

# Prenatal depression effects on the fetus and newborn: a review

Tiffany Field<sup>a,b,\*</sup>, Miguel Diego<sup>a</sup>, Maria Hernandez-Reif<sup>b</sup>

<sup>a</sup> *Touch Research Institutes, University of Miami, School of Medicine, P.O. Box 016820, Miami, Florida, 33101, United States*

<sup>b</sup> *Fielding Graduate University, United States*

Received 15 September 2005; received in revised form 1 February 2006; accepted 20 March 2006

## Abstract

A review of research on prenatal depression effects on the fetus and newborn suggests that they experience prenatal, perinatal and postnatal complications. Fetal activity is elevated, prenatal growth is delayed, and prematurity and low birthweight occur more often. Newborns of depressed mothers then show a biochemical/physiological profile that mimics their mothers' prenatal biochemical/physiological profile including elevated cortisol, lower levels of dopamine and serotonin, greater relative right frontal EEG activation and lower vagal tone. Elevated prenatal maternal cortisol is the strongest predictor of these neonatal outcomes. Moderate pressure massage can alleviate these effects including reducing prematurity.

© 2006 Elsevier Inc. All rights reserved.

*Keywords:* Prenatal Depression; Cortisol; Fetus; Newborn

## 1. Pregnancy and birth complications

Depression is prevalent in pregnant women, affecting 10–25% of women (Anderson, Sundstrom-Poromaa, Wulff, Astrom & Bixo, 2003, 2004; De Tychev et al., 2005; Marcus, Flynn, Blow & Barry, 2004; Stowe, Hostetter, & Newport, 2005). Prenatal depression increases in severity from the first to the second trimester (Hoffman & Hatch, 2000), negatively affecting fetal development and neonatal outcome. Prenatal and perinatal complications include higher rates of placental abnormalities (Jablesky, Morgan, Zubrick, Bower & Yellachich, 2005), preeclampsia (Kurki, Hiilesmaa, Raitasalo, Mattila & Ylikorkala, 2000) and spontaneous abortion (Nakano et al., 2004; Sugiura-Ogasawara et al., 2002). Depressed women are also more likely to deliver prematurely (Jesse, Seaver, Wallace, 2003; Moncuso, Schetter, Rini, Roesch & Hobel, 2004; Orr, James & Blackmore Prince 2002), and they often have neonates who require intensive care for postnatal complications including bronchopulmonary dysplasia and intraventricular hemorrhage (Chung, Lau, Yip, Chlu & Lee, 2001).

Neonates of depressed mothers are also at greater risk for being low birthweight (<2500 g) and small for gestational age (<10th percentile) (Field et al., 2004a; Hoffman & Hatch, 2000), with low birthweight being one of the leading causes of fetal morbidity and mortality (National Center for Health Statistics, 2004). As many as 20% of low birthweight infants experience fetal growth retardation, the second leading cause of perinatal mortality (Bernstein & Gabbe, 1996). These infants continue to experience growth retardation across the first year of life (Patel, Rodrigues, DeSouza, 2002; Rahman, Iqbal, Bunn, Lovel & Harrington, 2003).

\* Corresponding author. Tel.: +1 305 243 6781(Business)

E-mail address: [tfield@med.miami.edu](mailto:tfield@med.miami.edu) (T. Field).

Behaviorally, biochemically and physiologically fetuses and neonates of depressed mothers also differ. Fetuses of depressed women show elevated heart rates (Allister, Lester, Carr & Liu, 2001), greater activity levels (Dieter et al., 2001) and increased physiological reactivity (Monk et al., 2004). Newborns of depressed mothers perform less optimally on the Brazelton neonatal behavior assessment scale, and they show less positive affect (Abrams, Field, Scafidi & Prodomidis, 1995; Field, Diego, Dieter, Hernandez-Reif, Schanberg, Kuhn, Yando & Bendell, 2004a; Lundy, Field & Pickens, 1997; Lundy et al., 1999). Their negative affect continues into later infancy (Huot, Brennan, Stowe, Plotsky, & Walker, 2004), and their cortisol responses to mild stressors are predictive of negative affect even at the toddler stage. Infants of depressed mothers also show inferior mental, motor and emotional development (Murray & Cooper, 1997; Patel, Rodriguez & DeSouza, 2002; Sondergaard et al., 2003), and later social and emotional problems during childhood including less emotional well-being as well as internalizing and externalizing problems (Luoma et al., 2001, 2004; O'Connor, Heron, Glover, Golding & ALSPAC Study Team, 2002a, 2002b, 2003).

