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Methadone Maintenance and Breastfeeding in the Neonatal Period

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ABSTRACT

OBJECTIVE. In a sample of methadone-maintained breastfeeding women and a matched group of formula-feeding women, this study evaluated concentrations of methadone in breast milk among breastfeeding women and concentrations of methadone in maternal and infant plasma in both groups.

METHODS. Eight methadone-maintained (dose: 50–105 mg/day), lactating women provided blood and breast milk specimens on days 1, 2, 3, 4, 14, and 30 after delivery, at the times of trough and peak maternal methadone levels. Paired specimens of foremilk and hindmilk were obtained at each sampling time. Eight matched formula-feeding subjects provided blood samples on the same days. Infant blood samples for both groups were obtained on day 14. Urine toxicological screening between 36 weeks of gestation and 30 days after the birth confirmed that subjects were not using illicit substances in the perinatal period.

RESULTS. Concentrations of methadone in breast milk were low (range: 21.0–462.0 ng/mL) and not related to maternal dose. There was a significant increase in methadone concentrations in breast milk over time for all 4 sampling times. Concentrations of methadone in maternal plasma were not different between groups and were unrelated to maternal dose. Concentrations of methadone in infant plasma were low (range: 2.2–8.1 ng/mL) in all samples. Infants in both groups underwent neurobehavioral assessments on days 3, 14, and 30; there were no significant effects of breastfeeding on neurobehavioral outcomes. Fewer infants in the breastfed group required pharmacotherapy for neonatal abstinence syndrome, but this was not a statistically significant finding.

CONCLUSION. Results contribute to the recommendation of breastfeeding for methadone-maintained women.

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Key Words

lactation, breast milk, methadone

Abbreviations

NAS—neonatal abstinence syndrome
LOQ—limit of quantification

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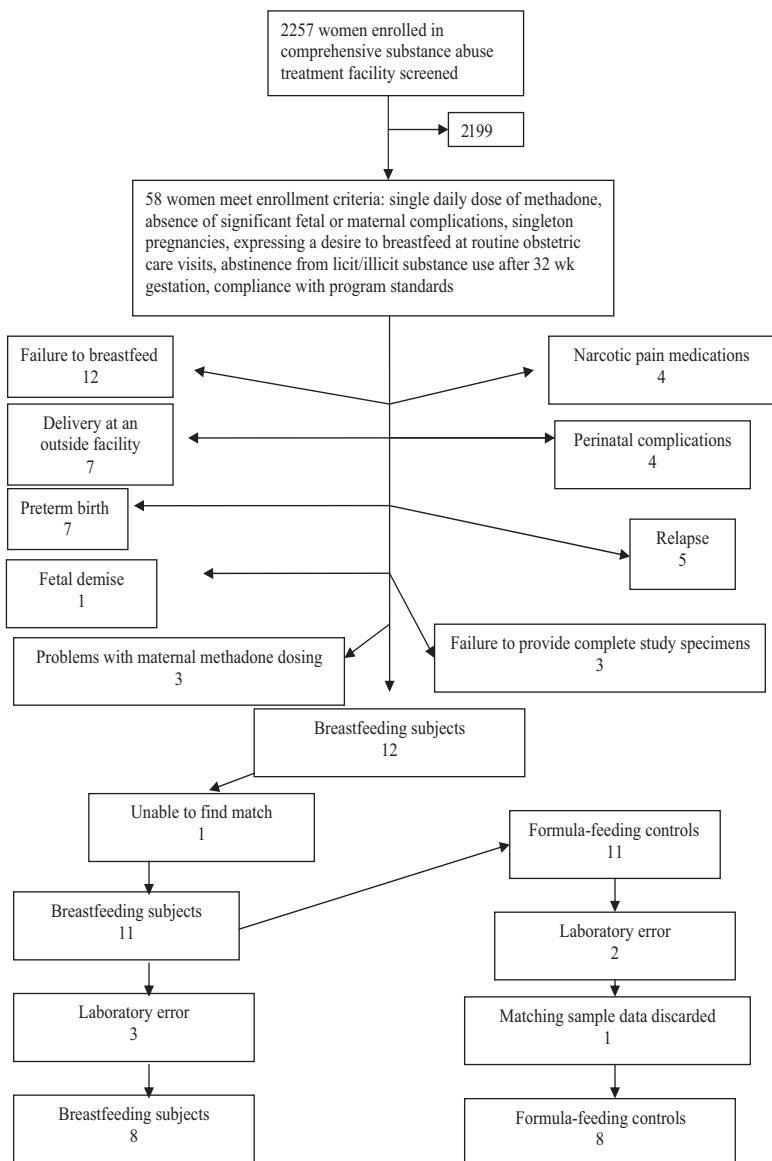
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PROBLEMS RELATED TO opiate dependency during the perinatal period have well-known consequences for the mother and child.^{1,2} Methadone maintenance therapy, the only pharmaceutical treatment recommended for this population in the United States, is currently the standard of care^{3,4} and offers major benefits as well as risks. For opiate-dependent pregnant women, methadone decreases illicit opiate use^{5–7} and the likelihood of fetal death and HIV infection.⁸ Infants of methadone-maintained mothers are less often premature or of low birth weight and have less acute fetal distress than do infants exposed to heroin.^{3,9–12} Maternal methadone pharmacotherapy can predispose infants to neonatal abstinence syndrome (NAS) after birth; >60% of methadone-exposed infants display NAS,¹³ and this syndrome may be more severe in methadone-exposed, compared with heroin-exposed, infants.^{8,14} Methadone exposure may create a biological vulnerability in exposed children, making them more susceptible to impoverished environments.¹⁵ Improving the quality of early caregiving experiences is likely to be particularly effective in reducing the risk for developmental problems in this group of infants.¹⁶

