Mother-Infant Antidepressant Concentrations, Maternal Depression, and Perinatal Events

Dorothy Sit, MD; James M. Perel, PhD; Stephen R. Wisniewski, PhD; Joseph C. Helsel, BS; James F. Luther, MA; and Katherine L. Wisner, MD, MS

Objective: The authors explored the relationship of cord-maternal antidepressant concentration ratios and maternal depression with perinatal events and preterm birth.

Method: The investigators examined 21 mother-infant pairs that had antidepressant exposure during pregnancy. The antidepressants included serotonin reuptake inhibitors (SRIs) and nortriptyline (a norepinephrine inhibitor and mild SRI). The mothers were evaluated with the Structured Clinical Interview for *DSM-IV*. Depression ratings were repeated at 20, 30, and 36 weeks' pregnancy. At delivery, investigators assessed cord and maternal antidepressant concentrations, neonatal outcomes on the Peripartum Events Scale (PES), and gestational weeks at birth. The investigators performed this study at the Women's Behavioral HealthCARE Program, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pennsylvania, from April 2003 until September 2006.

Results: Mean ± SD cord-to-maternal concentration ratios were 0.52 ± 0.35 (range, 0.00–1.64) for the parent drug and 0.54 ± 0.17 (range, 0.28–0.79) for the metabolite. Nine of 21 mothers (43%) had a major depressive episode. From examining the maximum depression ratings, the mean ± SD Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms Version score was 16.0 ± 7.6. One third (7/21) of infants had at least 1 perinatal event (PES ≥ 1). The frequency of deliveries complicated by any perinatal event was similar in depressed and nondepressed mothers. There was no significant association between perinatal events and cord-to-maternal antidepressant concentration ratios or maternal depression levels. Exposure to short half-life antidepressants compared to fluoxetine resulted in more perinatal events (7/16 = 44% vs 0/5 = 0%; $P = .06$). Fourteen percent (3/21) of infants were preterm. Preterm birth was not associated with cord-to-maternal metabolite concentration ratios, depression levels, or exposure to fluoxetine.

Conclusions: Antidepressant-exposed infants experienced a limited number of transient perinatal events. No association between cord-maternal concentration ratios or maternal depression and perinatal events could be identified. Contrary to other reports, we detected no increased risk for perinatal events with fluoxetine therapy compared to the short half-life antidepressants.

Trial Registration: clinicaltrials.gov Identifier: NCT00279370

J Clin Psychiatry 2011;72(7):994–1001

Submitted: *August 3, 2010; accepted October 26, 2010 (doi:10.4088/JCP.10m06461).*

Corresponding author: *Dorothy Sit, MD, Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh, 3811 O'Hara St, Oxford 410, Pittsburgh, PA 15213 (sitdk@upmc.edu).*

In the United States, 14.5% of women develop a new episode of depression during pregnancy.[1] An estimated 90,000 pregnant women (2.8%) each year are prescribed serotonin reuptake inhibitors (SRIs).[2] With final trimester exposure to an SRI, infants have a 3-fold increased risk for neonatal behavioral syndrome compared to infants exposed in early pregnancy only or with no antidepressant exposure.[3] Respiratory distress, feeding problems, jitteriness, altered muscle tone, agitation, irritability, and increased crying are typical symptoms of neonatal behavioral syndrome or poor neonatal adaptation.[3–15] The symptoms of poor adaptation remit within 2 weeks.[10] Rarely, infants (1/313 quantifiable cases) require intensive care for more difficult adaptation, such as dehydration, temperature dysregulation, or seizures.[3]

The pharmacologic characteristics of individual antidepressants may impact risk for neonatal syndrome.[3] Several reports of neonatal syndrome have involved paroxetine.[6,9,16–20] Among paroxetine-exposed neonates, there are reports of reversible cardiac conduction abnormalities[19] and the need for enhanced supportive care and prolonged hospitalization.[20] Paroxetine is the most potent inhibitor of serotonin reuptake,[21] with a short half-life and strong affinity for muscarinic cholinergic receptors. The high rate of clinical signs in these newborns may be related to increased turnover of serotonin or lingering SRI effects in some patients[10] versus serotonin withdrawal and cholinergic overdrive in others.[3,18]

Fluoxetine, with a long half-life and active parent compound and metabolite, is another agent that is associated with neonatal syndrome. Elevated infant fluoxetine levels at birth could result in serotonergic toxicity and may explain the high rates of neonatal syndrome in 31% with third-trimester exposure compared to 9% with early gestational exposure.[7,9] Persistent pulmonary hypertension of the newborn (PPHN) is a rare disorder in 1 to 2 per 1,000 newborns.[22] Late pregnancy treatment with fluoxetine and other SRIs has been associated with an increased risk for PPHN from 2.91 (95% CI, 0.94–6.78)[23] to 5.7 (95% CI, 2.5–13.1).[22] Others did not detect risk for PPHN with maternal antidepressant therapy.[24–26]

Maternal depression also is associated with adverse obstetric outcomes. Examples include preterm birth,[27–29] low birth weight,[30] and stillbirth or neonatal death (relative risk = 2.4 and 2.2, respectively; 95% CI, 1.1–5.1 and 1.4–3.3, respectively).[31] Precursors or sequelae of perinatal depression (past depression, discontinued treatment, limited support, low educational level, nutritional inadequacies, poor maternal health practices)[32] and associated stress create an adverse environment for fetal development.[33] A dysregulated stress response may trigger a cascade of abnormal psychological and biological processes. Impaired psychological responses, and/or hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis may adversely influence pregnancy or neonatal outcomes in some patients.

Clinical Points

- Antidepressant-exposed newborns may experience transient perinatal events.
- After birth, newborns of mothers who needed an extended duration of SRI therapy during pregnancy or newborns with exposure to shorter half-life drugs (eg, paroxetine or venlafaxine) require careful clinical monitoring for perinatal events.
- Since unremitting depression can result in increased risk for perinatal events or preterm birth, clinicians are advised to screen for maternal depression symptoms, treatment adherence, and proper dosing to ensure a lasting antidepressant response.

