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Prenatal depression effects on the fetus and the newborn

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Abstract

Prenatal mood and biochemistry levels were assessed in women with ($N = 70$) and without ($N = 70$) depressive symptoms during their second trimester of pregnancy. At the neonatal period maternal and neonatal biochemistry, EEG and vagal tone levels were assessed, neonatal behavioral states were observed and the Brazelton neurobehavioral assessment was conducted. The mothers with depressive symptoms had higher prenatal cortisol levels and lower dopamine and serotonin levels. Mothers with depressive symptoms were also more likely to deliver prematurely and have low birthweight babies. The newborns of mothers with depressive symptoms had higher cortisol levels and lower dopamine and serotonin levels, thus mimicking their mothers prenatal levels. On the Brazelton Scale, the newborns of depressed mothers had less optimal habituation, orientation, motor, range of state, autonomic stability and depressed scores. A path analysis was conducted to assess the effects of prenatal depression and the mothers' prepartum biochemistry on gestational age and birthweight. As predicted in the model proposed, prenatal depression was related to prepartum cortisol and norepinephrine levels, and cortisol levels were in turn negatively related to prematurity, and norepinephrine levels were positively related to low birthweight.

Keywords: Fetus; Vagal tone; Depressed mother

1. Introduction

Recent studies on newborns of depressed mothers suggest that depressive-like behavior emerges as early as birth. Inferior performance has been noted, for example, on the Brazelton Neonatal Behavior

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Assessment Scale including lower scores on the orienting and motor scales, greater irritability, lower activity levels, less robustness and more depressive-like behavior (Abrams, Field, Scafidi, & Prodromidis, 1995; Lundy, Field, & Pickens, 1996; Zuckerman, Als, Bauchner, Parker, & Cabral, 1990). Other examples include lesser attentiveness and expressivity during a neonatal imitation paradigm (Lundy et al., 1996).

Physiological and biochemical data converge on the behavioral data suggesting that newborns of depressed mothers are different from birth (Field, 1995; Jones, Field, Fox, Lundy, & Hart, 1998; Lundy, Field, Cigales, & Cuadra, 1997). Newborns of depressed mothers, for example, have been noted to have lower vagal tone and greater relative right frontal EEG activation (Jones et al., 1998). Lower vagal tone and greater relative right frontal EEG activation have also been noted in the depressed mothers of these infants (Jones et al., 1998). Greater relative right frontal EEG activation has been observed in chronically depressed adults even during behavioral remission (Henriques & Davidson, 1990; Tomarken, Davidson, & Henriques, 1990), as well as in older infants of depressed mothers (Dawson, Klinger, Panagitotides, Hill, & Spieker, 1992; Field, Fox, Pickens, & Nawrocki, 1995; Jones, Field, Davalos, & Pickens, 1997). Biochemically, elevated norepinephrine and cortisol levels have been noted in depressed pregnant women (Lundy et al., 1999). The depressed mothers prenatal biochemical profiles were later mimicked by their newborns' biochemical profiles (Lundy et al., 1999).

These data combined suggest that the behavioral, physiological and biochemical differences noted in newborns of depressed mothers may be related to in utero exposure to their mothers different biochemical profiles. In the Lundy et al. (1999) retrospective study, we noted that depressed women had higher cortisol and norepinephrine levels as well as lower dopamine levels during their last trimester of pregnancy. Their newborns subsequently showed the same pattern of elevated cortisol and norepinephrine levels and lower dopamine levels. The same newborns also showed inferior performance on the Brazelton Neonatal Behavior Assessment Scale including the orientation, reflex, excitability and withdrawal clusters. Stepwise regression analyses using the mothers prenatal data revealed that their norepinephrine and dopamine levels during pregnancy significantly predicted their newborns norepinephrine and dopamine levels as well as their Brazelton scores, suggesting a prenatal biochemical influence on neonatal outcome. In the Lundy et al. (1999) study, the mothers elevated norepinephrine levels may have directly affected fetal neurotransmitter/neurohormone levels and/or may have reduced uterine blood flow, indirectly affecting neurobehavioral development.

Very few studies have been conducted on depression effects on fetal development and neonatal outcome. However, those few studies suggest that maternal neurotransmitter/neurohormone levels may affect prenatal development. In studies by Glover and her colleagues, strong relationships have been noted between maternal and fetal cortisol levels (Gitau, Cameron, Fisk, & Glover, 1998; Glover, Teixeira, Gitau, & Fisk, 1999). Maternal norepinephrine on the other is not related to fetal norepinephrine levels but is associated with impaired blood flow, as measured indirectly by elevated uterine artery resistance (Giannakoulopoulos, Teixeira, Fisk, & Glover, 1999). Elevated norepinephrine would be expected to lead to fetal growth deprivation and subsequent low birthweight. Elevated cortisol, on the other hand, would be expected to lead to prematurity, as has been noted by Wadwha, Porto, Garite, Chicz-DeMet, and Sandman (1998). In their study, prematurity was predicted at a 0.98 reliability by elevated corticotropic hormone (a precursor of cortisol) at 28 weeks gestation in the mother.