## 2. Infant neurobehavioral dysregulation

The earliest studies on infants of depressed mothers focused on mother–infant interactions during early infancy. These studies revealed less positive affect, less attentiveness and more fussiness during mother–infant interactions (Field, 1984) as well as during their interactions with non-depressed adults (Field et al., 1988). Physiological measures were also taken during these interactions. In one set of studies, vagal tone was recorded from 3–6-month-old infants of depressed and non-depressed mothers at rest and during interactions with their mother and a stranger. Lower vagal tone may reflect autonomic nervous system dysregulation, and it has been associated with less optimal performance on attention and learning tasks. In these studies, infants of depressed mothers exhibited lower vagal tone both at rest (Field et al., 1995b; Pickens & Field, 1995) and during interactions with their mothers (Field et al., 1988; Pickens & Field, 1993, 1995). Similarly, resting frontal EEG was recorded in infants of depressed and non-depressed mothers. Infants of depressed mothers showed greater relative right frontal EEG activation that mimicked their depressed mothers' EEG profiles (Dawson, 1994; Field et al., 1995a). Greater relative right frontal EEG activation has been associated with negative affect and depression (Davidson, 2000) and with poor emotion regulation (Fox, 1994).

Although postpartum depression was the focus of these studies, at least one study had suggested that the depressed mothers showed depressed affect as early as their third trimester of pregnancy, suggesting prenatal depression effects as well (Field et al., 1985) or a combination of prenatal and postnatal environmental conditions (Field, 1992). According to a multivariate cumulative risk model proposed by Field (1992), infants of depressed mothers may have a genetic predisposition and/or may be exposed to a chemically and physiologically imbalanced prenatal environment. This can result in the development of neurobehavioral dysregulation that then interacts postnatally with their mothers' poor arousal modulation and negative interaction style, in turn, potentially leading to later psychopathology.

## 3. Neonates of depressed mothers

Because prenatal depression had been noted in many of these mothers, infants of depressed mothers were then studied even earlier, shortly after birth. In these studies, the Brazelton neonatal behavior assessment scale was administered within 24 h after birth. In one study, newborns of depressed ( $N=47$ ) versus newborns of non-depressed mothers ( $N=36$ ) received inferior orientation and motor scores, and they showed more irritability and less activity, robustness and endurance during the assessment (Abrams et al., 1995). In another study, we coded the facial expressions of newborns born to depressed ( $N=20$ ) and non-depressed mothers ( $n=20$ ) during the Brazelton assessment and during the modeling of happy, sad, and surprised faces (Lundy, Field & Pickens, 1997). Consistent with our previous study (Abrams et al., 1995), newborns of mothers with depressive symptoms had lower scores on the orientation cluster of the Brazelton scale. They also showed fewer interest and more precry expressions during the Brazelton. During the facial expression modeling, the newborns of the depressed mothers also showed less attentiveness and fewer facial expressions in response to the modeled happy and surprise facial expressions.

Finally, in a third study, we monitored the physiology and behavior of sixty-three newborns of depressed and non-depressed mothers (Jones et al., 1998). Consistent with findings on older infants (Field et al., 1995a,b), the neonates of depressed mothers showed greater relative right frontal EEG activation and lower vagal tone. They also received lower scores on the Brazelton. Taken together, these data suggested a profile of neurobehavioral dysregulation as early as birth in infants of depressed mothers. These findings implicated prenatal depression as a contributing factor.

#### 4. Prenatal depression effects on the neonate

A series of studies were then conducted to examine prenatal depression effects on fetal development and neonatal outcomes. In the first study, we recruited sixty-three pregnant women during their last trimester (Lundy et al., 1999). The depressed women had higher cortisol and norepinephrine levels and lower dopamine levels. Their newborns also had higher cortisol and norepinephrine levels and lower dopamine levels, thus mimicking their mothers' biochemical profile. The neonates of depressed mothers also showed inferior performance on the orientation, reflex, excitability, and withdrawal clusters of the Brazelton scale. The elevated prenatal cortisol and norepinephrine levels of the depressed women suggested a chemically imbalanced prenatal environment, while the elevated cortisol and norepinephrine levels and inferior Brazelton scores of the neonates of prenatally depressed mothers suggested a profile of dysregulation that may have resulted from that prenatal environment and/or intrinsic genetic factors/predispositions.

