Birth Outcomes Following Prenatal Exposure to Antidepressants

Kimberly H. Pearson, M.D.; Ruta M. Nonacs, M.D., Ph.D.; Adele C. Viguera, M.D., M.P.H.; Vicki L. Heller, M.D.; Laura F. Petrillo, M.D.; Mina Brandes, M.D.; John Hennen, M.D.†; and Lee S. Cohen, M.D.

Received Feb. 9, 2007; accepted May 29, 2007. *From the Perinatal and Reproductive Psychiatry Program, Massachusetts General Hospital, Boston (Drs. Pearson, Nonacs, Viguera, Petrillo, and Cohen); the Department of Obstetrics and Gynecology, Brigham and Women's Hospital, Boston, Mass. (Dr. Heller); the Department of Psychiatry, The Johns Hopkins Hospital, Baltimore, Md. (Dr. Brandes); and the Department of Psychiatry, McLean Hospital, Belmont, Mass. (Dr. Hennen).*

†Deceased.

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Corresponding author and reprints: Kimberly H. Pearson, M.D., Perinatal and Reproductive Psychiatry Program, Massachusetts General Hospital, 185 Cambridge St., 2nd floor, Boston, MA 02114 (e-mail: khpearson@partners.org).

Background: Antidepressant use during pregnancy and the peripartum period is common despite the absence of clear evidence-based guidelines to direct clinical use of these compounds.

Method: We compared obstetrical and neonatal outcomes as recorded in medical records among 84 pregnant women with major depressive or anxiety disorders (DSM-IV criteria) who took antidepressants during pregnancy (cases) versus a 2:1 age- and parity-matched control group of 168 unexposed women. Women in the case group had sought psychiatric consultation regarding the use of medication from the Perinatal and Reproductive Psychiatry Program at the Massachusetts General Hospital between 1996 and 2000.

Results: There were no significant differences among cases versus controls and their offspring, with respect to various neonatal and obstetrical outcomes, including gestational age and weight, although 1-minute Apgar scores were slightly lower in exposed infants. Admissions to the special care nursery were more frequent, but briefer and based on relatively minor indications, among case newborns. There were no significant differences in neonatal outcomes between exposures to serotonin reuptake inhibitor (SRI) and tricyclic (TCA) antidepressants.

Conclusion: This retrospective cohort study found no evidence of major increases in risk of adverse obstetrical or neonatal outcomes following prenatal exposure to antidepressants, nor between SRIs and TCAs. Larger, prospective studies with specific neurobehavioral measures are required to resolve current uncertainties about safe and effective use of antidepressants by pregnant women.

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Mood and anxiety disorders are common in women and typically emerge during the childbearing years.[1] Although pregnancy has traditionally been considered a time of emotional well-being, recent data indicate that about 10% of women experience clinically significant depressive symptoms during pregnancy.[2–5] Furthermore, women with histories of mood and anxiety disorders appear to be at high risk for recurrent illness during pregnancy, particularly in the setting of medication discontinuation.[6,7] Thus, women with recurrent or severe psychiatric illness may elect to continue the use of psychotropic medications during pregnancy; however, data regarding neonatal outcomes remain incomplete.

Adverse obstetrical and neonatal outcomes fall into at least 4 broad categories: (1) organ malformation; (2) prematurity or low birth weight; (3) neonatal toxicity or withdrawal, also frequently referred to as "poor neonatal adaptation"; and (4) sustained behavioral abnormalities. While these outcomes may be related, they are distinct, probably involve dissimilar mechanisms, and have different clinical implications. Most antidepressants are believed to carry no risk of teratogenicity,[8–13] although several recent unpublished reports have suggested an increased risk of cardiac malformation in infants exposed to paroxetine during the first trimester.[14] Several studies indicate the absence of sustained developmental impairments in children exposed to antidepressants in utero.[15,16]

With respect to "neonatal toxicity," in particular, recent studies have described a spectrum of adverse events in

newborns exposed to antidepressants near the time of delivery, including jitteriness, irritability, hypoglycemia, feeding difficulties, respiratory distress, abnormal muscle tone, and excessive constant crying.[8,17–21] Other studies have found that newborns exposed to serotonin reuptake inhibitors (SRIs) during the third trimester had higher rates of admission to a special care nursery,[8,22,23] higher risks of prematurity,[8,9,12] lower birth weight,[8,12] and persistent pulmonary hypertension.[24] These reports prompted the U.S. Food and Drug Administration (FDA) in October 2004 to issue stronger warnings in the packaging inserts regarding the use of SRI antidepressants and venlafaxine during pregnancy.[25]

While these studies have raised concerns regarding the use of antidepressants during pregnancy, many studies have found no adverse effects of prenatal exposure to antidepressants.[10,11,22,26,27] Many of the studies have been small in size and have not yielded important information regarding the broader clinical implications of these adverse outcomes, leaving clinicians to interpret conflicting reports and without clear guidelines regarding the use of antidepressants during pregnancy. The limited amount of controlled data and the inconsistent findings across studies evaluating the effects of prenatal antidepressant exposure prompted the current investigation. The aim of the current study was to compare neonatal outcomes in 2 groups of women, those with antidepressant exposure during pregnancy and those with no known exposure.