These prenatal depression neurotransmitter/neurohormone profiles might be expected, then, to alter fetal growth as well as neonatal outcome. Although many fetal behavior studies have been conducted (Lecanuet, Granier-Deferre, & Busnel, 1995), only a few recent ones have explored fetal behaviors in fetuses of depressed mothers (Allister, Lester, Carr, & Liu, 2001; Dieter et al., 2001; Dieter, Emory,

& Ansari, 2002; Monk, Fifer, Myers, & Sloan, 2002). In these studies, fetuses of depressed mothers showed hyperactivity (Dieter et al., 2001), elevated heart rates (Allister et al., 2001) and physiological hyper-reactivity (Dieter et al., 2002; Monk et al., 2002).

The present study improved on our previous studies by being a prospective, longitudinal study with the same sample being repeatedly assessed, first on the mothers' prenatal biochemistry and then on more comprehensive assessments at the neonatal stage that included maternal and neonatal biochemistry, vagal tone, EEG asymmetry and neonatal behavior during sleep and during the Brazelton Neonatal Behavior Assessment Scale. In addition, we wanted to determine in a prospective sample the differential effects of the mother's prenatal/biochemistry on neonatal outcome (birthweight and gestational age). In a hypothesized model based on the literature (Glover et al., 1999; Lundy et al., 1999; Wadwha et al., 1998) and tested by path analysis, elevated prenatal cortisol levels were expected to contribute to prematurity and elevated norepinephrine to low birthweight. Only cortisol and norepinephrine were entered in the path analysis inasmuch as catecholamines crossing the placenta are quickly metabolized by monoamine oxidase (Glover & Sandler, 1986) and only relationships between maternal cortisol and norepinephrine levels and fetal behavior and development have been reported in the literature. Also, based on the literature, the newborns' biochemical profiles were expected to be similar to their depressed mothers' levels during pregnancy, and the newborns' vagal tone and frontal EEGs were expected to mimic their mothers' vagal tone and frontal EEG values. Finally, less optimal performance was expected for the newborns of depressed mothers on the Brazelton Neonatal Behavior Assessment Scale.

2. Methods

2.1. Participants

Pregnant women were recruited during their second trimester ($M = 20.1$ weeks, $R = 16$–28 weeks) from obstetrician–gynecologists offices. The pregnant women were assigned to a depressed (depressive symptoms) or non-depressed group based on their scores on the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). The first 70 women who had elevated scores ($\geq$16) were recruited for the depressive symptom group (M CES-D score = 24.0), while the first 70 women scoring in the normal range ($\leq$12) were recruited for the non-depressed group (M CES-D score = 8.0). Approximately 30% of the women who were interviewed had elevated scores on the CES-D, and none of these women were in treatment or taking psychotropic drugs. The women's medical charts were also screened to exclude any women who showed recreational drug use during pregnancy based on routine drug screens.

The follow-up sample at the neonatal period (following 22% attrition) included 119 women (58 with elevated depressive symptoms scores) of lower-middle socioeconomic status ($M = 3.1$ on Hollingshead, 1975). The women averaged 25.8 years of age, 37% were single, and their ethnicity was distributed: 43% Hispanic, 34% African-American, 14% White Non-Hispanic and 9% Other. Eighty-four percent of the infants were full-term (i.e., >37 weeks GA). A significantly greater number of the infants of mothers with depressive symptoms were born prematurely (25% versus 7%, $P < 0.01$). Twenty-three percent of the infants were low birthweight (i.e., <2500 g). A significantly greater proportion of the infants of mothers with depressive symptoms were low birthweight (34% versus 14%, $P < 0.01$). The infants were tested within 2 days after birth ($M = 1.9$ days). Fifty-eight percent of the depressed group were female infants and 54% of the non-depressed group were female infants. The two groups did not differ on any

of the background variables except the prematurity and low birthweight rates which were then entered as a covariate in the data analyses.

2.1.1. Procedure

At their prescribed ultrasound session (*M* gestational age = 20.1 weeks) the mothers were given the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977), the Spielberger Trait Anxiety Inventory (Spielberger, Gorsuch, & Lushene, 1970), and the Profile of Mood States (POMS) Anger Scale (McNair, Lorr, & Droppleman, 1971). First morning urine samples were obtained from the mothers during the prenatal visit and from them and their newborns within 24 h after delivery. The CES-D was given again shortly after the delivery, and the medical records were used to score the Obstetric Complications Scale (OCS) and the Postnatal Complications Scale (PNS) (Littman & Parmelee, 1978). The Brazelton Neonatal Behavior Assessment Scale (Brazelton, 1984) was also given within the first two days after birth. In addition, at that time, the mothers and newborns EEGs and vagal tone were recorded and the newborns sleep states and activity were coded.

