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A Prospective, Naturalistic, Blinded Study of Early Neurobehavioral Outcomes for Infants Following Prenatal Antidepressant Exposure

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Abstract

Objective—This study examined the potential effects of antidepressant exposure in pregnancy on early infant neurobehavioral outcomes.

Method—In this prospective, naturalistic study, neurobehavioral assessments using the Brazelton Neonatal Behavioral Assessment Scale (BNBAS) were completed by blinded raters between March 2001 and August 2005 on 64 infants who were born to mothers in 1 of 3 categories: (1) women with a history of *DSM-IV*-diagnosed major depressive disorder (MDD) who were treated with antidepressants during pregnancy, (2) women with a history of *DSM-IV*-diagnosed MDD who discontinued or chose not to be treated with antidepressants during pregnancy, and (3) a nonpsychiatric control group. Summary scores for the BNBAS were obtained within the first week of life and at 6 to 8 weeks of age.

Results—No significant differences were observed between groups at either the first week after delivery or at 6 to 8 weeks of age on any of the summary scores for the 7 major clusters of the BNBAS.

Conclusions—Antidepressant exposure during pregnancy does not appear to have major adverse effects on indices of early infant neurobehavioral development during the first 2 months of life as assessed by the BNBAS. While this finding is encouraging, further studies with larger samples and longer follow-up are needed.

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The highest prevalence of depressive disorders in women occurs during the childbearing years.[1] Pregnancy does not protect women from depression,[2] and clinically significant depressive symptoms affect up to 20% of pregnant women.[3] For women with histories of major depressive disorder (MDD) who discontinue antidepressant medication close to the time of conception, rates of relapse are as high as 68%.[4] Although many women will experience depressive symptoms that may warrant pharmacologic treatment with antidepressants,[5] few studies have examined the impact of in utero exposure to antidepressants on the neurobehavioral development of the infant.

To date, 10 prospective studies[6–15] and 1 retrospective study[16] have reported neurodevelopmental outcomes for infants with prenatal exposure to antidepressants, with a range of follow-up from 2 months to 4 to 6 years. Six of the prospective studies reported no adverse neurobehavioral effects of in utero antidepressant exposure, with assessments that included a neurologic examination,[6] the Bayley Scale of Infant Development,[7,8,12] the Reynell Developmental Language Scale,[8] and both a videotape assessment of mother-child interaction (Crowell Procedure) and a Child Behavior Checklist/Child Teacher Report.[13] A retrospective study by Simon et al[16] compared developmental outcomes at 2 years of age from pediatric records and found no differences between the 185 children exposed to selective serotonin reuptake inhibitors (SSRIs) and the 209 exposed to tricyclic antidepressants (TCAs) compared to matched unexposed control groups. While these negative studies are reassuring, differences in methodology, characterization of perinatal antidepressant exposure, and overlap in infant cohorts between several studies preclude definitive conclusions. Furthermore, 4 additional studies suggest that in utero antidepressant exposure is associated with adverse effects on early neurobehavioral development.[10,11,14,15]

The current study was designed to expand the small extant literature by combining rigorous, prospective, early assessment and documentation of prenatal medication and depression exposure with standardized, blinded, and repeated early newborn and infant neurobehavioral assessments utilizing a structured instrument, the Brazelton Neonatal Behavioral Assessment Scale (BNBAS).[17] In this prospective study, we compared BNBAS scores for infants of mothers with a history of MDD who were either treated or not treated with antidepressants in pregnancy and a nonpsychiatric control group. The BNBAS was originally designed as a clinical instrument to document the infant's contribution to the parent-infant system,[18] and it has been extensively utilized in research studies of early neurodevelopment, including those of at-risk infants, and studies of the effects of obstetric medications, mode of delivery, and/or maternal substance abuse. In the present study, we hypothesized that infants of mothers with prenatal antidepressant treatment would demonstrate adverse effects on neurobehavioral development, with less optimal performance on the BNBAS when compared to unexposed infants.

METHOD

This study, a prospective, naturalistic, blinded design, was conducted at the University of California at Los Angeles (UCLA) Semel Institute for Neuroscience and Human Behavior and approved by the UCLA Institutional Review Board. Participants included infants of subjects from a prior study by our group.[19] Ninety women who completed the original study were invited to participate in a follow-up study of their infant's development. Sixty-four (71.1%) of these women agreed and gave written informed consent for follow-up. Maternal demographic, and clinical characteristics for the original cohort are described in the study by Suri et al.[19] There were no significant demographic differences between the original cohort and those participating in the current study. Substance use, including cigarettes and alcohol, was uncommon among participants. In addition, birth outcomes for infants of mothers from the original study who agreed to participate in the follow-up study versus those who

declined participation (gestational age at birth, preterm birth, birth weight, Apgar scores, and special care nursery [SCN] admission) were comparable.

