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Maternal Fluoxetine Treatment in the Postpartum Period: Effects on Platelet Serotonin and Plasma Drug Levels in Breastfeeding Mother-Infant Pairs

C. Neill Epperson, MD*‡; Peter I. Jatlow, MD§; Kathryn Czarkowski, MA*; and George M. Anderson, PhD§||

ABSTRACT. *Objective.* Postpartum major depression, a frequently (10%) occurring complication of childbirth, adversely affects the mother's functioning, the mother-infant relationship, and the child's subsequent development and propensity for later psychopathology. Although selective serotonin reuptake inhibitors (SSRIs) are effective in treating postpartum depression, concerns have been raised regarding their use in lactating women. Although plasma drug levels of infants who are exposed to SSRIs through breast milk are low compared with those typically seen in patients, infant levels in some reports do seem to be at or near the drugs' reported affinities (K_D s) and IC_{50} s for inhibition at the serotonin (5-hydroxytryptamine [5-HT]) transporter. The impact of central serotonin 5-HT modulation by SSRIs during critical periods of brain development is unknown. These concerns have led our group to examine whether exposure through breast milk has a discernible effect on platelet 5-HT uptake. Taking advantage of the similarities between platelet and neuronal serotonin transporters, we previously used measurements of platelet 5-HT before and during maternal sertraline treatment to determine the degree of 5-HT transporter blockade in breastfed infants. We found that infants who were exposed to sertraline through their mothers' breast milk experienced little to no change in platelet 5-HT levels, suggestive of minimal effects on peripheral and central 5-HT transporter blockade. Compared with sertraline and most other SSRIs, fluoxetine and its active metabolite, norfluoxetine, have substantially longer plasma half-lives, and both compounds have been found in measurable quantities in plasma of nursing infants. Thus, to extend our previous work in this area, we measured platelet 5-HT levels and plasma drug levels in breastfeeding mother-infant pairs before and during maternal treatment with fluoxetine.

Methods. Maternal and infant transporter blockade was assessed by measurement of platelet 5-HT in 11 breastfeeding mother-infant pairs before and after 4 to 12 weeks of maternal fluoxetine (20–40 mg/d) treatment for postpartum depression. The study was approved by the Human Investigation Committee of Yale University School of Medicine, and each mother (mean age: 34.5

years; standard deviation [SD]: 5.3) gave written informed consent. Whole-blood 5-HT levels and plasma fluoxetine and norfluoxetine levels were determined by high-performance liquid chromatography.

Results. Five mothers were taking 20 mg of fluoxetine daily, 4 were taking 30 mg daily, and 2 were taking 40 mg daily. Mean infant age at the start of the study was 16.8 (SD: 8.8) weeks. All infants except 1 were <6 months of age and 4 were <3 months of age when their mothers began treatment. Six infants were breastfed exclusively; the remaining were breastfed between 3 and 8 times daily and were given supplemental feedings. Mean maternal postexposure 5-HT levels of 22.9 ng/mL (SD: 12.5) were markedly lower than mean preexposure (baseline) levels of 156.6 ng/mL (SD: 71.4; paired $t = 6.9$, $df = 10$). In contrast, the mean infant pre- and postexposure 5-HT concentrations of 217.1 (SD: 66.5) and 229.9 (SD: 83.5) ng/mL, respectively, were similar (paired $t = -0.24$, $df = 10$). However, the 1 infant with measurable plasma fluoxetine had a substantial decline in 5-HT to 40% of baseline. In samples obtained from the same infant 4 months later, plasma drug levels were undetectable (<1 ng/mL) and the platelet serotonin levels were no longer reduced (12% increase from baseline).