Hendrick et al[16] determined the maternal and umbilical cord blood antidepressant and metabolite concentrations in 38 mother/baby pairs. The mean ratios of cord to maternal serum concentrations ranged from 0.29 to 0.89. The lowest ratios were for the antidepressants sertraline and paroxetine; the highest were for citalopram and fluoxetine. In a separate study of tricyclic agents, the ratios of cord-to-maternal serum concentrations of nortriptyline and clomipramine were 0.68 and 0.60, respectively, for the parent compounds and 1.40 and 0.80, respectively, for the active metabolites.[34] The data suggest that some drugs produce less fetal exposure than others. Also, the duration of antidepressant exposure may be a factor in adverse newborn events.[35] However, limiting exposure by stopping or tapering antidepressant therapy before delivery may be detrimental to the depressed mother and may not improve newborn health.[36]

The authors explored the relationship of cord-maternal antidepressant concentrations and maternal depression with perinatal events and preterm birth. We hypothesized that higher ratios of cord-to-maternal concentrations, maternal depression levels, and exposure to fluoxetine (due to its long half-life) would be associated with increased frequency of perinatal events and preterm birth. Since cigarette smoking is common among depressed women, we explored smoking as a potential confounder.

METHOD

The University of Pittsburgh Institutional Review Board approved and annually reviewed the protocol. All subjects provided written informed consent. The study was registered at clinicaltrials.gov (Identifier: NCT00279370). The study was performed at the Women's Behavioral HealthCARE Program, Western Psychiatric Institute and Clinic, the University of Pittsburgh Medical Center, Pennsylvania, from April 2003 until September 2006. Maternal assessments were obtained at 20, 30, and 36 weeks' gestation and at delivery. Obstetric experts (a nursing doctorate and a physician with obstetric expertise) blind to the study hypotheses retrieved the neonatal data from a systematic record review of obstetric, birth, and infant hospital charts. Positive neonatal findings were validated with the second obstetric expert.

Maternal Subjects

The investigators prospectively followed mother-infant pairs enrolled in the parent study.[27] All pregnant women received SRI treatment from community physicians. The subjects were assessed with the Structured Clinical Interview for *DSM-IV* (SCID)[37] to confirm the diagnosis of major depressive disorder. Patients with alcohol or substance abuse or dependence (SCID and/or urine drug screen) or medical conditions that could affect outcomes (such as twin gestation and preexisting type I diabetes) were excluded. Tobacco smokers were enrolled in the study.

Procedure

Psychiatric episodes, antidepressant therapy (agent, dosage, decision to taper dose in late third trimester), smoking and use of concomitant medications were tracked for each gestational week with the Timeline technique.[38] Dose information was corroborated with the treating physician and/or pharmacy records for accuracy. To assess depression severity, the Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms Version (SIGH-ADS)[39] was administered at each assessment. The SIGH-ADS instrument incorporates all versions of the Hamilton Depression Rating Scale,[40] to evaluate the atypical neurovegetative symptoms of depression, and it has high intraclass reliability.

Infants

Newborns with antidepressant exposure may present with clinical signs shortly after birth. There is still no standard instrument to assess neonates with in utero antidepressant exposure.[11,41] For this study, the authors obtained obstetric and newborn hospital records to complete the Peripartum Events Scale (PES).[42] The PES is a validated and reliable 14-item instrument that was developed to quantify events

© Copyright 2011 Physicians Postgraduate Press, Inc.

related to delivery. Items include gestational weeks, birth weight, Apgar scores, neonatal complications (need for pH correction, volume correction, need for transfusion or plasma exchange, hypoglycemia, hypocalcemia, hyperbilirubinemia, treatment for sepsis, meconium aspiration pneumonitis, other, other serious event, special care admission, and any treatment to alleviate distress).

Laboratory Procedure

Umbilical cord and maternal blood samples were obtained at delivery by the obstetric cord blood team. The collected specimens were batched and stored at −80°C in the Clinical Pharmacology Program at Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh Medical Center,[43] in the laboratory of J.M.P. All mothers had been taking stable doses of antidepressants for 4 weeks or more prior to blood sampling. The steady-state drug concentrations represented trough levels, and they were used for comparisons among the subjects.

Plasma samples were analyzed for total drug concentrations in the Clinical Pharmacology Program at WPIC. The measured substances were sertraline, *N*-desmethylsertraline (norsertraline), citalopram, *N*-desmethylcitalopram (norcitalopram), fluoxetine, norfluoxetine, nortriptyline, *E*-10-hydroxynortriptyline (active metabolite), venlafaxine, and *O*-desmethylvenlafaxine. We adapted the pharmacologic analytic methods for citalopram, sertraline, nortriptyline and fluoxetine/norfluoxetine from those described by Rochat and colleagues,[44] Wisner et al[45] and Sit et al.[46,47] An Astec, lnc (Whippany, New Jersey) Cyclobond I 2000 AC, 5-µm, 25-cm, 4.6-mm ID column was used. Significant methodological changes were as follows: the extraction was shortened considerably by re-extracting from the isoamyl alcohol/heptane layer into a small volume of 0.1 M HCl, which was dried in a centrifuge evaporator and reconstituted. The detection was changed to filter emission fluorescence spectroscopy with a deuterium source (excitation at 240 nm) and with the photomultiplier tube window as the cutoff filter (295 nm). The internal standard was *S*-propranolol, and the mobile phase was 10/90 v/v acetonitrile/(12 mL/L aqueous diethylamine adjusted to pH 5.3 with acetic acid). The limits of quantitation (LOQ) for the parent compounds and metabolites were 1.5 ng/mL (sertraline, nortriptyline, citalopram and escitalopram) and 2 ng/mL (fluoxetine). The day-to-day coefficients of variation for the parent compounds and metabolites were between 2.6% and 8.2% for the medium and high controls and between 5.2% and 10.0% for the low control. Venlafaxine and the active metabolite *O*-desmethylvenlafaxine were measured using reversed-phase high performance liquid chromatography with ultraviolet detection at 225 nm. Extracted samples were evaporated in a SpeedVac system and reconstituted in 0.025 M potassium phosphate, pH 2.4 (Thermo Fisher Scientific, Waltham, Massachusetts). Separation and measurements were done via a Nucleosil-100 C18, 5-µm column, 120 mm × 4.6 mm with a flow rate of 1.0 mL/min (Macherey-Nagel, Düren, Germany). For venlafaxine and *O*-desmethylvenlafaxine , the LOQ was 5 ng/mL; the assay was linear from 5 to 1,000 ng/mL with an interassay coefficient of variation in the range of 2.5% to 6.8%. The cord and maternal plasma antidepressant concentrations were used to calculate cord-to-maternal concentration ratios.