All mothers included medically healthy women between the ages of 18 and 45 who were enrolled in the original prospective study in the first trimester of pregnancy. Women with a *DSM-IV* lifetime diagnosis of MDD[20] were categorized into 1 of 2 groups: (Group 1) women treated with antidepressant medication (AD) during pregnancy; and (Group 2) women not treated with AD at all in pregnancy or those who discontinued AD in the first trimester and/or had less than 10 days' exposure during the first half of pregnancy. A third group of women (Group 3) with no Axis I SCID diagnosis served as controls. The original investigation excluded women who were actively suicidal, met *DSM-IV* criteria for another current Axis I disorder, had a positive urine drug screen, or used medications with documented adverse effects on the fetus. All of the women in Group 1 took antidepressants for the second and third trimesters of pregnancy, with the majority taking medications for all 3 trimesters. Proportions from each of the 3 original groups that participated in this follow-up study were similar to each other (67% for Group 1, 77% for Group 2, and 74% for Group 3). Maternal mood was assessed at each monthly visit with the mood module for the Structured Clinical Interview for *DSM-IV* (SCID-IV Mood Module)[18] and the 21-item Hamilton Depression Rating Scale (HDRS).[21] Gestational age was determined from last menstrual period and verified by early ultrasound.[19]

Infants were assessed with the BNBAS within the first week after delivery and again at age 6 to 8 weeks. The BNBAS was performed by 1 of 2 raters blinded to maternal psychiatric and medication status. Both raters were trained and certified to .90 reliability by a BNBAS certification training program. The BNBAS includes 28 behavioral items and 18 reflex items that are administered in a particular sequence. The individual items are specified in Table 1. Items of the BNBAS are categorized into 7 clusters for scoring purposes; these clusters reduce the dimensionality of data, and they have been used by other studies of prenatal exposure and infant outcomes.[22–24] Clusters include (1) *Habituation,* defined as the ability to respond to and inhibit discrete stimuli while asleep; (2) *Orientation,* defined as the ability to attend to visual and auditory stimuli and the quality of overall alertness; (3) *Motor,* defined as a measure of motor performance and the quality of movement and tone; (4) *Range of state,* defined as a measure of infant arousal and state lability; (5) *Regulation of state,* defined as a measure of the infant's ability to regulate his or her state in the face of increasing levels of stimulation; (6) *Autonomic stability,* defined as signs of stress related to homeostatic adjustments of the central nervous system; and (7) *Reflexes,* defined as the number of abnormal reflexes.

The first BNBAS examination was performed within 1 week of delivery, at the hospital or in the neonate's home. The second assessment was performed between 6 to 8 weeks after delivery, either at UCLA or in the infant's home. To ensure optimal conditions for examination, the infant was tested midway between feedings, in a quiet, semidarkened room. The habituation cluster was administered first and only omitted if the infant was not in the appropriate sleep state. Primary outcome measures included summary scores for the 7 cluster groups.

Data Analysis

Outcome measures were analyzed for infants of the 3 original groups of mothers: (1) women with a history of MDD who were treated with antidepressants during pregnancy, (2) women with a history of MDD who discontinued or chose not to be treated with antidepressants during pregnancy, and (3) a nonpsychiatric control group. Scores for infants on the 7 primary outcome variables (habituation, orientation, motor, range of state, regulation of state, autonomic stability, and reflexes) were compared among groups using analysis of

covariance. Analyses were repeated, controlling for gestational age at delivery. To determine if depressive symptoms, operationalized as mean HDRS scores over the course of pregnancy, had an effect on outcome variables independent of group membership, a general linear model was used to predict BNBAS scores from both independent variables, group membership, and depression as well as their interaction. To determine if maximum depression or depression in the postpartum period had an effect on outcome, parallel analyses of the main summary scores were conducted, controlling for maximum HDRS scores during pregnancy and HDRS scores at 4 and 8 weeks after delivery. Following analysis of the primary hypotheses, additional exploratory analyses were conducted on the individual items of the BNBAS. The achieved significance levels were evaluated both as independent hypotheses tests and using Bonferroni correction to control for inflated type I error rates due to multiple testing.