Breast milk is optimal for infant nourishment,^{17–20} and it confers major well-known advantages to the infant/mother dyad. In particular, the practice of breastfeeding promotes positive early infant attachment experiences⁸ and decreases maternal stress responses.²¹ Previous research found that the intake of breast milk was associated with

FIGURE 1
Flow of study participants.



reduced NAS severity in infants born to drug-dependent mothers.²² The population of methadone-exposed infants and their mothers stand to receive particular benefits from this practice. In general, however, methadone-maintained women have low rates of breastfeeding, for a variety of reasons.²³ One barrier to lactation in this group is the lack of clear consistent guidelines regarding methadone maintenance and breastfeeding. Clinical investigations regarding lactation among methadone-maintained women are difficult to perform, and today there exists a relative dearth of clinical reports in this area. Despite widely variable sampling times and study parameters, research to date has shown that concentrations of methadone in breast milk are low, ranging from 50 to 270 ng/mL, that possible methadone intake by the infant ranges from 0.01 to 0.09 mg/day, and that these amounts are unlikely to have any effect on the breastfed infant.²⁴⁻³⁰ Previous research by our group offers consistent results³¹; however, the effects of even small amounts of methadone transmitted via breast milk

on developing infants are currently unknown. The purpose of this study was to delineate the concentrations of methadone found in the breast milk and plasma of lactating, methadone-maintained women, infant outcomes among matched samples of breastfed and formula-fed infants of methadone-maintained mothers, and plasma methadone concentrations among the infants of women in the 2 groups.

METHODS

Subjects and Study Design

Figure 1 describes the flow of study subjects. A total of 2257 women enrolled in a comprehensive substance abuse treatment program for pregnant and postpartum drug-dependent women, which was described elsewhere,³² were screened for project enrollment between January 2001 and September 2005. Criteria for enrollment consisted of meeting *Diagnostic and Statistical Man-*