Conclusions. The marked declines (to 9%–28% of baseline) in platelet 5-HT concentrations seen in mothers who were treated with the SSRI fluoxetine were similar to those observed in our study of sertraline in breastfeeding and other previous studies. In contrast, all but 1 infant experienced little or no decline in whole-blood (platelet) 5-HT concentrations after exposure to fluoxetine through breast milk. The substantial drop in platelet 5-HT seen in 1 infant and the coupling of this drop with measurable plasma fluoxetine level raises some concern. Possible reasons for the infant's measurable plasma fluoxetine level include his mother's high plasma drug level and his being breastfed exclusively. However, the observations may be coincidental, and the infant experienced no discernible adverse effects. These data suggest that most infants may continue to breastfeed without experiencing meaningful changes in platelet 5-HT transport while their mothers are treated with 20 to 40 mg of fluoxetine daily. Given the limited data regarding occurrence and extent of SSRI exposure and the uncertainties concerning the possible effects of exposure, it is premature to propose treatment guidelines. Our own advice to women who are thinking of combining breastfeeding and SSRI treatment will weigh a range of factors, including severity of postpartum depression, any demonstrated preferential response to a specific SSRI, and the mother's commitment to breastfeeding. Additional research is needed to establish more definitively the frequency of physiologically meaningful infant SSRI exposure during breastfeeding and to determine the be-

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havioral consequences of such exposure. *Pediatrics* 2003;112:e425-e429. URL: <http://www.pediatrics.org/cgi/content/full/112/5/e425>; fluoxetine, breastfeeding, postpartum, serotonin, serotonin transporter, platelets.

ABBREVIATIONS. SSRI, selective serotonin reuptake inhibitor; 5-HT, 5-hydroxytryptamine; SD, standard deviation.

The short- and long-term benefits of breastfeeding for both mothers and infants are well documented.¹ It is also apparent that postpartum major depression, a frequently (10%) occurring complication of childbirth, seriously affects the mother's functioning, the mother-infant relationship, and the child's subsequent development and propensity for later psychopathology.²⁻⁴ Although selective serotonin reuptake inhibitors (SSRIs) are effective in treating postpartum depression, concerns have been raised regarding their use in lactating women.

Appreciable drug levels are measured in breast milk of women who receive SSRIs, and plasma drug levels in the low ng/mL range have been reported in their nursing infants.⁵ Although infant plasma drug levels are low compared with those typically seen in patients, infant levels in some reports do seem to be at or near the drugs' reported affinities (K_{DS}) and IC_{50S} for inhibition at the serotonin (5-hydroxytryptamine [5-HT]) transporter.⁶⁻⁹ The impact of central serotonin 5-HT modulation by SSRIs during critical periods of brain development is unknown. Although 5-HT plays important roles in early neurodevelopment,¹⁰⁻¹⁴ the preclinical literature regarding the impact of SSRI exposure during neurodevelopment is inconsistent and difficult to generalize to humans.^{15,16}

These concerns have led our group to examine whether exposure through breast milk has a discernible effect on platelet 5-HT uptake. The platelet and neuronal 5-HT transporters are identical with respect to sequence and pharmacologic sensitivities.^{17,18} All platelet 5-HT is accumulated by uptake through the platelet membrane 5-HT transporter, and a number of studies have used the decline in platelet 5-HT seen after administration of reuptake inhibitors as an index of central and peripheral transporter blockade.¹⁹⁻²¹ Taking advantage of the similarities between platelet and neuronal serotonin transporters,^{17,18} we used measurements of platelet 5-HT before and during maternal sertraline treatment (50-100 mg daily) to determine the degree the 5-HT transporter blockade in breastfed infants.^{22,23} We found that infants who were exposed to sertraline through their mothers' breast milk experienced little to no change in platelet 5-HT levels, suggestive of minimal effects on peripheral and central 5-HT transporter blockade.

The widely prescribed SSRI fluoxetine (Prozac) is often used to treat postpartum depression. Compared with sertraline and other SSRIs, fluoxetine and, in particular, its active metabolite, norfluoxetine, have substantially longer plasma half-lives, and both compounds have been found in measurable quantities in infant plasma.²⁴⁻²⁹ Thus, to extend our

previous work in this area, we measured platelet 5-HT levels in breastfeeding mother-infant pairs before and during maternal treatment with fluoxetine.

METHODS

Subjects

The 11 breastfeeding mother-infant pairs who took part in this study were referred by their primary care provider to the Yale Behavioral Gynecology Program for evaluation and consultation regarding the treatment of postpartum depression and/or the use of antidepressants during lactation. Women were counseled regarding the possible risks and benefits of using fluoxetine and other antidepressants while breastfeeding; nonpharmacologic treatments were also discussed. All of the mothers were cohabiting with partners who were aware of their decision to breastfeed while taking fluoxetine. The study was approved by the Human Investigation Committee of Yale University School of Medicine, and each mother (mean age: 34.5 years; standard deviation [SD]: 5.3) gave written informed consent.

