1.6; range, 0.6–4.7.
[g]Ratio for fluoxetine: mean = 0.4; ratio for the active metabolite norfluoxetine: mean = 0.3.
[h]Ratio for venlafaxine: mean = 2.6; range, 1.6–3.0; ratio for the active metabolite *O*-desmethylvenlafaxine: mean = 3.5; range, 0.7–8.1.
[i]Expressed in percentage as the dose to the infant per kilogram of body weight relative to the maternal dose per kilogram of body weight.
[j]Detected in 6 of 10 infants.
[k]Drug could not be detected in any infants in the sample.
[l]Only the active metabolite norfluoxetine was detected.
[m]Venlafaxine was detected in 1 infant only; the active metabolite *O*-desmethylvenlafaxine was detected in all infants.
Abbreviation: SRI = serotonin reuptake inhibitor.

Table 2. Demographic Data and Total Clinical Symptom Score in the 20 Infants for Whom Data Were Available and in a Control Group of 68 Breastfed Infants Whose Mothers Used No Medication[a]

Variable	Treatment Group (N = 20)	Control Group (N = 68)
Females, %	50	51
Age, wk	19 (3–42)	16 (5–42)
Length, cm	62 (50–74)	63 (53–74)
Body weight, kg	6.6 (4.1–11.7)	6.6 (3.6–11.3)
Total symptom score	5.9 (0–13)	7.6 (0–16)
Sneezing	1.32 (0–2)	1.71 (0–3)
Regurgitation or vomiting	1.20 (0–2)	1.63 (0–3)
Yawning	0.95 (0–2)	1.40 (0–2)
Loud crying	0.90 (0–2)	0.99 (0–2)
Decreased sleep	0.75 (0–2)	0.78 (0–3)
Irritability	0.40 (0–2)	0.46 (0–3)
Tremor	0.20 (0–2)	0.18 (0–2)
Increased sleep	0.10 (0–2)	0.21 (0–3)
Decreased muscle tone	0.05 (0–1)	0.10 (0–2)
Suckling or feeding problems	0.05 (0–1)	0.16 (0–2)

[a]Values are shown as mean (range) unless otherwise noted. No significant differences between the groups were observed.

from 0.9% (sertraline) to 5.2% (citalopram and venlafaxine) of the maternal dose (Table 1). The drug exposure did not lead to detectable serum drug levels in any of the 12 infants of mothers being treated with sertraline or paroxetine. Moreover, citalopram was not detected in 4 of 10 serum samples from infants of citalopram-treated mothers; this drug was found in low concentrations in the remaining 6 infants, with a relative level of a maximum of 4.8% of the maternal serum drug concentration. Although the number of infants exposed to venlafaxine was low, it should be noted that all 3 infants had rather high serum levels of the active metabolite *O*-desmethylvenlafaxine, and venlafaxine was detected in 1 of the infants (Table 1); relative to the maternal serum drug concentrations, their mean serum drug level was 10.2%.

An adverse event form was completed for a subset of 20 of the 26 antidepressant-exposed infants. This group was compared with the control group of 68 infants of breastfeeding mothers not treated with any medication. The groups did not differ with respect to demographic data. There were no significant differences in the symptom scores between the 2 groups, with respect to either the total score or the different subitem scores (Table 2). In addition, we separately analyzed the 8 infants in whom the serum drug concentrations were above the limit of detection (data not shown). Their mean total symptom score was not significantly different from that of the remaining 12 infants in the treatment group (6.1 vs. 5.7, respectively).

Since genetically determined differences in drug metabolism may affect the clinical effects of certain drug exposures, we genotyped both the mothers (N = 24) and their infants (N = 25) with respect to the polymorphic *CYP2C19* and *CYP2D6* genes. As indicated in Table 3, we identified a mother treated with paroxetine (20 mg/day) and her infant who were both homozygous for the inactivating *CYP2D6*4* mutation; this is consistent with the presence of the CYP2D6 poor metabolizer phenotype. CYP2D6 is normally a major enzyme involved in the me-

Table 3. Overview of *CYP2D6* and *CYP2C19* Genotypes in SRI-Treated Breastfeeding Mothers and Their Infants, Subclassified With Respect to Exposure to Different Drugs[a]