2.1.2. Measures

2.1.2.1. The Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a 20-item self-report scale designed to measure depressive symptoms including depressed mood, feelings of guilt, worthlessness, helplessness and hopelessness, loss of energy and sleep and appetite disturbances (Radloff & Teri, 1986). The 20 symptoms are rated for frequency (over the past week) from rarely or none of the time to most or all of the time. A summary score ranges from 0 to 60 by summing all items. Reliability and validity have been acceptable across a variety of demographic characteristics including age, education, geographic area, and racial, ethnic and language groups (Radloff & Teri, 1986). The CES-D was given to the mother at the time of prenatal recruitment and again within 24 h following delivery. Although 6 mothers crossed over from depressed to non-depressed status, we did not exclude them because they had been depressed prenatally.

2.1.2.2. The State Trait Anxiety Inventory (Spielberger et al., 1970). The State Trait Anxiety Inventory was used to assess anxiety. This 20-question 4-point Likert scale forms a summed score from 20 to 80 for the trait subscale. Higher scores indicate greater anxiety. The Trait Anxiety Scale is comprised of items on how the subject typically feels including: I feel nervous and I feel calm. The scores increase in response to stress and decrease under relaxing conditions (Spielberger et al., 1970). Research has demonstrated that the State Trait Anxiety Inventory has adequate concurrent validity and internal consistency ($r = 0.83$; Spielberger et al., 1970). This scale was included because depression and anxiety are often comorbid states and because Glover et al. (1999) have reported relationships between anxiety and uterine artery resistance, which may affect fetal growth.

2.1.2.3. Profile of Mood States (POMS) Anger Scale (McNair et al., 1971). The POMS Anger Scale consists of 12 items on anger. They are rated on 5-point scales ranging from (0) not at all to (4) extremely. The scale has adequate concurrent validity and good internal consistency ($r = 0.95$; McNair & Lorr, 1964). This scale was included because depression and anger are often comorbid states.

2.1.2.4. First-morning urine samples. First-morning urine samples were collected from the women with and without depressive symptoms at their ultrasound visit and again within 24 h following delivery.

Newborn first morning urine samples were collected in the nursery also within 24 h following delivery. The samples were frozen and sent to Duke University Medical School to be analyzed by lab technicians who were blind to group assignment. The urines were assayed for norepinephrine, epinephrine, dopamine, serotonin and cortisol levels after correcting for creatinine levels. Norepinephrine, epinephrine, and cortisol levels were assessed because of their previously reported positive associations with prenatal depression (Lundy et al., 1999) and serotonin and dopamine because of their negative associations with depression. Dopamine was also assessed because of a recent animal model implicating a negative association between dopamine levels and depression (Weiss, Demetrikopoulos, West, & Bonsall, 1996).

2.1.2.5. Obstetric complications. Obstetric complications were assessed on the Obstetric Complications Scale (OCS; Littman & Parmelee, 1978) which is comprised of 41 items taken from the medical charts and rated as optimal or nonoptimal. Postnatal complications were quantified using the Postnatal Complications Scale (PNS; Littman & Parmelee, 1978) which consists of 10 items rated as optimal or nonoptimal.

2.1.2.6. Sleep/wake behavior. Sleep/wake behavior was continuously videotaped in compressed time (3 h sleep coded in 1 h using time lapse video) for an inter-feeding interval (2–3 h) before the Brazelton was performed on the first afternoon after birth. Thoman's studies of term infants sleep patterns suggest that an interfeeding interval time frame can provide a representative sample (Thoman, 1975), and Sostek and Anders (1975) have used nap recordings of this duration. The videotapes were coded for movements and sleep states that occurred during that period onto a laptop computer according to the procedures we have used in our other sleep studies (Field et al., 1986). Prior to sleep state coding the examiner was trained to 0.90 reliability. An adaptation of Thoman's Sleep State Criteria was used to define sleep/wake behavior categories (Thoman, 1975). Indeterminate sleep was also coded and defined as an uncodable sleep state or one that does not fit the criteria for the six sleep states in Thoman's (1975) system. Sleep was assessed because less quiet and more indeterminate sleep was associated with greater relative right frontal EEG activation in infants of depressed mothers in an earlier study (Jones et al., 1998).