ual of Mental Disorders, Revised Fourth Edition, criteria for opiate dependence and federal methadone maintenance guidelines and expressing a desire to breastfeed exclusively at obstetric care visits. To minimize confounding, inclusion was limited to women taking a single daily dose of methadone, with uncomplicated singleton pregnancies (ie, fetal measurements appropriate for gestational age and absence of fetal malformations or maternal complications such as gestational diabetes mellitus). Subjects were selected on the basis of abstinence from licit/illicit substance use for 1 month before study recruitment, recommendation from their counselors regarding compliance with program standards, and staff confidence in their ability to sustain continued abstinence during the perinatal period. Fifty-eight women met the criteria. Subjects were enrolled at 36 weeks of gestation, on the basis of prenatal ultrasonography performed at ~20 weeks of gestation, according to program standards. Women were placed on a morning (10:00–11:00 AM) methadone dosing schedule at the time of enrollment at 36 weeks of gestation, until 30 days after the birth, and were monitored for licit and illicit drug use according to program standards, which included random weekly urinalyses for opiates, cocaine, methadone, cannabinoids, phencyclidine, amphetamines, and benzodiazepines. Women who appeared intoxicated were counted as having clinical positive toxicological findings (ie, were counted as having positive results with or without positive urine test results). Women and their infants provided urine samples for toxicological testing at birth. All subjects provided additional urine samples, which were screened for cocaine and opiates, on Mondays, Wednesdays, and Fridays for 30 days after the birth. Any woman considered to have clinical positive toxicological findings or demonstrated to have positive urine test results at any point during the study (from 36 weeks of gestation to 30 days after the birth) was excluded from further participation. Subjects and control subjects did not differ, with respect to demographic features (parity and age) and substance use history, from program participant means for women meeting criteria for methadone maintenance. There was a preponderance of white women in the overall sample, which likely reflects cultural practices; black women have lower rates of breastfeeding in general.^{33,34} Forty-six women were excluded from further study participation, because of failure to breastfeed (12 women), preterm (estimated gestational age of <37 weeks) birth (7 women), delivery at another facility (7 women), relapse in the perinatal period (5 women), delivery through cesarean section and/or requirement for narcotic pain medications (4 women), perinatal complications (4 women), problems with morning methadone dosing (3 women), failure to provide complete study specimens (3 women), or fetal demise (1 woman). Twelve women over the 5-year period met study requirements; 1 subject was receiving a low dose of methadone, for which a matching control subject could not be found. Eleven women, matched with respect to race, parity (primiparous versus multiparous), age within 5 years, and methadone dose within 10 mg and desiring to bottle-feed their infants exclu-

sively, were enrolled as control subjects. Samples from 5 women (3 breastfeeding subjects and 2 control subjects) were unavailable for analysis because of laboratory error, and data from 1 control subject matched to a breastfeeding subject with missing data were discarded, leaving a sample of 8 breastfeeding subjects and 8 formula-feeding control subjects. Day 1 to 4 breast milk and plasma data for the 8 breastfeeding subjects were reported previously within a larger sample.³¹ The research was approved by the governing institutional review board, and written informed consent was obtained from all participants.

Breastfeeding women submitted 4 specimens (paired prefeeding and postfeeding specimens) of breast milk daily on days 1, 2, 3, 4, 14, and 30 after the birth. Days of life were determined as the 24-hour daytime periods nearest the delivery time, keeping the determined day of life as close as possible to the infant's actual day of life. Additional manipulation of the designated days of life was not possible because of methadone dosing restrictions; women continued to be medicated at 10:00 to 11:00 AM throughout the study period. Samples were obtained at the times of trough (just before the single daily oral dose) and peak (3 hours after the dose) maternal methadone levels. Peak plasma methadone levels in individuals treated chronically with orally administered methadone occur 2 to 4 hours after a daily oral dose.³⁵ Paired samples consisted of breast milk expressed before breastfeeding (foremilk) and breast milk expressed after the infant had ceased breastfeeding (hindmilk) from the same breast, which was identified at the time of sampling as the breast opposite that used at the last feeding. For all women, plasma samples were obtained at times of trough and peak maternal methadone levels. Previous research showed that postfeeding methadone breast milk concentrations increased ~33% from prefeeding concentrations; this was attributed to the increase in milk lipid content that occurs during feeding and the lipophilic nature of methadone.²⁹ Methadone dosing was either observed directly or confirmed by study personnel.

Infant plasma specimens were collected on day 14 after birth, concurrent with a heel stick for phenylketonuria screening. Infants were hospitalized for a minimum of 4 days after birth, which is the standard of care in the hospital of delivery, for observation for NAS. Infants underwent NAS scoring every 3 to 4 hours, with feedings, during their entire hospitalization. NAS scoring was based on a protocol modified from that described by Finnegan et al,³⁶ consisting of 19 weighted items with a maximal score of 41. Pharmacologic treatment was initiated with 2 consecutively obtained scores of >8. Treatment at the hospital of record involves a symptom-based algorithm that provides opiate replacement medication based on the severity of NAS symptoms displayed by the infant. Increasing doses are provided for escalating NAS scores until the infant achieves a plateau of NAS scores of <9. The infant is treated with this dose of medication for 48 hours, for stabilization, and then weaned gradually from the medication. Standardized protocols are used for escalation, weaning, and reescalation of phar-

