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Mother-Infant Antidepressant Levels, Maternal Depression and Perinatal Events

Dorothy Sit, M.D., James M. Perel, Ph.D., Stephen R. Wisniewski, Ph.D., Joseph C. Helsel, B.S., James F. Luther, M.A., and Katherine L. Wisner, M.D., M.S.

Abstract

Objectives—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 with antidepressant exposure during pregnancy. The antidepressants included serotonergic reuptake inhibitors (SRI) and nortriptyline (noradrenergic 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.

Results—Mean cord-to-maternal concentration ratios were 0.52 ± 0.35 (0.08–1.64) - parent drug and 0.54 ± 0.17 (0.28–0.79) - metabolite. Nine of 21 mothers (43%) had a major depressive episode. From examining the maximum depression ratings, the mean SIGH-ADS score was 16.0 ± 7.6 . One-third (7/21) of infants had at least one perinatal event ($PES \geq 1$). The frequency of deliveries complicated by perinatal event(s) was similar in depressed and non-depressed 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%; $p = 0.06$). 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.

Conclusion—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.

Keywords

Antidepressant Levels; Mother-Infant; Maternal Depression; Preterm Birth; Perinatal Events

Introduction

In the United States, 14.5% of women develop a new episode of depression during pregnancy (1). An estimated 90 000 (2.8%) pregnant women each year are prescribed

Corresponding Author: Dorothy Sit, M.D., Assistant Professor of Psychiatry, Women's Behavioral HealthCARE, Western Psychiatric Institute and Clinic, University of Pittsburgh, 3811 O'Hara Street, Oxford 410, Pittsburgh, PA 15213, Phone: 412-246-5248, Fax: 412-246-6960, sitdk@upmc.edu.

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serotonin reuptake inhibitors (SRI)(2). With final trimester exposure to SRI, infants have a threefold increased risk for neonatal behavioral syndrome, compared to infants exposed in early pregnancy only or 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 pharmacological characteristics of individual antidepressants may impact risk for neonatal syndrome (3). Several reports of neonatal syndrome involved paroxetine (6, 9, 16–20). Among paroxetine-exposed neonates, there are reports of reversible cardiac conduction abnormalities (19), 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 1–2 per 1000 newborns (22). Late pregnancy treatment with fluoxetine and other SRI has been associated with an increased risk for PPHN by 2.91 (95% CI=0.94–6.78) (23) to 5.7 (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 obstetrical outcomes. Examples include preterm birth (27–29), low birth weight (30) and stillbirth or neonatal death (RR=2.4 and 2.2 respectively; 95% CI=1.1–5.1; 1.4–3.3)(31). Precursors or sequelae of perinatal depression (past depression, discontinued treatment, limited supports, low education, 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.