Mothers and infants had blood drawn by venipuncture and heelstick, respectively, for determination of whole-blood 5-HT levels before the mother's initiation of fluoxetine treatment. Mothers then began fluoxetine (initial dose: 20 mg/d) and continued to breastfeed their infants according to their preferred schedule. Postexposure blood sampling occurred 4 to 12 weeks after the initiation of fluoxetine treatment and no sooner than 10 days after a change in fluoxetine dose. All blood samples were obtained between 10 AM and 2 PM, approximately 2 to 4 hours after the last breastfeeding session. Mothers and infant both underwent venipuncture to obtain approximately 5 mL of blood for whole-blood 5-HT and plasma fluoxetine levels. Blood was collected into tubes that contained dipotassium ethylenediaminetetraacetic acid using standard venipuncture techniques. All specimens obtained for whole-blood 5-HT analysis was kept at room temperature, and duplicate or triplicate samples were removed and stored at -70°C ; portions were also sent for automated platelet count (Hematology Laboratory, Yale-New Haven Hospital, New Haven, CT).

Whole-Blood 5-HT Analysis

Whole-blood 5-HT levels were determined in duplicate or triplicate by high-performance liquid chromatography with fluorometric detection as previously described.^{23,30} More than 99% of blood 5-HT is found within the platelet, and whole-blood 5-HT concentrations (ng/mL) can also be expressed on a per-platelet (ng/ 10^9 platelets) basis if a whole-blood platelet count is obtained.

Plasma Drug Analysis

Plasma fluoxetine and norfluoxetine levels were determined by reversed-phase high-performance liquid chromatography with ultraviolet detection (202 nm) as previously described.³¹ Day-to-day ($N = 3$) coefficients of variation for a 50-ng/mL control sample were 2.0% for fluoxetine and 2.6% for norfluoxetine. Drug levels were first determined in mother and infant plasma using standards ranging from 10 to 100 ng/mL. Results <10 ng/mL were considered semiquantitative, and most infant samples had fluoxetine levels less than the estimated detection limit of 1 ng/mL. For determining drug levels more accurately in an infant (9) plasma with an estimated 2.2 ng/mL of fluoxetine (and 2.7 ng/mL norfluoxetine), a second portion of the plasma sample was reanalyzed using standards ranging from 2 to 8 ng/mL. The standard curve was linear over this range, and, with the use of a control plasma spiked with 2 ng/mL of drug, fluoxetine and norfluoxetine were determined with within-day coefficients of variation ($N = 3$) of 14% and 4%, respectively. On reanalysis, the levels of fluoxetine and norfluoxetine observed in the infant 9 sample were 2.6 and 2.4 ng/mL, respectively (another reanalyzed infant [6] plasma sample showed <1 ng/mL fluoxetine on both analyses, whereas norfluoxetine levels of 3.6 and 3.0 ng/mL were observed on the first and second analysis, respectively.)

Statistical Analyses

To determine the impact of fluoxetine exposure on 5-HT levels, we conducted paired t tests comparing pre- and postexposure 5-HT levels separately for the mother and infant groups. Pearson correlations were performed to examine the relationship between

change in 5-HT levels over time and maternal drug dose, maternal fluoxetine and norfluoxetine levels, age of infant at the start of the study, fluoxetine and norfluoxetine levels, and breastfeeding status (exclusive or partial breastfeeding).

RESULTS

Exposure data for the 11 mother-infant pairs, including the mother's dose of fluoxetine, the infant's age, and mother and infant plasma drug and serotonin levels, are given in Table 1. Five of 11 mothers were taking fluoxetine 20 mg daily, 4 were taking 30 mg daily, and 2 were taking 40 mg daily. Mean infant age at the start of the study was 16.8 weeks (SD: 8.8). With the exception of 1 infant, all were <6 months old and 4 were <3 months of age when their mothers began treatment. Six infants were breastfed exclusively (1, 2, 3, 4, 7, and 9); the remaining were breastfed between 3 and 8 times daily and were given supplemental feedings or formula 2 to 3 times daily.