2.1.2.7. The Brazelton Neonatal Behavior Assessment Scale (Brazelton, 1984). The Brazelton Neonatal Behavior Assessment Scale was given on the first afternoon after birth. The Brazelton assessments were performed by researchers who were trained to 0.90 reliability and were blind to the group classification of the mothers and infants. This neurobehavioral examination consists of 28 items, each scored on a 9-point scale, and 20 elicited reflexes, each scored on a 3-point scale. The infant's performance was summarized according to the traditional Lester, Als, and Brazelton (1982) clusters, and Lester and Tronick's (1992) depression, excitability and withdrawal factors.

2.1.2.8. EEG for a baseline measure of relative right or left frontal EEG activation. At the neonatal stage EEG was recorded while the infant was in a quiet alert state in a bassinet. The researcher was blind to the mothers' depression status. EEG and behavior were recorded for 3 min while the infant was awake and alert. We have reported significant one-to-three month stability of EEG asymmetry ($r = 0.45$) (Jones, Field, Fox, Lundy, & Davalos, 1996) as well as significant 3-month to 3-year stability (Jones et al., 1997). At a separate time during the session the mother's EEG was recorded while she sat quietly with

her eyes open for 3 min. EEGs were recorded because both depressed mothers and their infants showed right frontal EEG activation in previous studies by our group (Field et al., 1995; Jones et al., 1998).

2.1.2.9. EEG recording. The EEG for both the mother and infant were recorded using lycra stretchable caps (manufactured by Electro-Cap, Inc.) that were positioned on the subject's head using anatomical landmarks (Bloom & Aneveldt, 1982). Electrode gel was injected into the electrodes at the following sites: F3, F4, P3, P4, and Cz (used as the reference), and impedances were brought below 5000 Ω. Additional electrodes were positioned on the external canthus and above the supra orbit of the right eye to record the subject's EOG, which was used to determine horizontal and vertical eye movement artifacts.

The EEG signals were obtained using a Grass Model 12 Neurodata Acquisition System with filters set at 1 Hz high pass and 100 Hz low pass and a gain of 20,000. Prior to data collection, the signal for each channel was calibrated. The output was directed to a Dell 325 D PC fitted with an Analog Devices RTI-815 A/D board. The sampling rate was 512 samples per second and the data were streamed across the computer screen and then saved to a hard disk using data acquisition sofiware (Snapstream, version 3.21, HEM Data Corp., 1991).

2.1.2.10. EEG analyses. EEG data were analyzed using an EEG analysis software package (EEG Analysis System, version 5.3, James M. Long, 1987–1990). The first step of this process involves the manual elimination of sections of data that are unusable due to artifact (eye movements, muscle activity or technical difficulties). The remaining artifact-free data were spectrally analyzed using discrete Fourier transforms to yield power data for the 1–30 Hz frequency bands in 1 Hz bins. The infant EEG data were spectrally plotted, revealing that the majority of activity fell within the 3–13 Hz frequency bins. The 3–13 Hz frequency band was used in this study and has also been used in previous newborn EEG research (Jones et al., 1998). The standard adult frequency band of 8–13 Hz was used in the mother's EEG analyses. Data analyses were conducted on the natural log power data for both hemispheres in the frontal and parietal regions, as is typically done in depression samples. EEG asymmetry scores were computed by obtaining the difference of the mean log power density scores of a right hemisphere site and its homologous left hemisphere site (LnRight–LnLeft). A score of '0' represents hemispheric symmetry, a negative score represents greater relative right frontal EEG activation and a positive score represents greater relative left frontal EEG activation.

2.1.2.11. Vagal tone. For this measure the mother's and infant's heart rate was recorded for a 3-min period while the infant was in an infant seat and the mother seated on a chair. Vagal tone was recorded because depressed mothers and their infants vagal tone values were similarly low in an earlier study (Jones et al., 1998). Three EKG electrodes were placed on the chest and back regions. The electrodes were connected to a Grass Model 12 Neurodata Acquisition system preamplifier with bandpass frequencies set at 1.0 and 100 Hz and a gain of 2000. The output was directed to a Dell 325 D PC fitted with an Analog Devices RTI-8 15 A/D board. The data were streamed across the computer screen at a sampling rate of 512 samples per second and then saved to a hard disk using data acquisition software (Snapstream, version 3.21, HEM Data Corp., 1991). After scoring for artifact, EKO data were converted to inter-beat intervals (IBI) using an EKG data analysis program (James Long Company, Caroga Lake, NY) and then to vagal tone using Delta-Biometrics, Inc., Mxedit software, which utilizes an algorithm developed by Porges (1991).