METHOD

Subjects

We reviewed obstetrical and neonatal records of 84 infants whose mothers used any type of antidepressant during any portion of pregnancy. Cases were women with primary major affective or anxiety disorders (*Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition [DSM-IV] criteria) treated with antidepressants who sought psychiatric consultation regarding the use of medication from the Perinatal and Reproductive Psychiatry Program at the Massachusetts General Hospital (MGH) between 1996 and 2000. Patients provided written consent for access to review their obstetrical and neonatal records for blinded analysis and aggregate reporting of findings, following approval by the MGH Institutional Review Board. Records were reviewed in 2000–2001, and diagnoses were determined by reviewing the obstetrical records.

Procedures

Medical records were evaluated by 2 psychiatrists (K.H.P., M.B.) and an obstetrician (V.L.H.) blinded to the mother's medication status in order to rate specific neonatal outcome measures. The following outcomes were evaluated: Apgar scores (at 1 and 5 minutes after birth), birth weight, gestational age, and admissions to special care nurseries (SCN) or neonatal intensive care units, as well as "timely discharge" with the mothers. Maternal-obstetrical factors rated were occurrences of pregnancy-associated hypertension or preeclampsia/eclampsia, premature rupture of membranes, induction of labor, use of caesarean section, and vacuum extraction or forceps-assisted delivery, as well as thickened meconium and postpartum maternal hemorrhage. We also scored the timing of drug exposure by trimester and whether infants were delivered at community or tertiary care hospitals.

Records of psychiatric cases were matched on a 1:2 ratio by age (within 5 years) and parity (within 1) to women not exposed to an antidepressant drug during pregnancy. Such control subjects were selected from the MGH Department of Obstetrics electronic records and were assessed for the same outcome measures as exposed cases by a physician rater (L.F.P.).

Statistical Analysis

We used conditional logistic regression to contrast binary outcomes for mothers and neonates of pregnancies involving antidepressant exposure (cases) or not (controls), as well as generalized linear regression modeling for continuous variables, except that Apgar scores were analyzed by ordered logistic-regression modeling methods—all with adjustment for factors not employed for matching (tobacco use, marital status), as well as for exact maternal age and parity, to obtain a z statistic and its associated p value. For some categorical analyses, we employed contingency tables to provide a χ^2 and p value (or Fisher exact p when cell size was ≤ 10). Categorical data are reported as N (%), and averaged continuous data are reported as means with standard deviations (SDs) or 95% confidence intervals (CIs), at stated degrees of freedom (df). Some comparisons were based on observed risk ratios (RRs) and their CIs. Statistical significance required a 2-tailed p value < .05. Analyses employed commercial microcomputer programs (Stata, Stata Corp., College Station, Tex.).

RESULTS

Sample Characteristics

Obstetrical and neonatal records were reviewed for 84 mother-infant pairs (cases) exposed to antidepressants during pregnancy. Women treated with antidepressants had a mean age of 33.4 (range, 20–42) years, 30.9% (26/84) were primiparous, and all had single births (Table 1). The comparison control group of 168 women was matched for age (mean = 33.3; range, 20–44 years) and parity (52/168, 30.9% primiparous), and all had single births. Cases and controls differed significantly with regard to marital status: 97% of the exposed cases were married versus 77% of the unexposed controls;

Table 1. Characteristics of Women Exposed to Antidepressant Treatment During Pregnancy and of Unexposed Control Subjects

Measure	Exposed (N = 84)	Unexposed (N = 168)	χ^2 or z Statistic	p Value
Age, mean ± SD (range), y	33.4 ± 4.6 (20–42)	33.3 ± 4.6 (20–44)	0.16	.87
Primiparous, N/N (%)	26/84 (31)	52/168 (31)	0	1.0
Tobacco use, N/N (%)[a]	12/50 (24)	86/158 (54)	14.07	< .001
Marriage, N/N (%)[b]	56/58 (97)	116/151 (77)	11.34	< .001
Hospital type, N/N (%)			NA	NA
Community	51/84 (61)	0 (0)		
Tertiary	33/84 (39)	168/168 (100)		

[a]Information on tobacco use missing for 34/84 cases and 10/168 controls.
[b]Information on marital status missing for 26/84 cases and 17/168 controls.
Abbreviation: NA = not applicable.