We then studied the effects of chronic prenatal depression on neonatal outcomes. In this study, eighty pregnant women were assessed for depression during mid-pregnancy (M gestational age = 25.9 weeks) and again shortly after delivery (Diego et al., 2004). Based on a diagnostic interview (SCID) the women were classified as depressed (1) only during the prenatal assessment; (2) only during the postpartum assessment; (3) during both the prenatal and postpartum assessments; or (4) reporting no depressive symptoms at either the prenatal or the postpartum assessments. The mothers' mood and biochemical profiles were assessed during pregnancy, and the EEG, biochemical profiles, and neurobehavioral profiles of their infants were assessed on the neonatal unit within one week after birth. As predicted, the newborns of the mothers with both prenatal and postpartum depression had elevated cortisol and norepinephrine levels, lower dopamine levels, and greater relative right frontal EEG asymmetry. They also experienced more obstetric complications and showed less optimal neurobehavioral profiles. The newborns in the prenatal depression group also showed greater relative right frontal EEG asymmetry and higher norepinephrine levels than newborns of non-depressed mothers.

In a subsequent study, we examined the effects of prenatal depression on prematurity and low birthweight (Field et al., 2004a). In this study, biochemical profiles 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 biochemical profiles, EEG and vagal tone were assessed, neonatal behavior states were observed, and the Brazelton assessment was conducted. The depressed women had higher prenatal cortisol levels and lower dopamine and serotonin levels, and they were more likely to deliver prematurely and have low birthweight babies. The newborns of the depressed mothers had higher cortisol levels and lower dopamine and serotonin levels, thus mimicking their mothers' prenatal levels. These newborns also had greater relative right frontal EEG activation and lower vagal tone than the neonates of non-depressed mothers. Finally, on the Brazelton Scale, they received less optimal scores on the habituation, orientation, motor, range of state, autonomic stability and depression scales. A path analysis was conducted to assess the effects of the mothers' prenatal depression and biochemical profile on their newborns' gestational age and birthweight. As predicted in the model we had proposed, prenatal depression was related to prenatal cortisol and norepinephrine levels. Prenatal cortisol levels were, in turn, related to prematurity, and norepinephrine levels were related to low birthweight (see Fig. 1).

These data replicated our previous prenatal depression findings, suggesting an imbalanced biochemical prenatal environment and less optimal neurobehavioral profiles in the neonates of depressed mothers (Diego et al., 2004; Lundy et al., 1999). Further, they replicated findings by others (Orr et al., 2002), indicating that depressed mothers are more likely to deliver premature and low birthweight babies. These data suggest not only that prenatal depression affects neonatal development, but also that these effects may be mediated at least in part by elevated maternal cortisol and norepinephrine during pregnancy.

#### 5. Prenatal predictors of neonatal biochemistry and physiology

To assess the predictive validity of the depressed woman's biochemistry, depressed and nondepressed ( $N=47$ ) mothers were recruited as usual from an ultrasound clinic (Field et al., 2004b). Their urine samples were assayed for cortisol, catecholamines (norepinephrine, epinephrine, dopamine) and serotonin. Their urines were assayed again at the neonatal period, and their newborns' urines were also assayed at that time. The depressed versus the nondepressed mothers showed significantly higher cortisol and norepinephrine and significantly lower dopamine levels across the pre- and postnatal assessments. At the postnatal period, all levels had decreased except the serotonin levels for both groups. Regression analyses on the mother's postnatal biochemistry with the prenatal biochemistry entered as predictor variables showed highly significant, specific relationships between each of the catecholamines, cortisol, and serotonin.