Table 1
Means for prenatal self-report measures fetal activity and complications scales (S.D.s in parentheses)

Prenatal variables	Group		*F* value	*P* level
	Depressed	Non-depressed		
Depression (CES-D)	24.0 (6.9)	8.0 (4.5)	82.20	0.001
Anxiety (STAI)	14.7 (6.1)	9.0 (6.0)	37.80	0.001
Anger (POMS)	15.3 (9.0)	5.5 (6.0)	34.80	0.001
Obstetric complications[a]	100.5 (27.7)	105.8 (21.1)	1.10	NS
Postnatal complications[a]	132.1 (36.1)	139.2 (29.7)	1.10	NS

NS: not significant
[a] Higher score is optimal.

3. Results

MANOVAs were performed separately for the prenatal variables (self-report and perinatal complications measures), biochemical data, Brazelton scores and sleep/wake and physiological measures (EEG and vagal tone). Any significant MANOVAs were followed by ANOVAs on the individual variables. Based on the literature and our previous studies the following hypotheses were made: (1) prenatally depressed mothers were expected to have elevated cortisol and norepinephrine levels; (2) their neonates were expected to have similarly high cortisol and norepinephrine levels; (3) the neonates of depressed mothers were expected to have inferior scores on the Brazelton Scale; and (4) the depressed mothers and their infants were expected to have similarly low vagal activity and greater relative right frontal EEG activation. Finally, a path analysis was conducted to assess the relationships between prenatal depression and the mediating prenatal biochemistry variables and neonatal outcome variables.

3.1. Group comparisons

3.1.1. Prenatal data

A significant MANOVA group effect (depressed versus non-depressed) for the set of prenatal variables (Wilk's lambda $F(6, 77) = 38.74$, $P < 0.001$) followed by ANOVAs (*F*s in tables) on the individual variables suggested that mothers with depressive symptoms had (see Table 1): (1) higher prenatal depression (CES-D) scores, as expected; (2) higher prenatal anxiety (STAI) scores; and (3) higher anger (POMS) scores.

3.1.2. Biochemical data

A significant MANOVA (Wilk's lambda $F(5, 102) = 2.91$, $P < 0.02$) followed by univariate ANOVAs on the prenatal biochemical measures suggested that the mothers with depressive symptoms had (see Table 2) elevated cortisol and lower levels of dopamine and serotonin during the prenatal period. A significant MANOVA (Wilk's lambda $F(5, 56) = 2.88$, $P < 0.05$) followed by univariate ANOVAs on the postnatal biochemical measures suggested that the mothers with depressive symptoms had higher norepinephrine levels at the newborn period. A significant MANOVA (Wilk's lambda $F(5, 42) = 2.66$, $P < 0.05$) followed by univariate ANOVAs on the infant biochemical measures suggested that the newborns of mothers with depressive symptoms had higher cortisol levels and lower dopamine and serotonin levels.

Table 2
Means for mothers prenatal and mothers and infants neonatal period cortisol, catecholamine (norepinephrine epinephrine and doparnine) and serotonin levels (S.D.s in parentheses)

	Group		*F* value	*P* level
	Depressed	Non-depressed		
Mothers prenatal				
Cortisol	343.7 (207.7)	263.7 (136.7)	7.9	0.01
Norepinephrine	55.4 (24.9)	49.4 (24.3)	1.7	NS
Epinephrine	6.0 (4.0)	5.3 (3.4)	1.5	NS
Dopamine	285.5 (124.8)	328.3 (127.2)	6.0	0.05
Serotonin	4006.7 (2075.8)	5121.7 (2336.2)	7.0	0.05
Mothers postnatal				
Cortisol	233.6 (158.4)	195.1 (129.0)	1.7	NS
Norepinephrine	41.2 (23.6)	33.6 (16.7)	3.0	0.05
Epinephrine	5.0 (2.3)	4.6 (2.9)	0.8	NS
Dopamine	244.8 (109.5)	264.7 (100.3)	0.7	NS
Serotonin	3861.2 (1511.6)	4803.8 (3483.2)	2.1	NS
Infants postnatal				
Cortisol	549.7 (193.5)	408.8 (200.22)	10.2	0.005
Norepinephrine	66.7 (31.8)	58.9 (41.9)	0.9	NS
Epinephrine	5.3 (3.1)	5.5 (3.4)	0.1	NS
Dopamine	400.0 (213.7)	504.6 (277.5)	3.5	0.05
Serotonin	6027.1 (4663.4)	9115.6 (6451.6)	3.1	0.05

3.1.3. Birth measures

A significant MANOVA (Wilk's lambda $F(10, 81) = 2.25$, $P < 0.05$) followed by univariate ANOVAs suggested that the newborns of mothers with depressive symptoms had inferior scores on the Brazelton Neonatal Behavior Assessment Scale including (see Table 3): (1) habituation, (2) orientation, (3) motor,

Table 3
Mean Brazelton scores (S.D.s in parentheses)