Table 2. Timing of Subjects' Exposure to Antidepressant Medication During Pregnancy

Measure	Recorded Cases (N = 79)
At conception only, N (%)	6 (7.6)
First and second trimester, N (%)	12 (15.2)
Third trimester, N (%)	67 (84.8)
Throughout entire pregnancy, N/N (%)	47/67 (70.1)

information on marital status was missing for 26/84 cases and 17/168 controls. Tobacco use during pregnancy also differed significantly, with 24% of cases and 54% of controls reporting smoking; information on tobacco use was missing for 34/84 cases and 10/168 controls. Maternal diagnosis was identified in the obstetrical record for each case and included major depressive disorder in 53.4% (31/58), panic disorder in 36.2% (21/58), obsessive-compulsive disorder in 5.2% (3/58), or other anxiety disorders in 5.2% (3/58); while all patients in the exposed group were referred for evaluation of a mood or anxiety disorder, a specific DSM-IV diagnosis was not identified in the obstetrical record for 26 cases.

Specific antidepressant exposures included fluoxetine (N = 17), nortriptyline (N = 13), sertraline (N = 13), paroxetine (N = 12), imipramine (N = 11), desipramine (N = 7), clomipramine (N = 4), phenelzine (N = 3), amitriptyline (N = 2), and bupropion (N = 2). By antidepressant type, these exposures consisted of SRIs (42/84 = 50.0%) > tricyclic antidepressants (TCAs) (37/84 = 44.0%) > others (5/84 = 6.0%). Mean duration of antidepressant exposure among cases during pregnancy was 32.5 (range, 4–40) weeks. Among cases, 28.6% (24/84) were also exposed to a benzodiazepine for anxiety or insomnia during pregnancy. Timing of exposure was recorded for 79 of 84 cases (Table 2).

Neonatal Outcomes

Apgar scores, birth weight, gestational age, premature delivery, caesarean section, and admission to a special care nursery were assessed for the entire sample (N = 252; Table 3). Minor but statistically significant differences between cases and controls were found for Apgar scores at 1 minute, which averaged about 0.34 points lower on a 1–10 scale among antidepressant-exposed infants (p = .009). Such differences were no longer found in 5-minute Apgar scores. The 2 groups did not differ with regard to gestational age, birth weight, and delivery by caesarean surgery (Table 3). Obstetrical complications were documented in 44 (52.4%) of the 84 antidepressant-exposed cases and 76 (45.2%) of the 168 unexposed controls (χ^2 = 1.14, df = 1, p = .284). The most frequent of these complications involved induced labor (44.2% of all complicated deliveries), which occurred at similar rates in the 2 groups (18/44 = 40.9% of cases vs. 35/76 = 46.1% of controls). The exposed and unexposed subjects did not differ with respect to frequency of other obstetrical complications. There was no significant difference between exposed infants with known diagnoses and those without documented diagnoses on any outcome variable (data not shown).

Admission to a special care nursery or neonatal intensive care unit was more frequent among the newborns of antidepressant-exposed cases, but this finding was not statistically significant (p = .084). Special care unit admissions were more common among antidepressant-exposed infants delivered at tertiary-care (9/33 = 27.3%) versus community hospitals (6/51 = 11.8%; z = 1.75, p = .080); this finding was not statistically significant. There was also a non–statistically significant increase in frequency of special care admission among newborns exposed to antidepressants late in pregnancy (third trimester, 14/67 = 20.9%) versus early in pregnancy (first or second trimester, 1/12 = 8.3%; Fisher exact p = .35). Of women on antidepressant and benzodiazepine treatment, 22.6% of their infants (7/31) were admitted to the SCN, whereas 15.1% of infants of women on antidepressant treatment alone (8/53) were admitted; this was not statistically significant (p = .39). Infants of mothers on concomitant benzodiazepine treatment did not differ significantly from other exposed infants on any other outcome variable (data not shown). The 15 antidepressant-exposed newborns who required special care were admitted for a range of indications including to rule out sepsis (N = 5), for observation (N = 2), transient tachypnea (N = 3), respiratory distress (N = 4), poor feeding (N = 1), or for exchange transfusion

Table 3. Outcome Variables of Newborn Infants Exposed and Not Exposed to Antidepressants During Gestation[a]