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 levels of nortriptyline and clomipramine were 0.68 and 0.60 respectively for the parent compounds, 1.40 and 0.80 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 levels and maternal depression with perinatal events and preterm birth. We hypothesized that higher ratios of cord-to-maternal levels, 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. Maternal assessments were obtained at 20, 30, 36 weeks gestation and delivery. Obstetrical experts (a nursing doctorate and a physician with obstetrical expertise) blind to the study hypotheses retrieved the neonatal data from a systematic record review of obstetrical, birth and infant hospital charts. Positive neonatal findings were validated with the second obstetrical 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, pre-existing 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 Rating Scale for Depression(40), to evaluate the atypical neurovegetative symptoms of depression and has high intra-class 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 obstetrical 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 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 obstetrical cord blood team. The collected specimens were batched and stored at -80 degrees Celsius in the Clinical Pharmacology Program at Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh Medical Center(43) in the laboratory of James M. Perel, Ph.D. All mothers were taking stable doses for four weeks or more prior to blood sampling. The steady state drug concentrations represented trough levels and 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 (or norsesertraline), citalopram, N-desmethylcitalopram (or norcitalopram), fluoxetine, norfluoxetine, nortriptyline, E-10-hydroxynortriptyline (active metabolite), venlafaxine and O-desmethylvenlafaxine. We adapted the pharmacologic analytical methods for citalopram, sertraline, nortriptyline and fluoxetine/norfluoxetine from that described by RoCHAT and colleagues (44), Wisner et al (45) and Sit et al, (46, 47). An Astec, Inc. (Whippany, NJ) Cyclobond I 2000 AC, 5-micron, 25 cm, 4.6 mm I.D. 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 photo-multiplier tube window as the cut-off 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 1.5ng/ml (sertraline, nortriptyline, citalopram and escitalopram) and 2ng/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 (ODV) were measured using reversed-phase high performance liquid chromatography with ultraviolet detection at 225 nm. Extracted samples were evaporated in a Speed-Vac system and reconstituted in 0.025 M potassium phosphate, pH 2.4. Separation and measurements were done via a Nucleosil-100 C-18, 5 um column, 120 mm x 4.6 mm with a flow rate of 1.0 ml/minute. For venlafaxine and ODV, the LOQ was 5ng/ml; the assay was linear from 5 to 1000 ng/ml with an inter-assay coefficient of variation in the range of 2.5–6.8%. 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 (<37weeks gestation). Logistic regression models were used to explore the association between the continuous variables (dose-corrected antidepressant concentrations, cord-to-maternal antidepressant concentration ratios, 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-9, venlafaxine-2, escitalopram-2, citalopram-1, nortriptyline-1, fluvoxamine-1 and fluoxetine-5) within standard dose ranges during pregnancy (Table 1). Twenty patients continued SRI treatment across all trimesters; one began sertraline after 36 weeks gestation for severe depression. After the first trimester, one 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 which have not been

reported to impact the metabolism of the co-prescribed drug (bupropionSR combined with venlafaxine or sertraline)(Table 1).

Cord and maternal antidepressant concentration ratios

Mean values and ranges of the cord-to-maternal concentration ratios were 0.52 ± 0.35 (0.08–1.64) - parent drug and 0.54 ± 0.17 (0.28–0.79) - 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 one mother-infant pair.

Maternal depression

Nine of 21 mothers (43%) had a major depressive episode in the third trimester (Table 1). The mean SIGH-ADS score (based on the maximum SIGH-ADS depression 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 (7/21) of infants had at least one perinatal event ($PES \geq 1$) (Table 2). The events included preterm birth, large for gestational age (LGA; $>4000g$), transient respiratory distress, low Apgar scores at 1 or 5 minutes, feeding problems or polycythemia. The range of cord-to-maternal ratios was 0.19–1.64 for infants with any perinatal event ($PES \geq 1$) 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, LGA) (Table 2).

For the *association between the cord-to-maternal concentration ratios and perinatal events*, the odds ratios (OR) were increased but not significant for mother-infant pairs with any perinatal event ($PES \geq 1$; $OR=2.3$, 95% $CI=0.2, 32.8$) or a higher number of perinatal events ($PES > 1$; $OR=11.8$, 95% $CI= 0, >999$) (Table 3). In the final trimester, mothers with major depression (3/9) and healthy non-depressed 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 ($PES \geq 1$) in 7/16 (44%) mother-infant pairs, whereas treatment with the long half-life agent fluoxetine did not result in any perinatal event (0/5=0%; $p=0.06$).