RESULTS

Analyzable prospective data were available for 59 infants at the first assessment, within 1 week of delivery (Time 1) and for 57 infants at the second assessment, 6 to 8 weeks postpartum (Time 2). Infants included those born to women with a history of MDD taking medication during pregnancy (n = 33), women with a history of MDD not taking medication during pregnancy (n=16), and women from a nonpsychiatric control group (n = 15). For infants who participated in the current study, those of mothers with prenatal antidepressant treatment across pregnancy were born significantly earlier compared to unexposed and control infants (mean ± SD = 38.1 ± 1.3 weeks versus 39.2 ± 1.0 weeks and 39.1 ± 1.5 weeks, respectively; $P = .01$). Other birth outcome variables for the 3 groups of infants in the current study, including birth weight, Apgar scores, preterm birth, and SCN admissions, were not significantly different (Table 2; $P > .05$ for all variables). Of the infants in the current study, 81% had BNBAS assessments at 1 week and again at 6 to 8 weeks of age. There were no significant differences in demographic or obstetric outcome variables between those infants with assessments at one versus both time points.

Despite differences in gestational age, there were no significant differences in summary scores of the BNBAS among the 3 study groups. Summary scores for the 7 clusters, presented in Table 2, were not significantly different among groups at either Time 1 or Time 2. When individual items from the major clusters were examined, some significant differences were noted (rapidity of buildup under the range of state cluster at Time 1, inanimate auditory under the orientation cluster at Time 2, and defense under the motor cluster at Time 2; Table 2). Following Bonferroni correction, however, none of the individual item differences remained significant.

Postpartum mood was assessed with the HDRS at 4 and 8 weeks after delivery (Table 2). Postpartum HDRS scores did not affect outcome variables (all P values >.05). While the percentage of male and female infants was not significantly different, summary scores for regulation of state and autonomic stability showed a sex effect. Girls demonstrated greater ability for state regulation, with higher mean±SD scores (4.85 ±0.00 vs 4.15 ±0.83 for boys; $P = .018$), and boys demonstrated greater autonomic stability, with higher mean ± SD scores (7.69 ± 0.63 vs 7.39 ± 0.89 for girls; $P = .031$). In an analysis of sex-by-group effect, there were no significant findings in any of the major clusters.

The majority of infants exposed to antidepressant medications during pregnancy were exposed to sertraline (36%) and fluoxetine (38%), with mean±SD maternal daily doses at delivery of 90.5 ±50.3 mg and 22.5 ± 7.5 mg, respectively. In an analysis comparing BNBAS outcomes by medication group (sertraline, fluoxetine, and other antidepressants)

and the nonpsychiatric control group, there were no significant differences for any of the summary scores.

Scores on the 21-item HDRS ranged from 0 to 36, with a mean of 9.3 during pregnancy. Depression, defined by mean HDRS scores across pregnancy (Table 2), and the interaction among groups (Group 1, Group 2, or Group 3) and depression did not have significant effects on BNBAS scores. Additionally, the relationship between maximum severity of depression (defined by maximum HDRS scores during pregnancy) and BNBAS scores was not significant. Lastly, antidepressant exposure, when controlling for depression, did not significantly change the results reported above.

DISCUSSION

This study contributes to the small but expanding literature that suggests that prenatal antidepressant use does not appear to have major adverse effects on infant neurobehavioral development.[6–9,12,13,16] Our prospective study with comparable numbers of subjects to previously published studies found no significant differences in blinded neurobehavioral assessments shortly after delivery and within 2 months of age among infants of mothers with a history of major depressive disorder and prenatal antidepressant treatment, infants of mothers with a history of major depressive disorder with minimal to no prenatal antidepressant exposure, and infants of healthy control mothers. The scale used, the BNBAS, is sensitive to medication effects, and our results can be contrasted with those of studies of other prenatal exposures, particularly cocaine, that utilize the BNBAS to assess neurobehavioral outcome. Morrow et al,[25] for example, found consistent but subtle deficits associated with prenatal cocaine exposure on almost all clusters of the BNBAS, partly mediated by effects on fetal growth, with effects being most pronounced in infants with exposure in all 3 trimesters. Our results, from a well-characterized and prospective sample, comport with the majority of studies of infant outcome of antidepressant exposure in pregnancy, and they add to the small but important body of literature.[6–8,12,13,16]

In contrast to our study, some earlier studies[10,11,14] have reported neurobehavioral effects of antidepressant exposure in utero. Differences in outcome between some of these positive studies and our study may be related to design (cross-sectional versus prospective, blinded versus nonblinded), the age at which infants were assessed, the method of infant or child assessment, a potential confound with other psychotropic medications, and a potential confound with substance abuse (which the mothers in our study were screened out for early in pregnancy if positive).