Measure	Exposed (N = 84)	Not Exposed (N = 168)	Statistic	p Value
Apgar score (1 min), mean ± SD (range)	7.55 ± 1.5 (3–9)	7.89 ± 1.5 (1–9)	2.62	.009
Apgar score (5 min), mean ± SD (range)	8.83 ± 0.6 (6–10)	8.73 ± 1.0 (1–10)	0.14	.89
Birth weight, mean ± SD (range), kg	3.28 ± 0.48 (2.3–4.6)	3.30 ± 0.63 (1.0–4.5)	0.23	.82
Gestational age, mean ± SD (range), wk	39.0 ± 1.7 (33–42)	38.9 ± 2.3 (28–42)	0.41	.68
Prematurity, N (%)	9 (10.7)	17 (10.1)	0.15	.88
Caesarean section, N (%)	14 (16.7)	45 (26.8)	1.83	.067
SCN admission, N (%)	15 (17.9)	17 (10.1)	1.73	.084
Timely SCN discharge, N/N (%)[b]	11/15 (73.3)	2/17 (11.8)	Exact	< .001
No. of days in SCN, mean ± SD (range)	1.3 ± 3.4 (3–21)	12.5 ± 3.4 (3–77)	3.42	< .001

[a]Reported are N (%) for categorical measures and mean ± SD (range) for continuous measures. χ^2 and z statistics are reported for dichotomous and continuous measures, respectively, based on least-squares and logistic regression modeling with adjustment for clustering on matching, except that Fisher exact test was used with cell counts ≤ 10.
[b]Timely discharge is leaving SCN at same time as mother's discharge.
Abbreviation: SCN = special care nursery of neonatal intensive care unit.

Table 4. Neonatal Outcomes Versus Antidepressant Exposure Type[a]

Measure	SRIs (N = 42)	TCAs (N = 37)	Statistic[c]	p Value
Prematurity, N (%)	3 (7.1)	6 (16.2)	Exact	.17
Low birth weight, N (%)	1 (2.4)	2 (5.4)	Exact	.58
SCN admission, N (%)	5 (11.9)	11 (29.7)	z = 3.48	.062
Timely SCN discharge, N/N (%)[b]	4/5 (80.0)	7/11 (63.6)	Exact	.98
Apgar score (1 min), mean ± SD	7.43 ± 1.70	7.57 ± 1.30	z = 0.91	.36
Apgar score (5 min), mean ± SD	8.86 ± 0.52	8.78 ± 0.63	z = 0.36	.72

[a]Reported are N (%) for categorical measures and mean ± SD for continuous measures. z Statistics are based on generalized linear modeling methods to contrast the treatment-type subgroups, except that Fisher exact test was used with cell counts ≤ 10. Five subjects taking other types of antidepressants are not included.
[b]Timely discharge is leaving SCN at same time as mother's discharge.
[c]TCA/SRI risk ratio = 2.50 (95% CI = 0.95 to 6.56).
Abbreviations: SCN = special care nursery of neonatal intensive care unit, SRIs = serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

for neonatal jaundice (N = 1). The 17 infants of controls who required such special care were also admitted for a range of indications, such as meconium aspiration and pneumothoraces (N = 1), apnea (N = 3), respiratory distress (N = 3), to rule out sepsis (N = 3), or suspected congenital cardiac abnormalities such as ventricular septal defect and patent foramen ovale (N = 2). Antidepressant-exposed neonates admitted to such specialized units remained there for an average of 11.2 fewer days than unexposed neonates and were 6.2 times more likely to be discharged from the hospital at the same time as their mothers (Table 3).

Effect of Antidepressant Class

The incidence of adverse neonatal outcomes following exposures to SRIs versus TCAs was very similar (Table 4). There was a trend toward higher risk of special care admission following exposure to a TCA versus SRI (29.7% vs. 11.9%), but this increase was not statistically significant (p = .062; Table 4). Prematurity, low birth weight, and Apgar scores did not differ by class of antidepressant (Table 4).

DISCUSSION

Many women with major affective or anxiety disorders are withdrawn from psychotropic medication just before or during pregnancy, a decision driven largely by fear of adverse effects of prenatal exposure to psychotropic medications. Consequences of such treatment discontinuation, particularly when done abruptly or rapidly such as when an unexpected pregnancy is diagnosed, are high rates of depressive relapse during pregnancy and the postpartum period.[6,7] Depression during pregnancy is not a benign event and has been associated with increased risk of complications at delivery, disrupted maternal-infant attachment, and potentially negative effects on fetal and neonatal development.[28–32] Growing awareness that comprehensive risk/benefit considerations must include a careful consideration of the mother's psychiatric well-being has led to more active interventions that include maintaining psychotropic medication during pregnancy and the neonatal period.[33] In turn, this shift in practice makes information regarding the reproductive safety of various psychotropic drugs all the more important.