	CYP2D6[b]						*CYP2C19*[b]		
Group	**1/*1* (EM)	**1/*3* (EM)	**1/*4* (EM)	**2×2/*4* (EM)	**4/*4* (PM)	**1/*2×2* (UM)	**1/*1* (EM)	**1/*2* (EM)	**2/*2* (PM)
Mothers (N = 24)[c]									
Citalopram (N = 9)	5	…	4	…	…	…	4	4	1
Sertraline (N = 6)	3	1	2	…	…	…	4	2	…
Paroxetine (N = 5)	2	…	1	1	1	…	4	1	…
Fluoxetine (N = 1)	…	…	1	…	…	…	…	1	…
Venlafaxine (N = 3)	2	1	…	…	…	…	2	1	…
Infants (N = 25)[c]									
Citalopram (N = 10)[d]	7	1	2	…	…	…	5	5	…
Sertraline (N = 6)	3	1	2	…	…	…	5	1	…
Paroxetine (N = 5)	2	…	1	…	1	1	4	1	…
Fluoxetine (N = 1)	1	…	…	…	…	…	…	1	…
Venlafaxine (N = 3)	2	…	1	…	…	…	3	…	…

[a]CYP2D6 is a major enzyme in the metabolism of paroxetine, fluoxetine, and venlafaxine, whereas CYP2C19 has an important role in the metabolism of citalopram and sertraline.
[b]Phenotypes indicated in parentheses.
[c]One of the mothers using paroxetine and her infant were not genotyped.
[d]N = 10 due to 1 pair of twins.
Abbreviations: CYP = cytochrome P450, EM = extensive metabolizer, PM = poor metabolizer, SRI = serotonin reuptake inhibitor, UM = ultrarapid metabolizer.

tabolism of paroxetine, and the maternal serum drug concentration was the highest measured (210 nmol/L) among the paroxetine-treated mothers. Still, the drug could not be detected in the serum of her infant, who was also a poor metabolizer subject. Yet, we found an infant with the *CYP2D6* duplication (*CYP2D6*2×2* variant) in combination with a normal *CYP2D6*1* allele, consistent with the ultrarapid metabolizer status by genotype. This infant was also among the 5 paroxetine-exposed infants with an undetectable serum drug level. Moreover, we identified a mother on treatment with citalopram (20 mg/day) who was homozygous for the inactivating *CYP2C19*2* mutation, consistent with the CYP2C19 poor metabolizer phenotype. CYP2C19 normally plays an important role in the metabolism of citalopram, and the mother had the highest concentration of those treated with this dose (394 nmol/L). Her twin infants, who were both heterozygous for the same mutation and thus extensive metabolizers, had detectable but low serum concentrations of citalopram. We also noted that the 5 infants with the *CYP2C19*1/*2* genotype tended to have higher mean serum citalopram concentrations than the 5 infants with the *CYP2C9*1/*1* genotype (3.0 vs. 0.8 nmol/L, respectively), and 3 of the 4 infants with no detectable citalopram concentration belonged to the *CYP2C9*1/*1* group (data not shown). For the other drugs, such comparisons could not be performed, either because of drug concentrations below the limit of detection or due to a skewed distribution of the various genotypes.

The triglyceride levels in breast milk may influence the milk drug concentrations. The mean triglyceride level in the milk samples was 44.6 mmol/L, ranging from 12 to 129 mmol/L in milk from the different mothers (data not shown). The triglyceride levels were significantly higher in postfeed samples (54.8 mmol/L) than in prefeed samples (36.7 mmol/L; $p < .0001$). There were also generally higher drug concentrations in postfeed than in prefeed milk (585 vs. 362 nmol/L for citalopram, 173 vs. 118 nmol/L for sertraline, 154 vs. 127 nmol/L for fluoxetine, 111 vs. 56 nmol/L for norfluoxetine, 649 vs. 430 nmol/L for venlafaxine, and 1902 vs. 1754 nmol/L for *O*-desmethylvenlafaxine). The difference was statistically significant for citalopram ($p = .045$) and of borderline significance for sertraline ($p = .065$). For fluoxetine and venlafaxine, the numbers of samples were too low to perform meaningful statistical testing. For paroxetine, there were very few postfeed samples in total. Significant or near-significant correlations were found between the triglyceride levels and the drug concentrations in milk: $r = 0.28$, $p = .058$ for citalopram; $r = 0.48$, $p = .004$ for sertraline; $r = 0.71$, $p < .001$ for paroxetine; $r = 0.85$, $p = .034$ for fluoxetine; $r = 0.95$, $p = .005$ for norfluoxetine; $r = 0.33$, $p = .153$ for venlafaxine; and $r = 0.41$, $p = .074$ for *O*-desmethylvenlafaxine.

DISCUSSION

The current study demonstrates that although serotonin reuptake inhibitors are excreted in breast milk, only low and often undetectable concentrations of medication can be measured in infant serum after exposure through breast milk. The study was conducted in a naturalistic setting, and the maternal serum drug concentrations measured indicated adequate compliance. We included milk samples that were obtained throughout a dose interval from each subject and included foremilk and hindmilk samples, and the samples were obtained at steady-state conditions. In addition, as we calculated our data via area under the

time-concentration curve values, it is likely that the results are representative of the situation in clinical practice.