Brazelton scores	Group		*F* value	*P* level
	Depressed	Non-depressed		
Habituation	5.0 (2.2)	5.9 (1.7)	4.3	0.05
Orientation	3.8 (1.3)	4.7 (1.6)	9.4	0.005
Motor	3.9 (1.2)	4.5 (1.0)	6.0	0.05
Range of state	3.4 (1.2)	3.9 (1.1)	4.6	0.05
Regulation of state	4.0 (1.7)	4.3 (1.5)	0.7	NS
Autonomic stability	5.7 (2.0)	6.6 (1.6)	5.7	0.05
Reflexes[a]	2.2 (1.5)	2.2 (1.8)	0.0	NS
Withdrawal symptoms[a]	3.1 (2.5)	2.5 (1.7)	1.4	NS
Excitability	2.1 (1.6)	2.0 (1.7)	0.0	NS
Depressed symptoms[a]	4.0 (3.0)	2.0 (1.4)	16.8	0.001

[a] Lower scores are optimal.

Table 4
Means for neonatal sleep activity EEO and vagal tone measures (S.D.s in parentheses)

	Group		*F* value	*P* level
	Depressed	Non-depressed		
Indeterminate sleep (% time)	54.0 (20.2)	35.5 (24.5)	9.5	0.005
Movement (% time)	71.0 (12.0)	62.0 (17.0)	5.8	0.05
EEG mothers	−0.15 (18)	0.01 (14)	14.6	0.001
EEG infants	−0.06 (10)	0.03 (11)	11.3	0.001
Vagal tone mothers	3.7 (0.24)	4.1 (0.46)	7.9	0.05
Vagal tone infants	4.2 (0.25)	4.7 (1.3)	3.2	0.05

(4) range of state, (5) autonomic stability and (6) depressed factor scores. A significant MANOVA (Wilk's lambda $F(6, 41) = 5.45$, $P < 0.001$) followed by univariate ANOVAs on newborn indeterminate sleep, movement (activity level), and mothers' and infants' EEG and vagal tone measures suggested the following (see Table 4): (1) a greater percent time spent in indeterminate sleep for newborns of mothers with depressive symptoms; (2) a greater percent time spent moving for newborns of depressed mothers; (3) greater relative right frontal EEG for depressed mothers and their newborns; and (4) lower vagal tone for depressed mothers and their newborns.

In order to explore whether differences in birth measures observed in infants of depressed mothers were a result of their mothers' prenatal symptoms of depression, prenatal biochemistry levels and/or low birthweight and prematurity, stepwise multiple regression analyses were conducted on significantly different neonatal outcome variables (see Tables 3 and 4) with prenatal CES-D scores and biochemistry and low birthweight and prematurity entered as the predictor variables. These analyses revealed the following (see Table 5): (1) prenatal symptoms of depression predicted neonatal indeterminate sleep, frontal EEG asymmetry and brazelton motor, orientation, autonomic stability and depression cluster scores; (2) prenatal cortisol predicted neonatal movement and vagal tone; and (3) prenatal norepinephrine

Table 5
Multiple regression analyses on significantly different neonatal outcome variables

Dependent variable	Significant predictors	Pr	R^2	*F*
Indeterminate sleep (% time)	CES-D	0.331	0.11	6.41*
Movement (% time)	Cortisol	0.349	0.12	6.10*
Infants EEG	CES-D	−0.458	0.21	11.95**
Infants vagal tone	Cortisol	−0.283	0.08	4.52*
Brazelton				
Habituation	Norepinephrine	−0.306	0.09	6.71*
Orientation	CES-D	−0.411	0.17	14.64**
Motor	CES-D	−0.328	0.11	8.81**
Autonomic stability	CES-D	−0.241	0.14	5.99*
	Norepinephrine	−0.231		
Depressed symptoms	CES-D	0.363	0.13	11.10**

Pr: partial correlation.
* $P < 0.05$.
** $P < 0.01$.

Table 6
Relations between prenatal depression scores (CES-D), prenatal maternal stress neurohormones (cortisol and norepinephrine) and neonatal outcomes (prematurity and low birthweight—LBWT)

	CES-D	Cortisol	Norepinephrine	Prematurity	LBWT
CES-D	1				
Cortisol	0.524**	1			
Norepinephrine	0.194*	0.271**	1		
Prematurity	0.348**	0.490**	0.158	1	
LBWT	0.308**	0.427**	0.310**	0.563**	1

* $P < 0.05$.
** $P < 0.01$.

predicted brazelton habituation and autonomic stability cluster scores. Low birthweight and prematurity did not significantly predict any of the neonatal outcome variables when prenatal symptoms of depression and prenatal biochemistry levels were taken into account.