The present observations indicate no clinically important differences in maternal or neonatal outcomes between 84 cases of women exposed to antidepressants during pregnancy and an age- and parity-matched sample of 168 unexposed controls (Table 3). While several recent studies have reported lower birth weight and shorter gestational age in antidepressant-exposed neonates,[8,9,12] the current report, as well as several other studies, observed no differences in birth weight or gestational

age between exposed and nonexposed groups.[10,11,18,19,22,23] Among antidepressant-exposed newborns, there were minor and transiently lower Apgar scores at birth. It is reassuring to note that in this and other studies that have demonstrated lower Apgar scores,[19,23] the differences in Apgar scores between exposed and nonexposed infants have been small (less than 1 point), and average Apgar scores in the exposed children remained high (above 7). Clinically, a score of 7 or greater at 5 minutes suggests that the baby's condition is good to excellent.

Among the antidepressant-exposed neonates, there was a nonsignificantly higher risk of needing special care after delivery, as well as fewer surgical deliveries (Table 3). Indications for special or intensive care tended to be less serious and admissions briefer among the newborn cases than among controls and did not include any indications of neuromotor or other behavioral abnormalities. The increased prevalence of special care admissions among antidepressant-exposed newborns accords with several earlier reports involving in utero exposure to SRIs.[22,23] In this study, rates of special care admission were not affected by antidepressant class (SRI vs. TCA, Table 4).

Interpretation of the tendency toward increased use of special or intensive services for antidepressant-exposed newborns is not straightforward since a number of factors influence the decision to use such services. They include maternal medical and psychiatric illness before or during pregnancy, high-risk deliveries based on obstetrical factors, known prenatal exposure to putative toxins, and biases of clinicians or local clinical traditions of certain institutions, particularly tertiary care facilities. (In this study, infants born in tertiary care facilities were about twice as likely to be admitted to the special care nursery than those born in a community hospital.) Thus, the decision to admit a newborn to a special care nursery may represent a reasonable precaution for an infant exposed to medication in utero and may not be an indication of a serious problem related to antidepressant exposure. This hypothesis is supported by the finding that the duration of stay in the special care nursery was much shorter for the antidepressant-exposed children than for nonexposed children, suggesting that they may have been admitted only for prudent observation.

This small survey study has a number of obvious limitations. Even with a total sample of 84 cases and 168 controls, the statistical power was probably adequate to detect differences in continuous variables such as Apgar scores, gestational age, birth weight, and days in special care, but more limited for the several binary outcomes that we considered (Table 3). With samples of the size available in this study, we estimate that the incidence of a binary adverse outcome would need to be nearly 4 times greater among the 84 cases than in 168 controls in order to be detected as a statistically significant difference. Obviously, none of the outcomes reported here were close to that level of difference, indicating that much larger samples would be required to detect differences on the order of 2-fold, or less. Additional limitations are the retrospective nature of the study and reliance on sometimes incomplete and potentially inaccurate clinically recorded data. Another methodological limitation is the lack of assessments of maternal mood during pregnancy or at the time of delivery. Ample evidence exists that depression and/or anxiety in the mother may contribute to poor neonatal outcomes, including premature delivery and low birth weight.[27,30]

The findings of this study are particularly timely in light of the recent FDA-required change in the labeling of SRI antidepressants, which warn of putative neonatal behavioral toxicity and recommend discontinuation of such treatment prior to delivery.[25] While multiple reports have indicated a spectrum of adverse outcomes among infants with histories of fetal antidepressant exposure,[18,19,21] the clinical significance of these symptoms has not been elucidated. In fact, even when noted, clinical intervention has not been required.[34] The present findings, though limited in statistical power and not specifically designed to detect possible subtle neurobehavioral differences between drug-exposed and unexposed neonates, provide no indication of serious maternal or neonatal risks associated with exposure to antidepressants in general or to SRIs in particular (Tables 3 and 4). In weighing the potential risks and benefits of continuing versus discontinuing antidepressant treatment during pregnancy, we again recommend that the impact on maternal health and, indirectly, on fetal stress, be considered. The risks associated with discontinuing ongoing medication of any type, especially abruptly, must be weighed against the limited evidence of major or sustained adverse effects on the newborn of continued prenatal drug exposure.

Drug names: bupropion (Wellbutrin and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), nortriptyline (Pamelor and others), paroxetine (Paxil and others), phenelzine (Nardil), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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