Our study did find differences in 3 of the individual items from the major clusters of the BNBAS (rapidity of buildup under the range of state cluster at Time 1, inanimate auditory under the orientation cluster at Time 2, and defense under the motor cluster at Time 2); however, these were no longer significant after Bonferroni correction. While the BNBAS assesses the physiologic, motor, slate, and attentional/interactional dimensions of infant neurobehavior, it is possible that SSRIs may influence an aspect of development that this scale does not measure. Although this study conducted 2 serial BNBAS assessments, it is also possible that additional later assessments would have captured a change in neurobehavioral development that becomes apparent in infants at an older age.

The current study attempted to isolate the effects of antidepressant exposure on neurobehavioral development by using a detailed prospective design with serial blinded assessments. Our study has several limitations, including a small sample size, a maternal population with homogenous demographic characteristics (educated, married, early prenatal care, and lack of substance use), lack of control for the setting of the BNBAS (home versus

hospital), and grouping of multiple individual antidepressants. While the difference in size between our 3 groups is a limitation that may have reduced the power of our within-group comparisons, the larger sample size of our main group of interest (history of MDD, taking antidepressants) provided more precise parameter estimates within that group. To ensure that nonsignificant findings were not due to small sample size, these results should be replicated in future large-scale studies with larger sample sizes. Future studies should also look at medication class (eg, SSRI, serotonin-norepinephrine reuptake inhibitor, TCA) and individual medications within an antidepressant class (eg, SSRIs) and also conduct repeated assessments over a longer period of follow-up, to support more specific information on neurobehavioral outcome to guide clinical recommendations. Other factors to consider include the limited normative base of the BNBAS, with results that can be influenced by numerous subtle factors, and the inability of our study to examine the effects of duration of exposure on neurobehavioral outcome, since most of the women who took antidepressants did so for the duration of pregnancy.

While our study attempted to control for history of major depressive disorder, women were not required to have active symptoms of depression at study entry. Most of our subjects were not severely depressed during pregnancy, and thus we cannot address the impact of depression per se on neurobehavioral outcomes. It is interesting to note that both treated and untreated depressed groups in this study had similar, relatively low depression scores across pregnancy. Scores may have been comparable for a variety of reasons. One possibility is that women in the treated group attempted to decrease or wean their medication and became symptomatic. Women who became symptomatic may have been advised by their treating psychiatrist to start medication. A third possibility is that women who were severely depressed and untreated may not have met inclusion criteria or been able or willing to participate in this study.

Overall, our study found that antidepressant use in pregnancy was not associated with significant neurobehavioral effects in infants, as assessed by the major clusters of the Brazelton Neonatal Behavioral Assessment Scale. Our study contributes to the small body of literature suggesting a lack of adverse neurobehavioral outcomes for infants exposed in utero to antidepressants. However, given the limited literature on infant neurobehavioral outcome with prenatal antidepressant exposure, future larger-scale studies are warranted. Any decision regarding treatment of depression during pregnancy must be made carefully, individually weighing the risks and benefits of treatment versus lack of treatment for both mother and developing infant.

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- Women are vulnerable to experiencing depression during the childbearing years.
- Prenatal antidepressant use does not appear to have major adverse effects on early infant neurobehavioral development.
- Clinicians can help guide patients in making pharmacologic treatment decisions for the treatment of depression during pregnancy, carefully weighing the risks and benefits to both the mother and the developing infant.

Table 1

Clusters for the Brazelton Neonatal Behavioral Assessment Scale

Habituation
Response decrement to light
Response decrement to rattle
Response decrement to bell
Response decrement to pin-prick
Orientation
Fixate and track inanimate visual object
Fixate and track animate visual object
Response to inanimate auditory stimuli
Response to animate auditory stimuli
Alertness
Motor
General tone
Maturity of movements
Pull-to-sit: measure of traction, head control, and strength of neck muscles
Defensive movement
Activity: measure of spontaneous and elicited activity
Range of state
Peak of excitement: amount of motor activity and crying
Rapidity of buildup: use of states in shift from quiet to agitated states
Irritability: frequency of upsetness, nature of stimuli that cause irritability
Lability of state
Regulation of state
Cuddliness: response to being held
Consolability
Self-quieting: activity infant initiates to quiet herself when crying
Hand-to-mouth: attempt by infant to comfort himself/herself
Autonomic stability
Tremulousness
Startles
Lability of skin color
Reflexes

Table 2

Demographic/Clinical Characteristics and BNBAS Results for Infants Exposed to Antidepressants, Infants Without Antidepressant Exposure, and Healthy Controls