Outcome Measures and Statistical Analysis

The outcome measures were any perinatal event recorded on the PES and preterm birth (< 37 weeks' gestation). Logistic regression models were used to explore the association between the continuous variables (dose-corrected antidepressant concentrations, cord-to-maternal antidepressant concentration ratios, and depression levels on the SIGH-ADS) or discrete variables (presence of a major depressive episode, exposure to fluoxetine, and smoking) with the outcome measures. Because the SRI agents share a common mechanism of action, we analyzed the cord-to-maternal ratios as a single group.[15]

RESULTS

Sample Characteristics

Twenty-one mother-infant pairs enrolled in the study. The mothers were predominantly white (20/21); the mean age was 31 years.

Antidepressant Exposure

Subjects received SRI therapy (sertraline [n = 9], venlafaxine [n = 2], escitalopram [n = 2], citalopram [n = 1], nortriptyline [n = 1], fluvoxamine [n = 1], and fluoxetine [n = 5]) within standard dose ranges during pregnancy (Table 1). Twenty patients continued SRI treatment across all trimesters; 1 began sertraline after 36 weeks' gestation for severe depression. After the first trimester, 1 patient switched from citalopram to sertraline for the rest of pregnancy. Another switched from escitalopram to nortriptyline. After 36 weeks' gestation, 19 subjects continued antidepressant monotherapy; 2 subjects received combined agents that have not been reported to impact the metabolism of the coprescribed drug (bupropion SR combined with venlafaxine or sertraline; Table 1).

Cord and Maternal Antidepressant Concentration Ratios

Mean ± SD values and ranges of the cord-to-maternal concentration ratios were 0.52 ± 0.35 (range, 0.00–1.64) for parent drug and 0.54 ± 0.17 (range, 0.28–0.79) for metabolite (Table 1). Comparatively higher mean cord-to-maternal concentration ratios were observed with venlafaxine (parent drug = 1.22 ± 0.59, *O*–desmethylvenlafaxine = 0.68 ± 0.17); venlafaxine cord concentrations exceeded the maternal concentrations in 1 mother-infant pair.

Maternal Depression

Nine of 21 mothers (43%) had a major depressive episode in the third trimester (Table 1). The mean ± SD SIGH-ADS score (based on the maximum SIGH-ADS depression

 © COPYRIGHT 2011 PHYSICIANS POSTGRADUATE PRESS, INC.

Table 1. Antidepressant Drug, Dose, Cord and Maternal Concentrations, Maternal Depression, and Smoking

Patient Number	PES Score	Drug[a]	Dose, mg/d		Taper at Week 36	Comment	Cord-Maternal Antidepressant Concentration Ratio		Cord Antidepressant Concentration, ng/mL		Maternal Antidepressant Concentration, ng/mL		MDE Third Trimester	SIGH-ADS Scores			Smoking Status
			Week 36	Delivery			Parent Drug[b]	Metabolite[b]	Parent Drug[b]	Metabolite[b]	Parent Drug[b]	Metabolite[b]		Week 20	Week 30	Week 36	
1	3	Sertraline	100	100	No		0.19	0.28	5.2	16.4	27.8	58.9	No	13	6	NA	No
2	0	Sertraline	50	50	No		0.24	0.31	2.7	7.9	11.2	25.9	No	NA	5	9	No
3	1	Sertraline	200	200	No	With bupropion SR	0.29	0.34	9.5	41.1	32.4	120	Yes	5	21	14	Yes
4	0	Sertraline	50	100	No	Switched from citalopram after first trimester	0.31	0.32	3.0	6.8	9.8	21.5	No	2	7	4	No
5	0	Sertraline	0[c]	100	No		0.31	0.39	6.2	9.2	19.8	23.4	Yes	33	15	29	Yes
6	0	Sertraline	75	100	No		0.35	0.38	11.0	37.3	31.5	97.0	Yes	24	14	19	No
7	0	Sertraline	75	75	No		0.60	0.55	3.5	15.8	5.8	28.5	Yes	21	19	12	No
8	1	Sertraline	100	100	No		0.63	0.41	6.2	13.4	9.9	33.0	Yes	6	5	18	No
9	0	Sertraline	100	50	Yes		0.99	0.60	6.7	19.0	6.8	31.9	Yes	5	5	12	No
10	2	Venlafaxine	75	75[d]	No	With bupropion SR	0.80	0.79	79.9	44.7	100	56.4	No	10			Yes
11	1	Venlafaxine	75	75[d]	No		1.64	0.56	46.4	105	28.3	188	No	13	15	10	Yes
12	1	Escitalopram	10	10[d]	No		0.00	0.67	0	3.6	5.6	5.4	Yes	18	16		No
13	0	Escitalopram	10	10[d]	No		0.50	0.77	6.7	2.0	13.5	2.6	No	8	6	11	No
14	2	Citalopram	50	50[d]	No		0.56	0.71	23.0	10.5	41.4	14.7	No	14	23	7	No
15	0	Nortriptyline	75	0	Yes	Switched from escitalopram after first trimester	0.47	0.65	10.6	20.1	22.6	30.8	No	15	18	10	No
16	0	Fluvoxamine	400	200	Yes		0.08		4.9		62.7		Yes	17	28	33	No
17	0	Fluoxetine	40	40	No		0.50	0.48	66.5	122	132	255	Yes	6	6	12	No
18	0	Fluoxetine	20	10	Yes		0.54	0.70	10.1	38.0	18.7	54.3	No	7	3	4	No
19	0	Fluoxetine	20	20[e]	No		0.55	0.60	89.1	48.7	162	80.7	No	11	NA	NA	Yes
20	0	Fluoxetine	30	30	No		0.64	0.68	30.0	13.0	47.0	19.0	No	9	4	6	No
21	0	Fluoxetine	40	0	Yes		0.69	0.69	2.5	37.4	3.6	54.5	No	8	11	4	No