macotherapy. NAS scores were obtained by clinical nursing staff members experienced in the treatment of drug-exposed neonates and unaware of the infant's enrollment in the study. No dyads had positive maternal or infant urine toxicological screening results at delivery. All infants underwent NICU Neonatal Neurobehavioral Scale evaluations on days 3, 14, and 30 of life. The NICU Neonatal Neurobehavioral Scale is a neurobehavioral assessment battery for drug-exposed and other high-risk infants.³⁷ The NICU Neonatal Neurobehavioral Scale assessments were performed by a study investigator (Dr Velez) trained and certified in its use and blinded with respect to group status.

Laboratory Analyses

Breast milk specimens containing methadone and metabolites were obtained from methadone-maintained breastfeeding mothers and stored in polypropylene vials at -20°C until the time of analysis. Preparation of breast milk specimens included methanolic protein precipitation, followed by solid-phase extraction.³⁸ Extracts were analyzed with a validated liquid chromatography/atmospheric pressure chemical ionization-tandem mass spectrometry method. Briefly, 0.5-mL aliquots of breast milk were mixed with internal standard and chilled methanol to precipitate proteins, followed by centrifugation. The organic supernatants were partially dried under nitrogen and subjected to solid-phase extraction. Eluates were evaporated to dryness under nitrogen, reconstituted in mobile phase, and analyzed for methadone with a LCQ Deca XP ion trap mass spectrometer (ThermoFinnigan, San Jose, CA). Identification and quantification of methadone were based on selected-reaction monitoring. The limit of quantification (LOQ) was 10 ng/mL, with a linear dynamic range of 10 to 500 ng/mL. Extraction efficiency was >97%, with interday and intraday imprecision of <20%.

Maternal blood samples were collected in lithium heparin-containing tubes, mixed well and centrifuged before separation of plasma, and frozen at -20°C in polypropylene tubes until analysis. Plasma specimens were analyzed through gas chromatography/mass spectrometry (Agilent, Dover, DE), after solid-phase extraction, by using minor chromatographic and extraction modifications of the method reported by Galloway³⁹ and Alburges.⁴⁰ The LOQ for methadone was 5.0 ng/mL, and the range of linearity was 5 to 2000 ng/mL. Intraday and interday imprecision was <20%.

Infant blood samples (200–400 µL) were collected in lithium heparin-containing vacuum tubes, mixed, and centrifuged at 500g to separate plasma. Infant plasma samples were stored at -20°C in polypropylene tubes until the time of analysis. Plasma specimens were of small volume and in some cases dried completely. In such cases, the dried residues were reconstituted in 200 µL of water and vortex-mixed well before specimen preparation. These data represent at most a twofold increase in concentration for the specimens that dried completely, and they present a worst-case scenario for methadone concentrations in infant plasma for both groups. Plasma specimens (200 µL) were diluted with

600 µL of acetonitrile, mixed, and centrifuged at 3130g for 5 minutes, to pellet the precipitated protein. Supernatants were dried completely under nitrogen, reconstituted with 200 µL of water, and analyzed with a validated liquid chromatography/atmospheric pressure chemical ionization-tandem mass spectrometry method.⁴¹ Identification and quantification of methadone were based on selected-reaction monitoring. The LOQ for methadone in infant plasma was 1 ng/mL, with a linear dynamic range of 1 to 500 ng/mL. Extraction efficiency was >87.5%, with interday and intraday imprecision of <20%.

Calculation of Infant Doses

The average infant methadone exposure was calculated from the average of prefeeding and postfeeding breast milk methadone concentrations per day and extrapolated to the total methadone dose ingestible per day by using average breast milk volumes per day of life, obtained from previously published information.⁴²