Mean maternal plasma concentrations of fluoxetine and norfluoxetine expressed in ng/mL were 125 (SD: 62.5) and 142 (SD: 56.2), respectively (Table 1). Ten infants had plasma fluoxetine levels of <1 ng/mL; 1 infant (9) had a fluoxetine level of 2.6 ng/mL. The mean infant plasma concentration of norfluoxetine was 3.2 (SD: 2.2), with a range from 1.4 to 8.7 ng/mL. There was no correlation between maternal plasma fluoxetine and norfluoxetine levels (Pearson $r = 0.24$, $N = 11$, $P = .47$). Mother and infant norfluoxetine levels were also not correlated (Pearson $r = -0.25$, $N = 11$, $P = .46$).

Mean maternal pre- and postexposure 5-HT levels were 157 ng/mL (SD: 71.4) and 23 ng/mL (SD: 12.5), respectively (Table 1, Fig 1). Paired t test revealed a highly significant decline in maternal whole-blood 5-HT levels with fluoxetine treatment ($t = 6.9$, $df = 10$, $P < .0001$). Individual postexposure maternal 5-HT values ranged from 9% to 28% of baseline (mean change to 14.5% [SD: 7%] of baseline). In contrast, the mean infant pre- and postexposure 5-HT concentrations of 217 ng/mL (SD: 66.5) and 230 ng/mL (SD: 83.5), respectively, were similar (paired $t = -0.24$, $df = 10$, $P = .82$). The mean infant individual percentage change from baseline was 3.6% (99% confidence interval: -26% to 33%). Infant age at the start of the study, maternal fluoxetine dose, maternal fluoxetine and norfluoxetine plasma levels, and exclusivity of breastfeeding did not correlate with change in infant 5-HT levels. Similar results for group comparisons and correlative analyses were obtained when 5-HT levels were expressed as ng/ 10^9 platelets.

One infant (9) was observed to have a substantial decrease in whole-blood 5-HT, decreasing from 133 ng/mL to 54 ng/mL, a 60% change from baseline (Fig 1). In samples obtained 4 months later (after the mother's switching to sertraline and then back again to fluoxetine, reducing the extent of breastfeeding and adding supplemental cereal feedings), plasma drug levels were undetectable (<1 ng/mL), and the platelet serotonin levels were no longer reduced (149 ng/mL, representing a 12% increase from baseline).

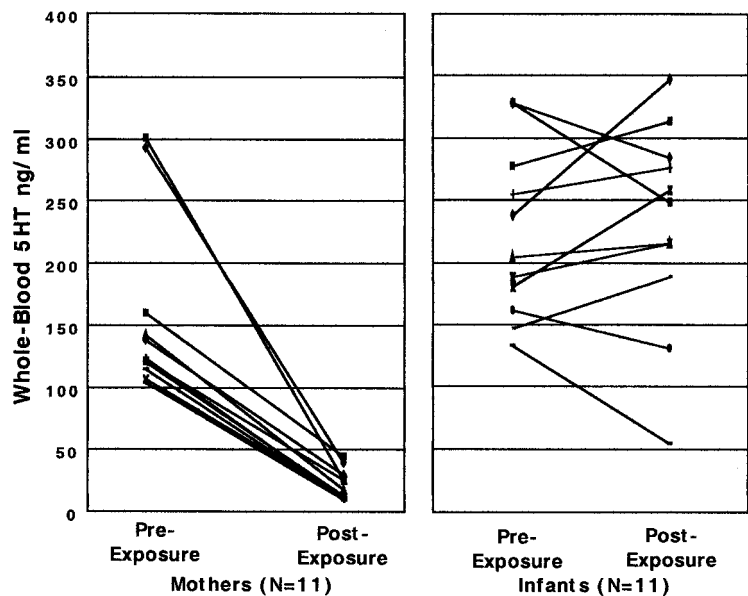
TABLE 1. Mother's Fluoxetine Dose, Plasma Drug Levels, and Whole-Blood Serotonin (5-HT) Levels in 11 Mother-Infant Pairs