3.2. Path analysis

An SEM-based path analysis was conducted using EQS (EQS version 5.7b, Multivariate Software, Inc., 1985–1998) in order to assess the effects of prenatal depression and maternal neurohormone/neurotransmitters on neonatal outcome variables. Missing data were replaced with mean values. Only data for dyads with less than three missing variables were included in this analysis ($N = 119$). Based on previous findings on the relationships between prenatal depression and maternal biochemistry and neonatal outcomes, the hypothesized model examined the direct and indirect (via prenatal biochemistry) effects of maternal depression on prematurity and low birthweight (LBWT). Analyses were conducted using the maximum likelihood estimation procedure on the variance/covariance matrix (Table 6). The independence model that tests the hypothesis that all variables are uncorrelated was easily rejected $\chi^2(10, N = 119) = 138.84$, $P < 0.001$. The hypothesized model was tested next revealing an adequate fit for the model, $\chi^2(2, N = 119) = 6.69$, $P = 0.036$, comparative fit index (CFI) $= 0.96$, RMSEA $= 0.18$ (Fig. 1).

Post hoc modifications were then performed in an attempt to develop a better fitting and simpler model. The Wald test indicated that eliminating the paths between prenatal depression and prematurity, norepinephrine and prematurity and between cortisol and low birthweight would not reduce the fit of the model. As such, in an effort to attain parsimony, these paths were removed. A bidirectional path between maternal cortisol and norepinephrine was added following results of the Lagrange multiplier test. The model was re-estimated, $\chi^2(10, N = 119) = 5.14$, $P = 0.27$, CFI $= 0.99$, RMSEA $= 0.05$, suggesting a significantly better fit for this model (Fig. 2). Analyses of direct effects revealed that prenatal depression was strongly predictive of prenatal cortisol (standardized coefficient $= 0.52$, $P < 0.001$), prenatal norepinephrine (standardized coefficient $= 0.19$, $P < 0.01$), prematurity (standardized coefficient $= 0.35$, $P < 0.001$) and low birthweight (standardized coefficient $= 0.31$, $P < 0.01$). This suggests that higher maternal depression during pregnancy results in elevated cortisol and norepinephrine levels, prematurity, and low bithweight. Furthermore, analyses of indirect effects revealed that the effect of maternal prenatal depression on prematurity (standardized coefficient for indirect effect $= 0.22$, $P < 0.01$) was mediated by cortisol and the effect of prenatal depression on low birthweight (standardized coefficient for indirect effect $= 0.22$, $P < 0.01$) was mediated by norepinephrine.

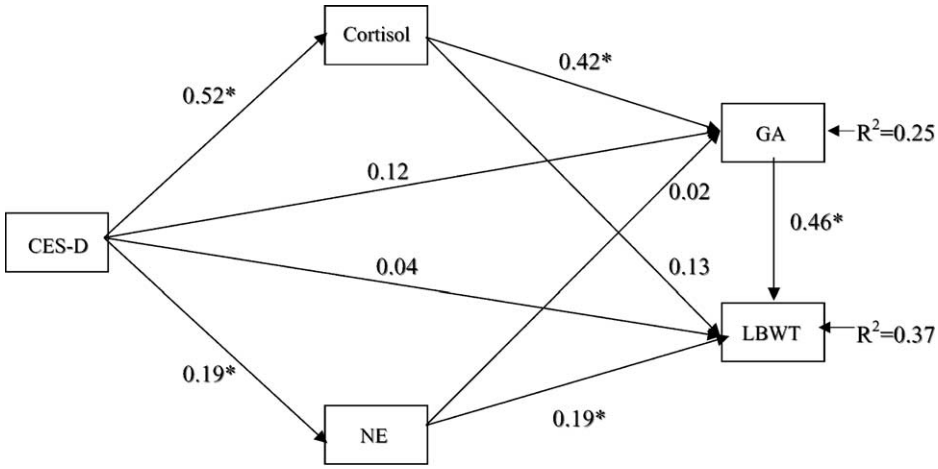

Fig. 1. Hypothesized structural equations model on prenatal depression scores (CES-D), prenatal maternal stress neurohormones (cortisol, CORT; norepinephrine, NE) and neontal outcomes (prematurity, GA; low birthweight, LBWT).