Statistical Analyses

Basic descriptive statistics (median, range, and interquartile range) were calculated to describe the study sample in terms of maternal demographic characteristics, birth outcomes, concentrations of methadone in breast milk and plasma, and breast milk/plasma methadone concentration ratios. Nonparametric paired comparisons (Wilcoxon signed rank tests) were performed to compare breastfeeding subjects and matched control subjects in terms of perinatal parameters and maternal and infant plasma methadone concentrations; Fisher's exact test was used for comparisons of categorical variables. Nonparametric correlation coefficients (Spearman correlations) were used to assess the strength of association between methadone concentrations in breast milk and plasma and between maternal methadone dose and breast milk/plasma methadone concentration ratio, at times relative to methadone dose (peak and trough, days 1–4, 14, and 30). Repeated-measures linear regression was used to determine whether there were significant changes over time on days 1 through 30 in breast milk methadone concentrations for each sampling time (trough before feeding, trough after feeding, peak before feeding, and peak after feeding) and whether there were effects of breastfeeding (yes or no), time (days 3, 14, and 30), or breastfeeding-time interaction for neurobehavioral outcomes. All analyses were performed by using SAS 9 statistical software (SAS Institute, Cary, NC). Statistical significance was set at $P < .05$ for all analyses.

RESULTS

Subjects

The median age for breastfeeding subjects and control subjects was 29 years; 5 pairs were white and 3 were black. Two pairs in each group were primiparous. Two women in each group received selective serotonin reuptake inhibitors

TABLE 1 Comparison of Perinatal Characteristics of the 2 Study Groups

Perinatal Characteristic	Breastfed Group (n = 8)	Formula-Fed Group (n = 8)	P
Birth weight, median (interquartile range), g	2830.0 (547.5)	2895.0 (562.5)	NS
Birth length, median (interquartile range), cm	49.5 (3.5)	49.5 (3.5)	NS
Head circumference, median (interquartile range), cm	32.8 (1.8)	32.5 (2.0)	NS
Apgar score at 1 min, median (interquartile range)	9.0 (1.0)	9.0 (0.5)	NS
Apgar score at 5 min, median (interquartile range)	9.0 (0.0)	9.0 (0.0)	NS
Day 3 NAS score, median (interquartile range)	4.5 (3.9)	6.8 (1.2)	NS
Highest NAS score, median (interquartile range)	6.5 (4.5)	11.0 (5.0)	NS
Infants requiring NAS pharmacotherapy, n	1	4	NS
Total time of treatment for infants treated for NAS, median (interquartile range), d	6	13.5 (10.5)	NA

NS indicates not significant; NA, not applicable.

(sertraline, 2 women; fluoxetine, 1 woman; paroxetine, 1 woman). Methadone doses among breastfeeding subjects and control subjects varied little in the postpartum period, and median values were as follows: 70 mg (range: 50–105 mg) at delivery, 70 mg (range: 50–105 mg) on day 14, and 70 mg (range: 50–105 mg) on day 30. There were 2 male infants in the breastfeeding group and 3 male infants in the control group. Two infants had minor complications in the postnatal period, which necessitated slightly prolonged hospitalizations. One breastfed infant (subject 7) required phototherapy for 6 days after birth because of physiologic jaundice. A second infant in the breastfed group (subject 13) developed a fever to 101.5°F on day 3 of life. He

received antibiotics and underwent a septic evaluation, which ultimately yielded negative results; antibiotic administration was stopped after 2 days. The patient was afebrile after day 4 of life. Both infants continued to breastfeed well throughout their hospital course and were retained in the final sample. Median birth parameters, Apgar scores, NAS scores, and NAS treatment variables are presented in Table 1. Perinatal parameters did not differ significantly between groups. More infants in the control (formula-fed) group required pharmacologic treatment for NAS (4 infants, compared with 1 breastfed infant), but this association was not statistically significant (Fisher's exact test, $P = .28$).

Maternal Plasma Methadone Concentrations

Plasma methadone concentrations according to group are presented in Table 2. There were no significant group differences for any sampling period. Correlations between maternal methadone dose and plasma methadone concentrations ranged from -0.53 (trough, day 2) to 0.23 (peak, day 4). These correlations were not significantly different from 0 with the exception of trough day 2 ($r = -0.53$; $P = .033$). Plasma methadone concentrations did not differ between women taking and not taking selective serotonin reuptake inhibitors (comparisons performed for both trough and peak plasma methadone levels; data not shown).