[a]Ten mothers used concomitant drugs that do not interfere with antidepressant activity: metoprolol, labetalol, aspirin, albuterol inhaler, nicotine patch, lidocaine nasal spray, levoxyl, promethazine, metamucil, and acetaminophen. [b]The measured parent compounds and metabolites were sertraline, *N*-desmethylsertraline (or norsertraline), citalopram, *N*-desmethylcitalopram (or norcitalopram), fluoxetine, norfluoxetine, nortriptyline, *E*-10-hydroxynortriptyline, venlafaxine, and *O*-desmethylvenlafaxine. [c]Patient began treatment after 36 weeks. [d]Dose estimated from 36-week data. [e]Dose estimated from 20-week data.

Abbreviations: MDE = major depressive episode, NA = not available, PES = Peripartum Events Scale, SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms Version.

rating for each mother; Table 1) was 16.0 ± 7.6. Despite ongoing depressive symptoms, 2 of the 9 mothers tapered their doses.

Infant Outcomes

Perinatal events. One third of infants (7/21) had at least 1 perinatal event (PES ≥ 1) (Table 2). The events included preterm birth, large for gestational age (> 4000 g), transient respiratory distress, low Apgar scores at 1 or 5 minutes, feeding problems, or polycythemia. The range of cord-to-maternal ratios was 0.00–1.64 for infants with any perinatal event (PES ≥ 1) versus 0.08–0.99 for the healthy infants (without any perinatal event) (Table 1). Three neonates with PES > 1 represented the more affected 10% of infants with adverse outcomes.[27] They were exposed to sertraline (preterm birth, polycythemia, and cyanosis), venlafaxine (low Apgar scores) and citalopram (feeding problems, large for gestational age) (Table 2).

For the association between the cord-to-maternal concentration ratios and perinatal events, the odds ratios (ORs) were increased but not significant for mother-infant pairs with any perinatal event (PES ≥ 1; OR = 2.3; 95% CI, 0.2–32.8) or a higher number of perinatal events (PES > 1; OR = 11.8; 95% CI, 0 to > 999) (Table 3). In the final trimester, mothers with major depression (3/9) and healthy nondepressed mothers (4/12) had similar rates of deliveries complicated by perinatal event(s) ($P > 1.0$). There was no association between maternal depression levels and any perinatal event (OR = 1.0; 95% CI, 0.9–1.2) (Table 3). Treatment with short half-life agents at 36 weeks (venlafaxine, escitalopram, citalopram, or sertraline) resulted in any perinatal event (PES ≥ 1) in 7/16 mother-infant pairs (44%), whereas treatment with the long half-life agent fluoxetine did not result in any perinatal event (0/5 = 0%; $P = .06$).

Preterm birth. Fourteen percent of the infants (3/21) included in this analysis had preterm births (< 37 weeks'

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 2. Neonatal Outcomes—PES Scores, Gestational Age at Birth, and Discrete Clinical Signs

Patient Number	PES Score	Drug	NICU	Low Apgar Score 1 min	Low Apgar Score 5 min	Gestational Age at Birth, wk	Birth Weight, g	Additional Complication
1	3	Sertraline	Yes	9	9	36	2,995	Polycythemia, respiratory distress
10	2	Venlafaxine	No	5	7	39	3,202	
14	2	Citalopram	No	8	9	40	4,426	Feeding problem
3	1	Sertraline	Yes	9	9	39	4,080	
8	1	Sertraline	No	8	9	39	3,780	Meconium aspiration pneumonitis, respiratory distress
11	1	Venlafaxine	Yes	7	9	36	3,027	
12	1	Escitalopram	Yes	7	9	32	2,120	
2	0	Sertraline	No	9	9	37	3,880	
4	0	Sertraline	No	8	9	39	3,335	
5	0	Sertraline	No	8	9	39	3,560	
6	0	Sertraline	No	8	9	39	2,790	
7	0	Sertraline	No	8	9	39	3,170	
9	0	Sertraline	No	8	9	40	2,854	
13	0	Escitalopram	No	8	9	39	3,095	
15	0	Nortriptyline	No	9	9	38	3,465	
16	0	fluvoxamine	No	9	9	39	4,085	
17	0	Fluoxetine	No	9	9	40	3,760	
18	0	Fluoxetine	No	9	9	40	3,330	
19	0	Fluoxetine	No	NA	NA	39	NA	
20	0	Fluoxetine	No	NA	NA	39	3,775	
21	0	Fluoxetine	No	8	9	40	3,757	

Abbreviations: NA = not available, NICU = neonatal intensive care unit, PES = Peripartum Events Scale.