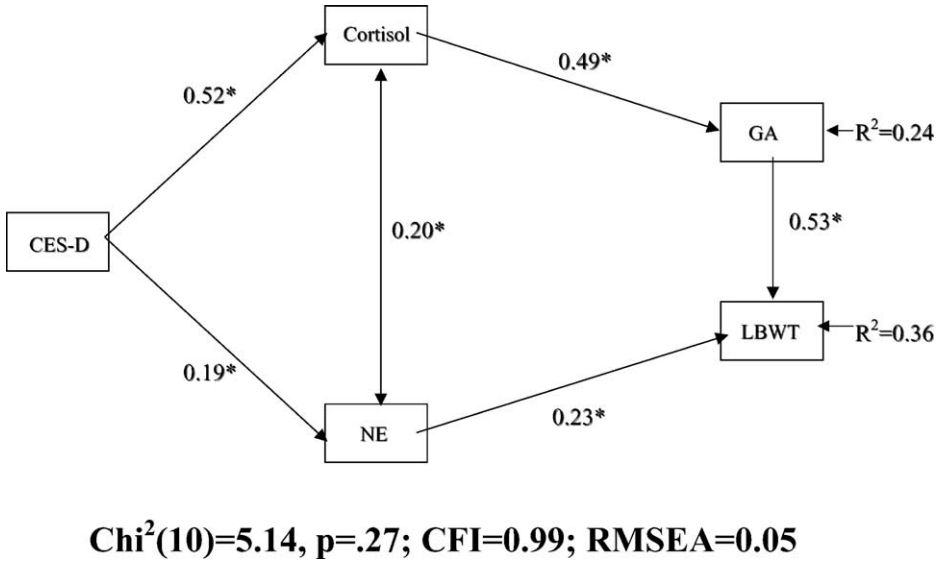

Fig. 2. Final structural equations model on prenatal depression scores (CES-D), prenatal maternal stress neurohormones (cortisol, CORT; norepinephrine, NE) and neonatal outcomes (prematurity, GA; low birthweight, LBWT).

4. Discussion

Several findings in this study replicated earlier findings by our group (Abrams et al., 1995; Jones et al., 1998; Lundy et al., 1999). Regarding the mothers' prenatal biochemistry, the elevated prenatal

cortisol levels in the women with depressive symptoms were consistent with the elevated cortisol levels in depressed pregnant women in the Lundy et al. (1999) study. According to Glover et al. (1999) 40% of the mothers' cortisol crosses the placenta. The depressed serotonin levels in the pregnant women and their newborns were, however, new findings from the current study. This neurotransmitter was not assessed in Lundy et al. (1999). However, the lower serotonin levels were not surprising given the general literature showing that serotonin reuptake inhibitors are effective antidepressants. The lower dopamine levels are consistent with Lundy et al. (1999) and with the recent animal model of Weiss et al. (1996), showing the extensive involvement of the dopaminergic system in depression. The mimicking of cortisol levels in the depressed mothers by their newborns was consistent with our previous study showing that depressed mothers had elevated prenatal cortisol levels, and their neonates had similarly high cortisol levels (Lundy et al., 1999). The similarly low vagal tone and greater relative right frontal EEG of the depressed mothers and their infants had been previously noted by Jones et al. (1998). Other findings that replicated our previous studies were the inferior Brazelton scores (Abrams et al., 1995; Lundy et al., 1999), and the greater percent time in indeterminate sleep (Jones et al., 1998).

The prenatal maternal depression effects on neonatal outcome (prematurity and low birthweight) appear to have been mediated by elevated prenatal cortisol and norepinephrine levels, as predicted by the literature and the model tested in our path analysis. Just as norepinephrine was related to uterine artery resistance and indirectly to blood flow and fetal growth in the study by Glover et al. (1999), norepinephrine was related to fetal growth (low birthweight) in the current study. And just as elevated corticotropin hormone (precursor of cortisol) was related to gestational age in a study by Wadwha et al. (1998), cortisol was related to prematurity in the current study. These data suggest the mediating effects of the mother's prenatal biochemistry on the development of the fetus as manifested by these neonatal outcome measures.

The less optimal neurobehavioral profiles exhibited by infants of depressed mothers was related to their mothers prenatal symptoms of depression and cortisol and norepinephrine levels, and does not appear to be a function of these infant's greater low birthweight and prematurity rates. Prenatal symptoms of depression and biochemistry accounted for between 8 and 21% of the variance in neonatal neurobehavioral profiles. The large proportion of unexplained variance in neonatal neurobehavioral profiles points to additional potential factors that were not accounted for in this study. Future research is needed to evaluate additional prenatal psychosocial, biochemical and physiological factors effects on fetal and neonatal neurobehavior and development. In addition, twin studies and research examining the relationship between paternal and neonatal physiological profiles would be helpful in disentangling the environmental/genetic contributions to neonatal behavior and development.

These data, like our earlier data, highlight the negative effects of prenatal depression on the fetus (Dieter et al., 2001) and the neonate (Field, 1998; Jones et al., 1998; Lundy et al., 1999). Further research is needed on the potential pathways between prenatal biochemistry and neonatal outcomes in depressed mothers including the effects of the comorbid conditions of anxiety and anger. The current data also highlight the need for interventions targeting the reduction of these negative mood states in pregnant women.

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