Breast Milk Methadone Concentrations

Methadone concentrations in breast milk are presented in Table 3 and Fig 2. With the exclusion of values from samples obtained on day 1 (available only for 2 subjects because of the small amount of colostrum expressible), concentrations of methadone in breast milk increased from prefeeding samples to postfeeding samples by 3.3% to

TABLE 2 Methadone Concentrations in Maternal Plasma According to Group

Sampling Period	Breastfeeding		Control		P
	n	Methadone Concentration, Median (Interquartile Range), ng/mL	n	Methadone Concentration, Median (Interquartile Range), ng/mL	
Day 1					
Trough	8	122.0 (119.0)	8	97.5 (110.5)	NS
Peak	8	228.5 (134.0)	8	271.5 (89.5)	NS
Day 2					
Trough	8	113.0 (115.0)	8	107.5 (123.0)	NS
Peak	6	345.5 (255.0)	7	324.0 (212.0)	NS
Day 3					
Trough	8	147.5 (99.0)	7	124.0 (159.0)	NS
Peak	8	306.5 (174.5)	8	299.5 (176.0)	NS
Day 4					
Trough	8	194.0 (86.5)	6	148.0 (79.0)	NS
Peak	8	386.5 (223.5)	7	359.0 (100.0)	NS
Day 14					
Trough	8	279.0 (206.5)	8	337.5 (300.0)	NS
Peak	8	500.0 (244.5)	8	477.0 (266.5)	NS
Day 30					
Trough	8	320.5 (231.5)	8	254.0 (220.5)	NS
Peak	8	506.0 (368.5)	8	439.0 (277.5)	NS

TABLE 3 Concentrations of Methadone in Breast Milk, Mean Ingestible Infant Doses, and Median Breast Milk/Plasma Methadone Concentration Ratios

Sampling Period	<i>n</i>	Breast Milk Methadone Concentration, ng/mL		Ingestible Infant Dose, Mean, mg/d	Median Breast Milk/Plasma Methadone Concentration Ratio	
		Median (Interquartile Range)	Range			
Day 1				0.004		
Trough	Prefeeding	4	67.0 (77.5)	40.0–179.0	0.92	
	Postfeeding	2	48.5 (23.0)	37.1–60.3	0.34	
	Peak	Prefeeding	2	98.0 (68.0)	63.6–132.2	0.47
	Postfeeding	2	115.0 (10.0)	109.5–120.0	0.46	
Day 2				0.012		
Trough	Prefeeding	6	35.0 (27.0)	21.0–121.0	0.38	
	Postfeeding	5	41.0 (16.0)	20.6–175.4	0.47	
	Peak	Prefeeding	5	64.0 (5.0)	27.4–135.7	0.22
	Postfeeding	5	103.0 (31.0)	31.6–112.9	0.23	
Day 3				0.037		
Trough	Prefeeding	8	54.0 (32.0)	38.1–136.3	0.43	
	Postfeeding	8	62.5 (48.5)	42.1–169.5	0.48	
	Peak	Prefeeding	8	106.0 (81.0)	45.1–193.3	0.23
	Postfeeding	6	126.5 (53.0)	52.3–182.8	0.35	
Day 4				0.075		
Trough	Prefeeding	8	74.0 (27.0)	54.7–158.2	0.41	
	Postfeeding	8	70.5 (32.5)	49.4–210.0	0.35	
	Peak	Prefeeding	8	161.0 (70.0)	80.0–281.4	0.33
	Postfeeding	8	199.0 (99.5)	109.2–239.5	0.48	
Day 14				0.125		
Trough	Prefeeding	8	121.0 (136.0)	60.5–257.9	0.42	
	Postfeeding	8	119.0 (182.0)	66.7–335.6	0.56	
	Peak	Prefeeding	8	201.0 (75.5)	105.2–367.1	0.53
	Postfeeding	8	231.0 (114.5)	61.9–462.0	0.54	
Day 30				0.152		
Trough	Prefeeding	8	92.0 (84.5)	32.8–222.7	0.38	
	Postfeeding	8	125.5 (217.0)	67.9–449.5	0.44	
	Peak	Prefeeding	8	194.0 (81.0)	83.4–407.1	0.49
	Postfeeding	8	220.5 (158.5)	159.2–359.5	0.55	

64.5% at trough sampling times and 6.6% to 21.5% at peak sampling times. Correlations between maternal methadone dose and breast milk methadone concentrations ranged from -0.61 (trough after feeding, day 4) to 0.57 (peak after feeding, day 4); none attained statistical significance. There was a significant increase in methadone concentrations in breast milk over time for all 4 sampling times, that is, trough before feeding ($F_{1,33} = 7.16$; $P = .012$), trough after feeding ($F_{1,30} = 11.36$; $P = .0021$), peak before feeding ($F_{1,30} = 14.78$; $P = .0007$), and peak after feeding ($F_{1,28} = 8.30$; $P = .0075$). The calculated average

amount of methadone ingestible by the infant was small across all sampling periods and was <0.2 mg/day at day 30.