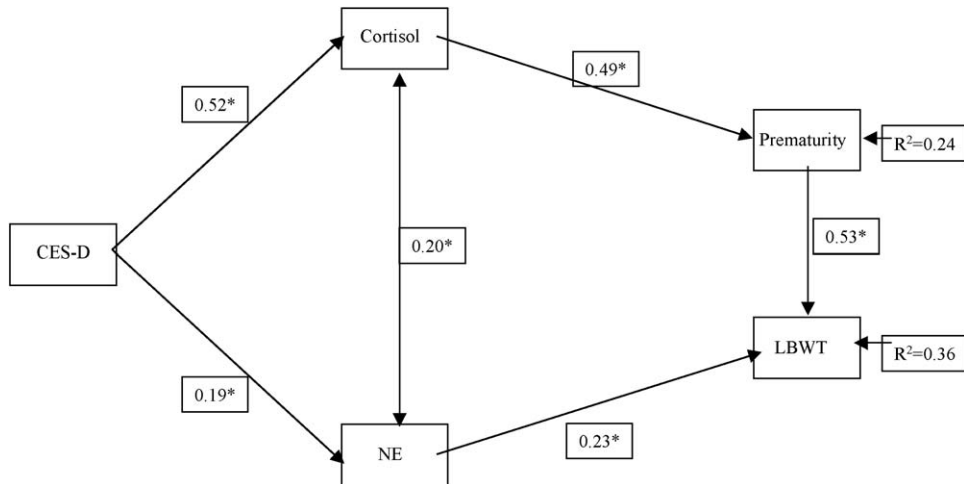


Fig. 1. The relationship between maternal depression and low birth weight and prematurity is mediated by maternal cortisol and norepinephrine.

The newborns' biochemistry values (except for epinephrine) were higher than the maternal values. Regression analyses on the neonatal biochemistry with the mother's prenatal biochemistry entered as predictor variables also suggested highly significant, specific relationships. The continuity between the mothers' and their newborns' neurotransmitter/neurohormone profiles, and data showing that elevated norepinephrine and cortisol predict to low birthweight and prematurity, respectively, highlight the importance of assessing these levels during pregnancy.

In a similar study assessing the predictive validity of the mother's prenatal physiology and biochemistry for neonatal outcome variables, we recruited 52 pregnant women during their second trimester (Field et al., 2004c). They were given EEGs and divided into greater relative right and greater relative left frontal EEG activation groups. The greater relative right frontal EEG women had lower dopamine levels during their second trimester and lower dopamine and higher cortisol levels during the neonatal period. The newborns of the right frontal EEG mothers, similarly, showed greater relative right frontal EEG and had lower dopamine levels. They also had lower serotonin levels, spent more time in indeterminate sleep and had inferior Brazelton scores. A discriminant function analysis based on the mothers' prenatal depression scores and biochemical measures correctly classified 74% of the women as greater relative right or left frontal EEG group members.

## 6. Prenatal depression effects on the fetus

Prenatal depression also affects fetal activity (Dieter et al., 2001). In this study, pregnant women with ( $N=45$ ) and without ( $N=45$ ) symptoms of depression (CES-D scores greater than 16) were given ultrasound examinations across the second and third trimesters. Fetal movements (single limb, multiple limb, gross body) were recorded for 5 min prior to a standard ultrasound examination. The analyses revealed that the fetuses of depressed women were more active at 5, 6 and 7 months gestation (see Fig. 2). These data suggested that fetal activity was affected by prenatal depression as early as 5 months gestation.

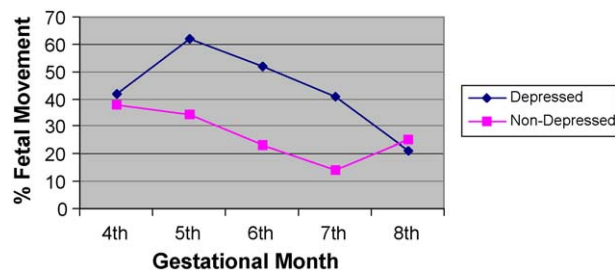


Fig. 2. Activity in fetuses of depressed and non-depressed mothers.

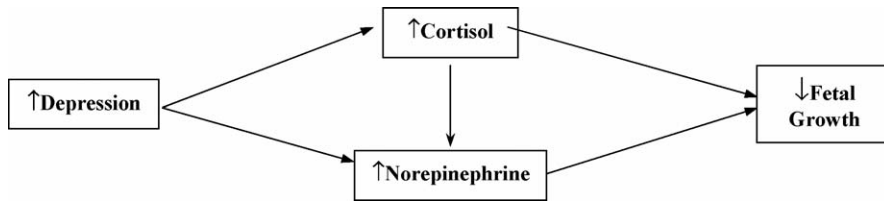


Fig. 3. Hypothesized Model depicting the expected relationship between maternal depression (and anxiety), cortisol, norepinephrine and fetal growth rate.