Table 3. Cord-to-Maternal Antidepressant Concentration Ratios and Maternal Depression Levels: Association With PES and Preterm Birth

Continuous Variables	N	Mean (SD)	Range	PES > 1 OR (95% CI)	PES ≥ 1 OR (95% CI)	Preterm Birth OR (95% CI)
All cord-to-maternal parent drug ratios	21	0.52 (0.35)	0.28–0.79	1.0 (0.03 to 35.6)	2.3 (0.2 to 32.8)	2.2 (0.09 to 54.6)
All cord-to-maternal metabolite ratios	21	0.54 (0.17)	0.08–1.64	11.8 (0.003 to > 999)	0.7 (0.002 to 203.2)	0.2 (< .001 to 310.6)
Maximum SIGH-ADS (depression level)	21	16.0 (7.6)	7–33	1.0 (0.8 to 1.2)	1.0 (0.9 to 1.2)	1.0 (0.8 to 1.2)

Abbreviations: OR = odds ratio, PES = Peripartum Events Scale, SIGH-ADS = Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms Version.

gestation). All 3 preterm infants had 1 perinatal event or more (PES ≥ 1) compared to the 18 full-term infants who did not have any perinatal event. Preterm birth affected 11% of mothers (1/9) with a major depressive episode vs 17% of nondepressed mothers (2/12) ($P > 1.0$). The odds ratio was increased but not significant for the association between preterm birth and cord-to-maternal parent drug concentration ratios (OR = 2.2; 95% CI, 0.1–54.6) (Table 3). Preterm birth was not associated with cord-to-maternal metabolite concentration ratios (OR = 0.2; 95% CI, < .001–310.6) (Table 3). The level of maternal depression (OR = 1.0; 95% CI, 0.8–1.2) was not related to preterm birth (Table 3). Treatment with fluoxetine did not result in preterm birth (0/5 = 0%; $P = .5$) (Table 2).

Five gravidas smoked cigarettes (Table 1). Of the mothers who smoked, 60% (3/5) delivered neonates with signs compared to 25% (4/16) who did not smoke ($P = .28$). Maternal smoking was not associated with perinatal events (OR = 0.2; 95% CI, 0.03–1.9) or preterm birth (OR = 0.6; 95% CI, 0.04–8.1).

DISCUSSION

In this sample, 33% of infants (7/21) with antidepressant exposure during pregnancy (venlafaxine, escitalopram, citalopram, and sertraline) had at least one perinatal event. The data are similar to those in reports of newborn signs with SRI exposure in the third trimester (rate = 30% [14/46]: fluoxetine, paroxetine, sertraline, and a combination of paroxetine and clonazepam)[17] or SRI exposure through most of pregnancy (rate = 30% [18/60]; paroxetine, fluoxetine, citalopram, sertraline, and venlafaxine).[9] Extended antidepressant treatment in pregnancy also may be associated with adverse events (shortened gestation, $z = 4.59$; decreased birth weight, $z = 2.61$; and respiratory distress, $z = 4.24$; $P < .001$) even after controlling for maternal depression.[35] In future research, the duration of total gestational antidepressant use must be explored as a separate characteristic related to neonatal outcomes.[35] Data on perinatal events were limited to information from obstetric and newborn records. Further study on perinatal outcomes could incorporate a more rigorous assessment tool such as the Brazelton Neonatal Assessment Scale.[48]

The infants experienced a limited number of transient perinatal events; 14% (3/21) had clinically important perinatal events (PES > 1). Similar to our findings, Rampono et al[15] detected low rates of clinically significant newborn outcomes related to neonatal abstinence (5% of all cases, 4% of infants exposed to selective serotonin reuptake inhibitors,

and 9% of infants exposed to venlafaxine) and transient behavioral effects of habituation ($r^2 = 0.14$, $P < .05$), social interactions ($r^2 = 0.09$, $P < .05$), autonomic effects ($r^2 = 0.09$, $P < .05$), and motor function ($r^2 = 0.33$, $P < .001$). Respiratory distress was uncommon (2/21 = 10% of the entire sample or 1/18 = 6% of the full-term births) and resolved spontaneously or after a brief neonatal intensive care unit stay. This finding was similar to rates described in a registry report of SRI-treated mothers (13.9%; N = 11,9547) compared to depressed mothers without SRI treatment (13.9% vs 7.8%; 95% CI, 0.042–0.079).[8] However, it is contrary to data from other groups that suggested high rates of respiratory distress of 20% (12/60),[9] 30% (14/46),[17] and 43% (31/73—citalopram or sertraline).[11] After controlling for the severity of maternal illness, respiratory distress still affected newborns with late [within 14 days of birth] and nonlate SRI exposure at similar rates (13.0%, n = 239; SD = 33.7 vs 11.7%, n = 239, SD = 32.2; $P = .788$, respectively).[36] In this study, the neonates of mothers who received fluoxetine did not develop respiratory complications, contrary to earlier findings of newborn distress with late exposure to fluoxetine.[22] Other investigators have suggested that maternal treatment with paroxetine is associated with neonatal respiratory compromise (9 cases among 55 exposed infants[20] and 7 cases among 109 exposed infants[5]). The infrequency of respiratory symptoms in the newborns in the current study may be explained partially by the absence of paroxetine exposure. In practice, newborns of mothers with an extended duration of SRI therapy during pregnancy[35,36] and newborns with exposure to specific agents like paroxetine or venlafaxine (shorter half-life) may require careful clinical monitoring after birth for perinatal events.