Breast Milk/Plasma Methadone Concentration Ratios

Median breast milk/plasma ratios are presented in Table 3. Ratios ranged from 0.29 (peak before and after feeding, day 2) to 0.88 (trough before feeding, day 1). The median trough prefeeding breast milk/plasma methadone concentration ratio was 0.42, trough postfeeding breast milk/plasma methadone concentration ratio 0.47, peak prefeeding breast milk/plasma methadone concen-

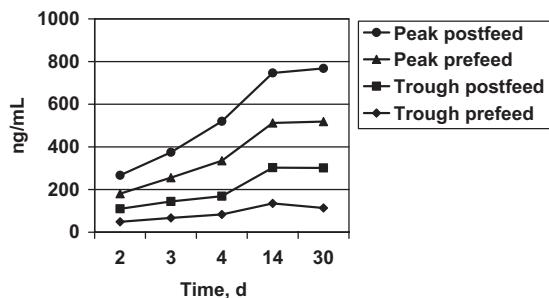


FIGURE 2

Mean breast milk methadone concentrations according to prefeed versus postfeed and trough versus peak maternal methadone level and day.

tration ratio 0.36, and peak postfeeding breast milk/plasma methadone concentration ratio 0.49.

Infant Plasma Methadone Concentrations

Infant plasma methadone concentrations according to subject are presented in Table 4. The concentrations of methadone in infant plasma samples ranged from 2.2 to 8.1 ng/mL. There was no significant correlation between maternal methadone doses and infant plasma methadone concentrations ($r = 0.25; P = .37$). There were no significant associations between infant plasma methadone concentrations and breastfeeding or receiving NAS pharmacotherapy.

Infant Neurobehavior

Repeated-measures regression models were fit for 9 neurobehavioral outcomes, namely, attention, quality of movement, regulation, nonoptimal reflexes, stress/abstinence, arousal, excitability and lethargy; data for the other 5 outcomes (habituation, handling, asymmetric reflexes, hypertonicity, and hypotonicity) were too

sparse for this type of analysis. There were no significant effects of breastfeeding and no breastfeeding-time interactions for any neurobehavioral outcomes.

DISCUSSION

Methadone-exposed neonates are at high risk for morbidity, poor early caregiving experiences, and neurobehavioral difficulties and stand to obtain particular benefits from the multiple well-known advantages of breastfeeding. In general, however, methadone-maintained women have low rates of lactation and frequently are discouraged from breastfeeding by the providers caring for their at-risk infants. Reasons for this include difficulties presented by the mothers and infants themselves, prejudices evidenced by treatment providers, a general paucity of research in this area, unclear guidelines regarding lactation among methadone-maintained women, an overall lack of knowledge regarding the amounts of methadone found in human milk, and the unknown effects on child development of small amounts of methadone delivered via breast milk over time.

This research reveals that concentrations of methadone in human milk in the first month of life are low and the amount of methadone ingestible by the infant is small (<0.2 mg/day by the end of the first month of life). However, the concentrations of methadone in human milk increase over time, particularly during the first 4 days after delivery. The concentrations of methadone in breast milk were unrelated to maternal dose.

Maternal plasma methadone concentrations were not different between the breastfeeding and formula feeding groups and also were unrelated to maternal methadone dose. Psychotropic medications have been found to increase plasma methadone concentrations in nonpregnant adults.^{43,44} In this sample, there were no associa-

TABLE 4 Maternal Methadone Doses and Concentrations of Methadone in Maternal Plasma, Breast Milk, and Infant Plasma on Day 14 According to Subject and Group