Twelve of the 25 women had been treated with the same drug also during pregnancy. In these cases, there is a theoretical possibility that at least a part of the drug level measured in the infants might have been caused by transplacental passage of the drug. However, in practice, we consider this factor to be negligible. All infants in this group were older than 2 weeks of age at inclusion (youngest was 17 days, mother taking paroxetine), and most were considerably older than 2 weeks. Given the elimination half-lives of the drugs studied (with the exception of fluoxetine), there is reason to believe that principally the entire drug amount transferred by transplacental passage would have been metabolized by the infant during the first few weeks postpartum, even though the capacity to metabolize drugs is generally decreased in neonates. For fluoxetine, the active metabolite norfluoxetine has an elimination half-life of several weeks, but in this case, the infant's age was 11 weeks.

In line with the low infant serum drug levels, there were no indications of adverse events in the infants according to the clinical symptom scores reported by the mothers. The reporting form was based on known adverse reactions after therapeutic use and previously suspected adverse events in breastfed infants,[25–27] but the questionnaire has not been formally validated. Also, it should be emphasized that the sample size was small, thus increasing a risk for type II errors. Moreover, no infants were investigated by a pediatrician, and it cannot be excluded that there might have been other symptoms that were not discovered or reported by the mothers, who could be biased toward underreporting symptoms in their children. Prior research in this area has yielded conflicting results, but in most studies, no adverse events have been reported (for an overview, see Burt et al.[16]).

In performing a genotype-based analysis of CYP2C6 and CYP2C19 activity in the women and their infants, our aim was to elucidate whether the existence of an especially low metabolic capacity (being a poor metabolizer) could be a risk factor for increased drug exposure and adverse events in the infants. In our study sample, we were fortunate to identify a paroxetine-treated mother and her infant who were both CYP2D6 poor metabolizers. This mother and infant thus represent a "worst-case" scenario, as high levels of the drug would be expected in the maternal serum and in the milk, in combination with a low capacity to metabolize paroxetine in the infant. Nevertheless, paroxetine could not be detected in the infant serum, despite a high maternal serum and milk drug level. A similar tendency was observed for the citalopram-treated CYP2C19 poor metabolizer mother, whose twin infants had only very low serum drug levels. These data further support the view that drug exposure in breastfed infants is minimal with respect to the resulting serum drug levels, at least in paroxetine-, sertraline-, or citalopram-treated lactating mothers.

As antidepressants are lipophilic drugs, their excretion in breast milk is expected to vary with milk triglyceride content.[33] Such relationships were also revealed in the present study. Yet, the nutritional value of human milk is also linked to its triglyceride levels. Therefore, any effort to avoid the rather minimal additional drug exposure imposed by breast milk containing "high" versus "low" triglyceride levels should probably not be recommended, especially due to the considerable and unpredictable variability in the triglyceride levels during a dose interval (data not shown), which makes it very difficult to accurately predict the impact of discarding single portions of milk.

Finally, even though the infants are exposed to very low drug levels through breast milk, some concern has been alleged as to possible long-term effects, e.g., with regard to neurobehavioral development, in the infant. Although there is generally a lack of long-term data concerning infant antidepressant drug exposure through breast milk, some information is available on exposure in utero.[34–38] In these studies, no detrimental long-term effects have been revealed. These results are reassuring, as SSRI exposure in utero causes serum concentrations that are at least 5- to 10-fold higher than exposure through milk.[37–39] It can also be assumed that the fetal brain is more vulnerable than the infant brain.

We found, in accordance with previous studies, that the infant serum concentrations were below the limit of detection for sertraline and paroxetine, low but detectable in most infants for citalopram, and highest for fluoxetine and venlafaxine. It should, however, be noted that for technical reasons, the limit of detection was lower for citalopram than for sertraline and paroxetine. If a limit of detection of 5 nmol/L had been used for citalopram, 9 of 10 infants would have had a concentration below this limit. Regardless of the limits of detection, the infant serum drug levels were highest for fluoxetine and venlafaxine (plus its active metabolites), amounting to a mean of 6.4% and 10.2%, respectively, of the maternal drug levels.

In conclusion, we have demonstrated that the serum drug levels in breastfed infants were low or undetectable during maternal serotonin reuptake inhibitor treatment, even though some of the mothers and infants had a genetically determined impaired capacity to metabolize the drugs. Moreover, there was no evidence of any harmful effect in the infants. Taking the results from the present study as well as from previous studies into account, we suggest that when antidepressant treatment is indicated in women with postpartum depression, they should not be advised to discontinue breastfeeding.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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