Pair	Maternal Dose (mg/d)	Infant Age (Weeks)	Maternal Drug Concentration (ng/mL)		Maternal 5-HT (ng/mL)		Infant Drug Concentration (ng/mL)		Infant Whole-Blood 5-HT Levels (ng/mL)		
			Fluoxetine	Norfluoxetine	Preexposure	Postexposure	Preexposure	Postexposure	Preexposure	Postexposure	Preexposure
1	20	9	66	96	138	30	<1.0	3.2	328	284	87%
2	20	14	28	67	160	44	<1.0	2.4	328	248	76%
3	20	1	103	105	142	18	<1.0	5.6	204	215	105%
4	20	8	114	113	106	12	<1.0	8.7	180	258	141%
5	20	25	68	214	121	26	<1.0	1.4	188	215	114%
6	30	22	143	214	120	13	<1.0	3.6	161	131	81%
7	30	20	138	215	123	11	<1.0	2.6	255	276	108%
8	30	26	151	156	104	10	<1.0	1.6	146	188	129%
9	30	18	227	86	114	11	2.6	2.7	133	54	40%
10	40	27	105	109	293	39	<1.0	1.5	238	347	146%
11	40	21	227	181	301	26	<1.0	2.4	277	313	113%
Mean	27.3	16.8	124.5	141.5	156.6*	22.9*		3.2	217.1†	229.9†	103.6%
SD	7.9	8.8	62.5	56.2	71.4	12.5		2.2	66.5	83.5	31.1

* Paired t tests demonstrate a significant decline in whole-blood 5-HT with fluoxetine exposure ($t = 6.9$, $df = 10$, $P < .0001$).

† Paired t test revealed no significant change in whole-blood 5-HT in the infant group ($t = 0.24$, $df = 10$, $P = .82$).

Fig 1. Mother and infant serotonin (5-HT) levels before and after exposure to fluoxetine. Mothers were taking fluoxetine 20 to 40 mg/d. Infants who were exposed to fluoxetine through breast milk did not experience a significant blockade of 5-HT transport.



DISCUSSION

The marked declines (to 9%–28% of baseline) in platelet 5-HT concentrations seen in mothers who were treated with the SSRI fluoxetine were similar to those observed in our study^{22,23} and other previous studies.^{21,32,33} In contrast, all but 1 infant experienced little or no decline in whole-blood (platelet) 5-HT concentrations after exposure to fluoxetine through breast milk.

The apparent absence of platelet 5-HT transporter blockade in most nursing infants of mothers who were being treated with fluoxetine is consistent with our previous findings with breastfeeding infants who were exposed to sertraline. However, the substantial drop in platelet 5-HT seen in infant 9 stands apart, and we believe that this observation deserves mention, especially considering the rebound in platelet serotonin levels after the reduction in breastfeeding. Although the coupling of this drop in platelet 5-HT with measurable plasma fluoxetine in a single infant raises concerns, the findings may be coincidental, and it is important to note that this infant experienced no discernible adverse effects. Possible reasons for the observable plasma fluoxetine level in infant 9 include the high maternal drug level and the infant's being breastfed exclusively; no viral infection was apparent at the time of blood draw. The explanations offered for the higher plasma drug level in infant 9 are conjectural, and we want to be careful not to overemphasize the significance of the observations in this 1 infant.

This infant as well as infants 3, 4, 5, 6, 7, and 11 participated in a parallel study of the impact of in utero and/or breastfeeding exposure to SSRIs on infant development. Bayley Scale scores conducted in these infants (age range: 24–56 weeks) revealed that all but 1 were within 1 SD of the mean on mental and motor developmental indices. Infant 7 scored an 82 (mild delay) on the motor index and a 92 (normal range) on the mental index at 24 weeks of age primarily because he was not yet sitting up on his own.

CONCLUSIONS

These data suggest that most young and exclusively breastfed infants may continue to breastfeed without experiencing meaningful changes in platelet 5-HT transport while their mothers are treated with fluoxetine at 20 to 40 mg daily. Although it is premature to suggest treatment guidelines based on the limited available data, our own advice to nursing women will weigh a range of factors, including severity of postpartum depression, a demonstrated preferential response to a specific SSRI, and the mother's commitment to breastfeeding. Additional research is needed to establish more definitively the frequency of physiologically meaningful infant SSRI exposure during breastfeeding and to determine the behavioral consequences of such exposure.

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