	Maternal Groups			Statistic		
Characteristic	**History of MDD, Taking AD (n = 33)**	**History of MDD, No AD (n = 16)**	**Controls (n = 15)**	***F***	***df***	***P***
Maternal age, mean (SD), y	34.0 (3.7)	32.7 (4.7)	34.7 (3.7)	1.11	2,61	.34
Education, mean (SD), y	17.3 (2.2)	17.25 (2.7)	18.5 (2.2)	1.56	2,61	.21
Parity, mean (SD)	2.4 (1.3)	2.4 (1.5)	1.9 (0.9)	0.68	2,61	.58
HDRS score, mean (SD)	10.2 (3.3)	10.4 (4.4)	6.2 (2.8)	7.57	2,61	<.01
Maximum HDRS score across pregnancy, mean (SD)	18.5 (55)	16.4 (6.4)	10.7 (1.2)	9.57	2,61	<.01
HDRS scores at 8 wk postpartum, mean (SD)	6.8 (5.8)	9.1 (6.1)	4.5 (3.1)	2.05	2,50	.14
Delivery outcome						
Gestational age,[a] mean (SD), wk	38.1 (1.3)	39.2 (1.0)	39.1 (1.5)	5.33	2,61	<.01
Preterm births (<37 wk), n (%)	4 (12)	0	1 (7)	3.34	2	.19
Birth weight, mean (SD), kg	3.3 (0.6)	3.4 (0.4)	3.3 (0.4)	0.46	2,61	.63
Apgar score, mean (SD)						
At 1 minute postpartum	7.8 (1.2)	8.2 (0.8)	8.0 (0.7)	0.75	2,55	.48
At 5 minutes postpartum	8.8 (0.4)	8.9 (0.3)	9.0 (0)	1.83	2,55	.17
				X^2	*df*	*P*
Special care nursery admissions, n (%)	6 (18)	2 (12)	0 (0)	4.88	2	.09
Male offspring, n (%)	18 (55)	8 (50)	10 (67)	0.97	2	.62
BNBAS Scores, mean (SD)						
Time 1: 1 wk of age	n = 31	n = 14	n=14	*F*	*df*	*P*
Habituation	5.90 (2.27)	7.1 (2.17)	6.06 (1.90)	0.58	2,31	.56
Orientation	4.68 (1.93)	4.84 (1.77)	5.01 (1.75)	0.12	2,48	.88
Motor	5.15 (0.72)	5.31 (0.79)	5.03 (0.69)	0.51	2,55	.61
Regulation of state	5.39 (1.19)	5.67 (1.23)	4.61 (1.87)	2.12	2,54	.13
Range of state	3.29 (1.01)	3.68 (0.65)	3.47 (1.01)	0.79	2,54	.46
Rapidity of buildup	2.33 (1.57)	3.75 (2.05)	3.18 (1.40)	3.28	2,47	.05*
Autonomic stability	7.06 (0.97)	6.76 (1.45)	7.41 (0.63)	1.29	2,55	.28
Reflexes	2.32 (1.70)	1.86 (1.35)	1.86 (1.17)	0.70	2,56	.50

Characteristic	Maternal Groups			Statistic		
	History of MDD, Taking AD (n = 33)	History of MDD, No AD (n = 16)	Controls (n = 15)	*F*	*df*	*P*
Time 2: 6–8 wk of age	n = 31	n = 13	n = 13	*F*	*df*	*P*
Habituation	6.04 (2.12)	4.50 (1.22)	8.75 (0.00)	2.16	2,11	.16
Orientation	6.17 (2.13)	6.87 (0.85)	6.84 (1.68)	1.17	2,54	.32
Inanimate auditory	4.93 (2.11)	6.10 (0.74)	6.64 (1.29)	4.35	2,45	.02*
Motor	5.89 (0.71)	6.20 (0.74)	5.94 (0.52)	0.97	2,54	.39
Defense	7.19 (0.91)	7.00 (1.16)	6.31 (1.18)	3.39	2,54	.04*
Range of state	3.14 (0.96)	3.25 (1.04)	3.42 (0.96)	0.38	2,54	.68
Regulation of state	4.46 (1.05)	4.29 (0.95)	4.63 (0.77)	0.41	2,54	.67
Autonomic stability	7.48 (0.75)	7.67 (0.61)	7.61 (0.94)	0.31	2,54	.74
Reflexes	3.13 (2.45)	2.46 (1.61)	1.92 (1.38)	1.65	2,54	.20

[a]On the basis of last menstrual period.

*Not significant after Bonferroni correction.

Abbreviations: AD = antidepressant medication, BNBAS = Brazelton Neonatal Behavioral Assessment Scale, HDRS = 21-item Hamilton Depression Rating Scale, MDD = major depressive disorder by SCID.