Preterm Birth—Fourteen percent (3/21) of the infants included in this analysis had preterm births (<37 weeks gestation). All 3 preterm infants had one or more perinatal events ($PES \geq 1$) compared to the 18 full-term infants who did not have any perinatal event. Preterm birth affected 11% (1/9) of mothers with a major depressive episode vs 17% (2/12) of non-depressed mothers ($p>1.0$). *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%; $p=0.5$)(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 ($p=0.28$). 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% (7/21) of infants with antidepressant exposure during pregnancy (venlafaxine, escitalopram, citalopram, and sertraline) had at least one perinatal event. The data are similar to reports of newborn signs with SRI-exposure in the third trimester (rate=30% [14/46]; fluoxetine, paroxetine, sertraline, combination of paroxetine and clonazepam)(17) or SRI-exposure through most of pregnancy (rate=30% [10/60] paroxetine, fluoxetine, citalopram, sertraline, 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 $z=4.24$; $p<0.001$) 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 outcome (35). Data on perinatal events were limited to information from obstetrical and newborn records. Further study on perinatal outcomes could incorporate a more rigorous assessment tool such as the Brazelton Neonatal Assessment Scale (Brazelton, 1973)(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 SSRIs and 9% of infants exposed venlafaxine) and transient behavioral effects of habituation ($r^2=0.14$, $p<0.05$), social-interactions ($r^2=0.09$, $p<0.05$), autonomic effects ($r^2=0.09$, $p<0.05$) and motor function ($r^2=0.33$, $p<0.001$). 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 NICU stay. This finding was similar to rates described in a registry report of SRI-treated mothers (13.9% $N=119547$) 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 14days of birth] and non-late SRI exposure at similar rates (13.0% $n=239$; $sd=33.7$ vs 11.7% $n=239$ $sd=32.2$; $p=0.788$, 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 suggested that maternal treatment with paroxetine is associated with neonatal respiratory compromise 9/55 (20) and 7/109 (5). The infrequency of respiratory symptoms in the newborns 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 ($PES\geq 1$; 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 cord-maternal concentration ratios reported by

other investigators (15). Infants exposed to SRI with short or medium half-lives (venlafaxine, sertraline, citalopram, escitalopram) developed perinatal event(s) (12, 15). Treatment with short-half life drugs e.g. venlafaxine (half-life in adult=6hrs, newborn=12–15hrs; o-desmethylvenlafaxine half-life adult=12hrs, newborn=10–37hrs) (12) may result in increased cord concentrations (15), 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, fluoxetine resulted in substantial cord-to-maternal concentration ratios (fluoxetine= 0.59 ± 0.08 ; norfluoxetine= 0.63 ± 0.09) (15, 16, 49). 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 cytochromes (CYP) - 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 e.g. 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 SRI associated with perinatal events, citalopram, sertraline and venlafaxine, are less protein-bound drugs; cord concentrations 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.

CYP enzymes metabolize the SRI. Developmental stage and genetic polymorphisms are important in the drug metabolizing capacity. CYP activity begins in the fetal months (3A7), shortly after birth (2E1, 2D6), the first week of life (3A4, 2C9, 2C19) and 1–3 months of age (1A2) (54). CYP 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 major depressive episode and non-depressed 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-noradrenaline 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 mid-range 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 under-dosed or noncompliant with treatment. Treatment non-response and resistance contribute to persistent symptoms. Since, unremitting depression 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.

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Table 1

Antidepressant Drug, Dose, Cord and Maternal Concentrations, Maternal Depression and Smoking

ID#	PES	Drug	Dose 36wk	delivery	Taper at 36wks	Comment	Cord-Maternal Ratios		Cord Concentration		Maternal Concentration		MDD 3rd Trim		Sigh-ADS Scores		Smoking
							parent drug	metabolite	parent drug	metabolite	parent drug	metabolite			20wk	30wk	36wk
1	3	sertraline	100	100	-		0.19	0.28	5.2	16.4	27.8	58.9	0	13	6	n/a	-
2	0	sertraline	50	50	-		0.24	0.31	2.7	7.9	11.2	25.9	0	n/a	5	9	-
3	1	sertraline	200	200	-	with bupropion SR	0.29	0.34	9.5	41.1	32.4	120	1	5	21	14	yes
4	0	sertraline	50	100	-	1st trim-citalopram	0.31	0.32	3.0	6.8	9.8	21.5	0	2	7	4	-
5	0	sertraline	**0	100	-		0.31	0.39	6.2	9.2	19.8	23.4	1	33	15	29	yes
6	0	sertraline	75	100	-		0.35	0.38	11.0	37.3	31.5	97.0	1	24	14	19	-
7	0	sertraline	75	75	-		0.60	0.55	3.5	15.8	5.8	28.5	1	21	19	12	-
8	1	sertraline	100	100			0.63	0.41	6.2	13.4	9.9	33.0	1	6	5	18	-
9	0	sertraline	100	50	yes		0.99	0.60	6.7	19.0	6.8	31.9	1	5	5	12	-
10	2	venlafaxine	75	*75	-	with bupropion SR	0.80	0.79	79.9	44.7	100	56.4	0	10			yes
11	1	venlafaxine	75	*75	-		1.64	0.56	46.4	105	28.3	188	0	13	15	10	yes
12	1	escitalopram	10	*10	-		0.00	0.67	0	3.6	5.6	5.4	1	18	16		-
13	0	escitalopram	10	*10	-		0.50	0.77	6.7	2.0	13.5	2.6	0	8	6	11	-
14	2	citalopram	50	*50	-		0.56	0.71	23.0	10.5	41.4	14.7	0	14	23	7	-
15	0	nortriptyline	75	0	yes	1st trim-escitalopram	0.47	0.65	10.6	20.1	22.6	30.8	0	15	18	10	-
16	0	fluvoxamine	400	200	yes		0.08		4.9		62.7		1	17	28	33	-
17	0	fluoxetine	40	40	-		0.50	0.48	66.5	122	132	255	1	6	6	12	-
18	0	fluoxetine	20	10	yes		0.54	0.70	10.1	38.0	18.7	54.3	0	7	3	4	-
19	0	fluoxetine	***20	***20	-		0.55	0.60	89.1	48.7	162	80.7	0	11	n/a	n/a	yes
20	0	fluoxetine	30	30	-		0.64	0.68	30.0	13.0	47.0	19.0	0	9	4	6	-
21	0	fluoxetine	40	0	yes		0.69	0.69	2.5	37.4	3.6	54.5	0	8	11	4	-