We detected associations between the cord-to-maternal antidepressant concentration ratios and perinatal events (PES ≥ 1; OR = 2.3 and PES > 1; OR = 11.8) or preterm birth (OR = 2.2) that were large but not statistically significant. One explanation for the failure to find a relationship between cord-to-maternal ratios and perinatal events is that antidepressant exposure during pregnancy results in very few clinically important perinatal events (except for preterm birth).[27] Another explanation is that the small sample size reduced the power to detect any significant association. Infants with any perinatal event and the healthy newborns had wide ranges of cord-to-maternal concentration ratios. The cord-to-maternal concentration ratios were comparable to those reported by other investigators.[15] Infants exposed to SRIs with short or medium half-lives (venlafaxine, sertraline, citalopram, and escitalopram) developed at least 1 perinatal event.[12,15] Treatment with short-half life drugs, eg, venlafaxine (half-life in adult = 6 hours, in newborn = 12–15 hours; *O*-desmethylvenlafaxine half-life in adult = 12 hours, in newborn = 10–37 hours),[12] may result in increased cord concentrations[15] and higher peak and lower trough levels. Wide variations in the drug concentrations could introduce risk for discontinuation or toxicity effects in the neonate,[12,15,16] depending on the time of the last dose. We focused the analysis of perinatal events and preterm birth outcomes related to cord-to-maternal antidepressant concentration ratios (indicator of infant exposure). The outcomes also could be related to maternal antidepressant exposure (which varies depending on the dose and individual variability in maternal metabolism). Future research may incorporate measures of maternal exposure (such as maternal antidepressant concentrations) to more fully explain perinatal events and preterm birth.

Similar to earlier findings,[15,16,49] fluoxetine resulted in substantial cord-to-maternal concentration ratios in our study (mean ± SD ratios in fluoxetine = 0.59 ± 0.08; in norfluoxetine = 0.63 ± 0.09). In contrast to reports of high cord-to maternal fluoxetine concentration ratios associated with newborn complications,[4,16] we did not detect complications among the fluoxetine-exposed neonates. Multiple cytochrome P450 enzymes (CYPs)—2D6, 2C9, 3A4 and, to a lesser degree, 2C19—demethylate fluoxetine.[50,51] The (competitive) inhibitory effects of fluoxetine and norfluoxetine on CYP 2D6[21] could counter the pregnancy-related induction of the 3A4 and 2D6 enzymes[52,53] to result in higher cord-to-maternal concentration ratios. Researchers have detected measurable (albeit declining) levels of the active moieties in 2-month old infants with fetal exposure.[49]

Additional factors related to drug absorption, distribution, metabolism, and elimination can influence the passage of drug from mother to newborn and contribute to newborn clinical signs or perinatal events. Across gestation, the fetus absorbs drug circulating in the amniotic fluid from the skin, gastrointestinal, and pulmonary surfaces.[34,54] Drug in the maternal circulation also can reach the fetus by active transport across the placenta by transporter proteins.[34,41,54–56] Newborns usually have decreased drug-binding plasma proteins and increased endogenous compounds, eg, bilirubin, which displace drug from protein-binding sites. These unique characteristics of the newborn can result in high concentrations of free fractions of drugs.[54] The SRIs associated with perinatal events, citalopram, sertraline, and venlafaxine, are less protein-bound drugs; measures of cord concentrations very likely underestimated the unbound fraction of the drugs.[21,57,58] Increased drug free fractions may explain the heightened drug effects and perinatal events in some mother-infant pairs.

Cytochrome P450 enzymes metabolize the SRIs. Developmental stage and genetic polymorphisms are important in the drug metabolizing capacity. Cytochrome P450 activity begins in the fetal months (3A7), shortly after birth (2E1, 2D6), during the first week of life (3A4, 2C9, 2C19) and at 1 to 3 months of age (1A2).[54] Cytochrome P450 genetic polymorphisms may result in slowed or rapid drug biotransformation.[54] Further research is needed to explore the effects of maternal, newborn, and placental CYP on the maternal-newborn passage of antidepressants and eventual perinatal outcomes.

In this small sample, we detected comparable rates of preterm birth among antidepressant-treated mothers with a

© Copyright 2011 Physicians Postgraduate Press, Inc.

major depressive episode and nondepressed mothers (11% vs 17%). This finding differs from published reports of increased risk for preterm birth (< 37 weeks) in mothers on selective SRI or serotonin-norepinephrine reuptake inhibitors (n = 732) compared to all deliveries in the population (n = 860,215; OR = 1.60; 95% CI, 1.19–2.15).[59] In one study, the frequency of preterm delivery was increased in medicated depressed mothers vs unmedicated depressed mothers or healthy comparators (14%, 0%, and 5.3%, respectively).[60] The investigators also observed high rates of admission to the special care nursery of infants born to depressed medicated mothers compared to the other groups (21%, 9%, and 0%, respectively).[60] It is prudent to provide careful clinical monitoring of babies with antidepressant exposure or babies born to depressed mothers in their first days of life.

Inadequate dosing may partially explain the persistence of depression during pregnancy. Mothers of the newborns with perinatal events received midrange dosing. Dose requirements often increase across pregnancy.[46] Since these mothers continued to have moderate or severe symptoms while being treated, they may have been underdosed or noncompliant with treatment. Treatment nonresponse and resistance contribute to persistent symptoms. Since unremitting depression very likely leads to increased risk for perinatal events or preterm birth, clinicians must provide ongoing screening of depression symptoms, treatment adherence, and dosing to ensure a lasting antidepressant response.

Drug names: acetaminophen (Ofirmev), albuterol (Proventil-HFA, Ventoline HFA, and others), bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), metoprolol (Toprol, Lopressor, and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), propranolol (Inderal, InnoPran, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

Author affiliations: Women's Behavioral HealthCARE (Drs Sit and Wisner) and the Department of Psychiatry (Dr Perel and Mr Helsel), Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center; Department of Epidemiology, Graduate School of Public Health (Dr Wisniewski and Mr Luther); University of Pittsburgh, Pennsylvania.