Patient No.	Group	Maternal Methadone Dose, mg	Methadone Concentration, ng/mL				NAS Treatment
			Maternal Plasma, Trough/Peak	Breast Milk Before Feeding, Trough/Peak	Breast Milk After Feeding, Trough/Peak	Infant Plasma	
1	Breastfed	50	351/653	61.6/115.0	105.2/61.9	3.0 ^a	No
2	Formula-fed	50	356/510			2.3 ^a	No
3	Breastfed	80	139/382	60.5/122.6	208.9/226.2	2.5 ^a	No
4	Formula-fed	75	567/939			2.2	No
5	Breastfed	105	270/709	62.9/66.7	156.2/184.6	2.4	No
6	Formula-fed	100	528/404			3.2	No
7	Breastfed	80	207/433	208.7/242.5	226.8/235.6	4.5 ^a	No
8	Formula-fed	80	319/572			2.4 ^a	Yes
9	Breastfed	65	487/643	188.0/287.9	367.1/462.0	2.8 ^a	No
10	Formula-fed	75	185/444			2.7	Yes
11	Breastfed	60	147/358	122.4/78.5	192.6/146.6	2.6	No
12	Formula-fed	65	484/774			2.4	No
13	Breastfed	70	288/425	120.3/87.2	251.5/257.2	8.1	No
14	Formula-fed	70	134/321			2.4	Yes
15	Breastfed	60	416/567	257.9/335.6	171.3/303.8	2.4 ^a	Yes
16	Formula-fed	65	227/409			2.2	Yes

NAS treatment indicates requirement for pharmacologic treatment of NAS for the infant after birth (yes or no).

^aReconstituted sample.

tions between selective serotonin reuptake inhibitor exposure and maternal plasma methadone concentrations or methadone dose.

Infant plasma methadone concentrations measured on day 14 of life were low (uniformly detected among all samples) and were unrelated to maternal methadone dose, maternal plasma methadone concentrations, and breastfeeding. Furthermore, infant plasma methadone concentrations were not related to the infant's need for pharmacotherapy for NAS or NAS scores. Previous research found that breastfeeding does not alter serum methadone levels in infants up to 96 hours of age, with no correlation between maternal serum methadone concentrations in the last trimester and methadone concentrations in the neonates.⁴⁵ There were no differences in infant neurobehavior on days 3, 14, and 30 of life according to group assignment or time. It is likely that the benefits of breastfeeding outweigh any risk of the small concentrations of methadone found in breast milk; however, more research is required to determine the effects of small amounts of methadone on developing children.

Limitations of this research principally include small group sizes, a feature common to research regarding breastfeeding and methadone maintenance. Another limitation involves a high level of bias in measurements of a few of the infant plasma specimens that dried during frozen storage and were diluted with water before specimen preparation. In the cases in which reconstitution with water was necessary, the plasma methadone concentration values may be overestimated. We are aware of only 2 other reports of methadone concentrations in neonatal plasma. In one, only 1 of 8 breastfed infants' plasma concentrations were greater than the method LOQ of 5 ng/mL, measured with high performance liquid chromatography.²⁹ Those data are consistent with the concentrations found in this study by using liquid chromatography/tandem mass spectrometry, with a LOQ of 1 ng/mL. The other study measured infant serum methadone concentrations through radioimmunoassay for 20 infants within 96 hours after birth.⁴⁵ Much higher concentrations were found immediately after birth, but some cross-reactivity with methadone metabolites might have been present. Therefore, although some of our results might be higher than actual infant methadone plasma concentrations, the data represent a contribution to our understanding of the transfer of methadone to infants via breast milk. Future research should evaluate breast milk, maternal and infant plasma methadone concentrations, and developmental outcomes among methadone-maintained women and their infants who are breastfed for longer periods of time. In general, these results support the recommendation for breastfeeding among methadone-maintained women if it is appropriate and desired.

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EUROPE'S DRUG INSURERS TRY PAY-FOR-PERFORMANCE

"To overcome European state-run health-care systems' increasing stinginess about paying for new drugs, some pharmaceutical companies are taking a novel approach: pay for performance. Johnson & Johnson has promised to reimburse Britain's National Health Service when patients don't respond to the US company's blood-cancer drug Velcade, in a deal expected to start later this month. In France, J&J has made another agreement on its schizophrenia treatment, Risperdal Consta, offering to pay back the French health-care service some of the money it spends on the drug if tests don't show the injectable medication helps patients stay on regular doses. And France's health-care service says it has discussed pay-for-performance contracts with GlaxoSmithKline PLC, but won't reveal details. A Glaxo spokeswoman says the company has talked with European governments about 'pricing-for-value' deals, but declined to provide specifics. Drug companies are offering these deals instead of simply lowering prices in part because they are fearful of setting precedents that would cause insurance payers world-wide to demand price cuts."

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