* dose estimated from 36wk data

** patient began treatment after 36wks

*** dose estimated from 20wk data

Subjects with PES≥1 are highlighted

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).

The measured parent compounds and metabolites were: sertraline, N-desmethylsertraline (or nonsertaline), citalopram, N-desmethylcitalopram (or norcitalopram), fluoxetine, norfluoxetine, nortriptyline, E-10-hydroxynortriptyline, venlafaxine and O-desmethylvenlafaxine.

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

ID#	PES	Drug	NICU	Low Apgar	Gest Age	BirthWt (grams)	Additional Complication(s)
				1min	5min		
1	3	sertraline	Yes	9	9	2995	polycythemia, resp distress
10	2	venlafaxine	0	5	7	3202	
14	2	citalopram	0	8	9	4426	feeding problem
3	1	sertraline	Yes	9	9	4080	
8	1	sertraline	0	8	9	3780	meconium, resp distress
11	1	venlafaxine	Yes	7	9	3027	
12	1	escitalopram	Yes	7	9	2120	
2	0	sertraline	0	9	9	3880	
4	0	sertraline	0	8	9	3335	
5	0	sertraline	0	8	9	3560	
6	0	sertraline	0	8	9	2790	
7	0	sertraline	0	8	9	3170	
9	0	sertraline	0	8	9	2854	
13	0	escitalopram	0	8	9	3095	
15	0	nortriptyline	0	9	9	3465	
16	0	fluvoxamine	0	9	9	4085	
17	0	fluoxetine	0	9	9	3760	
18	0	fluoxetine	0	9	9	3330	
19	0	fluoxetine	0	n/a	n/a	n/a	
20	0	fluoxetine	0	n/a	n/a	3775	
21	0	fluoxetine	0	8	9	3757	

n/a=not available

Cord-to-Maternal Antidepressant Concentration Ratios and Maternal Depression Levels: Association with PES and Pre-Term Birth

Table 3

Continuous Variables	N	Mean and SD	Range	PES>1	PES ≥ 1	Pre-Term Birth
				OR (95% CI)	OR (95% CI)	OR (95% CI)
All Cord-to-Maternal Parent Drug Ratios	21	0.52, 0.35	0.28–0.79	1.0 (0.03, 35.6)	2.3 (0.2, 32.8)	2.2 (0.09, 54.6)
All Cord-to-Maternal Metabolite Ratios	21	0.54, 0.17	0.08–1.64	11.8 (0.003, >999)	0.7 (0.002, 203.2)	0.2 (<.001, 310.6)
Maximum SIGH-ADS (Depression Level)	21	16.0, 7.6	7–33	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)