Potential conflicts of interest: **Dr Sit** has received a donation of light therapy units from Uplift Technologies. for an ongoing National Institute of Mental Health (NIMH) study (K23 MH082114).
Dr Perel is a consultant and expert witness on atomoxetine and other non-psychostimulants in the treatment of ADHD for a consortium of 10 pharmaceutical companies and is a consultant on SSRI metabolism and pharmacokinetics/pharmcodynamics in "The Effect of Gastric Bypass on SSRI PK/PD," Award by American Society of Bariatric Surgery (G. Hamad, PI). **Dr Wisniewski** receives grant support from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the NIMH and has consulted with Cyberonics (2005–2009), ImaRx Therapeutics (2006), Bristol-Myers Squibb (2007–2008), Organon (2007), and Case-Western University (2007). **Dr Wisner** has received a donation of active and placebo transdermal estradiol patches from Novogyne (Novartis) for an NIMH-funded study (R01 MH057102) and has participated in an advisory group for Eli Lilly. **Messrs Helsel** and **Luther** report no financial or other relationship relevant to the subject of this article.
Funding/support: Dr Sit's contributions were supported by the National Institute of Mental Health (NIMH) R01 MH60335 (K. Wisner, PI), Junior Faculty Scholar's Program R25 MH060473 (P. Pilkonis, PI), and Career Development Award K23 MH082114 (D. Sit, PI). Dr Wisner's effort was supported primarily by NIMH R01 MH60335 Antidepressant Drug Use During Pregnancy), R01 MH071825-Identification and Therapy of Postpartum Depression, R01 MH075921-Antimanic Use During Pregnancy, and R01 MH057102-Transdermal Estradiol for Postpartum Depression.
Previous presentation: The authors presented the data at the American Psychiatric Association 162nd Annual Meeting; May 2009; San Francisco, California.
Acknowledgment: The authors thank the staff at Women's Behavioral HealthCARE for their efforts to perform the research, support the subjects, and organize the extensive data collection.

REFERENCES

1. Gaynes BN, Gavin N, Meltzer-Brody S, et al. *Perinatal Depression: Prevalence, Screening Accuracy, and Screening Outcomes. Summary, Evidence Report/Technology Assessment No. 119*. Rockville, MD: Agency for Healthcare Research and Quality; 2005.
2. Reefhuis J, Rasmussen SA, Friedman JM. Selective serotonin-reuptake inhibitors and persistent pulmonary hypertension of the newborn [comment]. *N Engl J Med*. 2006;354(20):2188–2190, author reply 2188–2190.
3. Moses-Kolko EL, Bogen D, Perel J, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA*. 2005;293(19):2372–2383.
4. Rampono J, Proud S, Hackett LP, et al. A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol*. 2004;7(3):329–334.
5. Källén B. Neonate characteristics after maternal use of antidepressants in late pregnancy. *Arch Pediatr Adolesc Med*. 2004;158(4):312–316.
6. Sanz EJ, De-las-Cuevas C, Kiuru A, et al. Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet*. 2005;365(9458):482–487.
7. Chambers CD, Johnson KA, Dick LM, et al. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med*. 1996;335(14):1010–1015.
8. Oberlander TF, Warburton W, Misri S, et al. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. *Arch Gen Psychiatry*. 2006;63(8):898–906.
9. Levinson-Castiel R, Merlob P, Linder N, et al. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med*. 2006;160(2):173–176.
10. Laine K, Heikkinen T, Ekblad U, et al. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Arch Gen Psychiatry*. 2003;60(7):720–726.
11. Boucher N, Bairam A, Beaulac-Baillargeon L. A new look at the neonate's clinical presentation after in utero exposure to antidepressants in late pregnancy. *J Clin Psychopharmacol*. 2008;28(3):334–339.
12. Boucher N, Koren G, Beaulac-Baillargeon L. Maternal use of venlafaxine near term: correlation between neonatal effects and plasma concentrations. *Ther Drug Monit*. 2009;31(3):404–409.
13. Galbally M, Lewis AJ, Lum J, et al. Serotonin discontinuation syndrome following in utero exposure to antidepressant medication: prospective controlled study. *Aust N Z J Psychiatry*. 2009;43(9):846–854.
14. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med*. 2010; 40(10):1723–1733 [epub ahead of print].
15. Rampono J, Simmer K, Ilett KF, et al. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry*. 2009; 42(3):95–100.
16. Hendrick V, Stowe ZN, Altshuler LL, et al. Placental passage of antidepressant medications. *Am J Psychiatry*. 2003;160(5):993–996.
17. Oberlander TFMS, Misri S, Fitzgerald CE, et al. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. *J Clin Psychiatry*. 2004;65(2):230–237.
18. Haddad PM, Pal BR, Clarke P, et al. Neonatal symptoms following maternal paroxetine treatment: serotonin toxicity or paroxetine discontinuation syndrome? *J Psychopharmacol*. 2005;19(5):554–557.
19. Dubnov-Raz G, Juurlink DN, Fogelman R, et al. Antenatal use of selective serotonin-reuptake inhibitors and QT interval prolongation in newborns. *Pediatrics*. 2008;122(3):e710–e715.
20. Costei AM, Kozer E, Ho T, et al. Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med*. 2002;156(11): 1129–1132.

21. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther*. 2000;85(1):11–28.
22. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354(6):579–587.
23. Källén B, Olausson PO. Maternal use of selective serotonin re-uptake inhibitors and persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf*. 2008;17(8):801–806.
24. Andrade SE, McPhillips H, Loren D, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. *Pharmacoepidemiol Drug Saf*. 2009;18(3):246–252.
25. Wichman CL, Moore KM, Lang TR, et al. Congenital heart disease associated with selective serotonin reuptake inhibitor use during pregnancy. *Mayo Clin Proc*. 2009;84(1):23–27.
26. Wilson KL, Zelig CM, Harvey JP, et al. Persistent pulmonary hypertension of the newborn is associated with mode of delivery and not with maternal use of selective serotonin reuptake inhibitors. *Am J Perinatol*. 2011;28(1):19–24.
27. Wisner KL, Sit DK, Hanusa BH, et al. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. *Am J Psychiatry*. 2009;166(5):557–566.
28. Li D, Liu L, Odouli R. Presence of depressive symptoms during early pregnancy and the risk of preterm delivery: a prospective cohort study. *Hum Reprod*. 2009;24(1):146–153.
29. Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry*. 2004;49(11):726–735.
30. Alder J, Fink N, Bitzer J, et al. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? a critical review of the literature. *J Matern Fetal Neonatal Med*. 2007;20(3):189–209.
31. King-Hele S, Webb RT, Mortensen PB, et al. Risk of stillbirth and neonatal death linked with maternal mental illness: a national cohort study. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(2):F105–F110.
32. Misra DP, Guyer B, Allston A. Integrated perinatal health framework: a multiple determinants model with a life span approach. *Am J Prev Med*. 2003;25(1):65–75.
33. Wadhwa PD, Culhane JF, Rauh V, et al. Stress and preterm birth: neuroendocrine, immune/inflammatory, and vascular mechanisms. *Matern Child Health J*. 2001;5(2):119–125.
34. Loughhead AM, Stowe ZN, Newport DJ, et al. Placental passage of tricyclic antidepressants. *Biol Psychiatry*. 2006;59(3):287–290.
35. Oberlander TF, Warburton W, Misri S, et al. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: population-based study. *Br J Psychiatry*. 2008;192(5):338–343.
36. Warburton W, Hertzman C, Oberlander TF. A register study of the impact of stopping third trimester selective serotonin reuptake inhibitor exposure on neonatal health. *Acta Psychiatr Scand*. 2010;121(6):471–479.
37. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Edition*. Washington, DC: American Psychiatric Press; 1996.
38. Post RM, Roy-Byrne PP, Uhde TW. Graphic representation of the life course of illness in patients with affective disorder. *Am J Psychiatry*. 1988; 145(7):844–848.
39. Williams JBW, Terman M. *Structured Interview Guide for the Hamilton Depression Rating Scale With Atypical Depression Supplement (SIGH-ADS)*. New York, NY: New York State Psychiatric Institute; 2003.
40. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
41. Ter Horst PG, Jansman FG, van Lingen RA, et al. Pharmacological aspects of neonatal antidepressant withdrawal. *Obstet Gynecol Surv*. 2008;63(4): 267–279.
42. O'Hara MW. Social support, life events, and depression during pregnancy and the puerperium. *Arch Gen Psychiatry*. 1986;43(6):569–573.
43. Wisner KL, Perel JM, Peindl KS, et al. Effects of the postpartum period on nortriptyline pharmacokinetics. *Psychopharmacol Bull*. 1997;33(2): 243–248.
44. Rochat B, Amey M, Baumann P. Analysis of enantiomers of citalopram and its demethylated metabolites in plasma of depressive patients using chiral reverse-phase liquid chromatography. *Ther Drug Monit*. 1995;17(3): 273–279.
45. Wisner KL, Hanusa BH, Perel JM, et al. Postpartum depression: a randomized trial of sertraline versus nortriptyline. *J Clin Psychopharmacol*. 2006;26(4):353–360.
46. Sit DK, Perel JM, Helsel JC, et al. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. [see comment] *J Clin Psychiatry*. 2008;69(4):652–658.
47. Sit DK, Perel JM, Luther JF, et al. Disposition of chiral and racemic fluoxetine and norfluoxetine across childbearing. *J Clin Psychopharmacol*. 2010;30(4):381–386.
48. Brazelton TB. *Neonatal Behavioral Assessment Scale*. Philadelphia: Lippincott; 1973.
49. Heikkinen T, Ekblad U, Palo P, et al. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. *Clin Pharmacol Ther*. 2003;73(4):330–337.
50. Scordo MG, Spina E, Dahl ML, et al. Influence of CYP2C9, 2C19 and 2D6 genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. *Basic Clin Pharmacol Toxicol*. 2005;97(5):296–301.
51. Eap CB, Bondolfi G, Zullino D, et al. Concentrations of the enantiomers of fluoxetine and norfluoxetine after multiple doses of fluoxetine in cytochrome P4502D6 poor and extensive metabolizers. *J Clin Psychopharmacol*. 2001;21(3):330–334.
52. Tracy TS, Venkataramanan R, Glover DD, et al; National Institute for Child Health and Human Development Network of Maternal-Fetal-Medicine Units. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. *Am J Obstet Gynecol*. 2005;192(2):633–639.
53. Wadelius M, Darj E, Frenne G, et al. Induction of CYP2D6 in pregnancy. *Clin Pharmacol Ther*. 1997;62(4):400–407.
54. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157–1167.
55. Kapur G, Mattoo T, Aranda JV. Pharmacogenomics and renal drug disposition in the newborn. *Semin Perinatol*. 2004;28(2):132–140.
56. Wang JS, Newport DJ, Stowe ZN, et al. The emerging importance of transporter proteins in the psychopharmacological treatment of the pregnant patient. *Drug Metab Rev*. 2007;39(4):723–746.
57. Ereshefsky L, Dugan D. Review of the pharmacokinetics, pharmacogenetics, and drug interaction potential of antidepressants: focus on venlafaxine. *Depress Anxiety*. 2000;12(suppl 1):30–44.
58. Anderson GD. Children versus adults: pharmacokinetic and adverse-effect differences. *Epilepsia*. 2002;43(suppl 3):53–59.
59. Lennestål R, Källén B. Delivery outcome in relation to maternal use of some recently introduced antidepressants. *J Clin Psychopharmacol*. 2007; 27(6):607–613.
60. Suri R, Altshuler L, Hellemann G, et al. Effects of antenatal depression and antidepressant treatment on gestational age at birth and risk of preterm birth. *Am J Psychiatry*. 2007;164(8):1206–1213.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

© Copyright 2011 Physicians Postgraduate Press, Inc.