Prenatal depression also affects fetal growth. A recently completed study conducted on a cross-sectional sample of 98 pregnant women and fetuses assessed the effects of prenatal depression on estimated fetal weight (Diego et al., 2006). In this study, maternal biochemical data (cortisol and norepinephrine) and fetal growth measures were collected during mid-gestation. Prenatal depression was negatively related to biparietal diameter, head circumference and estimated fetal weight, even after the variance for gestational age had been partialled out. These findings are consistent with research relating low birthweight to maternal depression (Field et al., 2004a; Hoffman & Hatch, 2000; Teitebaum, Bourdon & Locke, 1990). Path analyses suggested that the prenatal depression effects on estimated fetal weight were mediated by both prenatal cortisol and norepinephrine levels, with prenatal cortisol being the stronger variable (Diego et al., 2006). To estimate the clinical significance of these findings, we calculated the percentage of fetuses of mothers with high and low cortisol values whose estimated fetal weight fell below or above average for their respective gestational age. These analyses revealed that a significant number of mothers with high cortisol values (84%) had fetuses with below average estimated fetal weight.

Similar data were collected on a sample of 39 pregnant women and their fetuses/neonates (Diego, 2004). Maternal depression was assessed using the Structured Clinical Inventory Diagnoses (SCID), and symptoms of depression and anxiety were measured using the Center for Epidemiological Studies (CES-D) and State Anxiety Inventory (STAI). Maternal urinary cortisol levels were also assayed, and fetal growth rate (grams/week) was estimated from the difference between birthweight and estimated fetal weight over the difference in gestational age at birth and gestational age when fetal weight was estimated. Analyses of variance revealed that fetuses of clinically depressed mothers had lower growth rate than fetuses of non-depressed mothers (see Fig. 3).

Correlation analyses on the same data base suggested that prenatal depression and anxiety were comorbid, and depression and anxiety were significantly related to prenatal cortisol. Regression analyses revealed that only cortisol was a significant predictor of fetal growth rate, suggesting that the effects of maternal depression and anxiety on fetal growth rate were mediated by cortisol.

These results led us to compare high and low cortisol groups (Field et al., 2006). Three-hundred depressed pregnant women ( $M = 20$  weeks gestation) divided by a median split into high and low level urinary cortisol level groups. The high cortisol group had higher CES-D depression scores and higher inhibition (BIS) scores prenatally. Their fetuses had smaller head circumference, abdominal circumference, biparietal diameter and fetal weight. The high cortisol group neonates were shorter gestational age and lower birthweight, and they had lower Brazelton habituation and higher Brazelton reflex scores. Discriminant function analyses suggested that cortisol levels more accurately classified short gestation and low birthweight groups than CES-D depression scores. These data highlighted the importance of monitoring cortisol levels during pregnancy.

In a study by another group using a similar split on pregnancy cortisol, this time taken in late pregnancy, similar outcomes were noted (de Weerth, Zijl, & Buitelaar, 2003). In this study, the infants were divided into two groups based on their mothers' late pregnancy cortisol values: (high or low). A trend was noted for the high cortisol group infants to be delivered earlier than the low cortisol group infants. During behavior observations, the high cortisol group infants showed more crying, fussing and negative facial expressions. Supporting these findings, the high cortisol mothers reported more difficult temperament in their infants, especially during the first two months of life.

## 7. Potential underlying mechanisms

The effects of prenatal depression on fetal development appear to be mediated by elevated cortisol and norepinephrine levels (Field et al., 2004a; Lundy et al., 1999). Depression in general has been associated with both

hypothalamic pituitary adrenal (HPA) axis (i.e. elevated cortisol and corticotrophic releasing hormone (CRH)) and sympathoadrenal hyperactivation (i.e. elevated norepinephrine levels and cardiovascular function) (Arborelius, Owens, Plotsky & Nemeroff, 1999; de Kloet, 2003).

Data from a wide range of animal and human studies indicate that maternal neuroendocrine function during pregnancy significantly affects fetal development. Animal models using mice, sheep and primates demonstrated that glucocorticoid infusions led to decreased placenta size (Jensen, Gallaher, Breier, Harding, 2002), fetal growth restriction (Jensen et al., 2002; Kutzler, Ruane, Coksaygan, Vincent & Nathanielsz, 2004) and premature delivery (Kutzler et al., 2004). These effects resulted from both high doses of glucocorticoids administered over short periods of time (Kutzler et al., 2004) and low doses chronically administered to the mother (Jensen et al., 2002). Further, glucocorticoid infusions negatively affected the development of the lungs, heart, vasculature and brain (Jensen et al., 2002; Kutzler et al., 2004). Elevated prenatal norepinephrine has been associated with preeclampsia (Kaaja et al., 1999), and low birthweight (Field et al., 2004a) and may be related to fetal growth restriction (Bassett & Hanson, 1998).

Prenatal depression may affect fetal growth through complex pathways involving HPA axis and sympathoadrenal dysregulation. Elevated maternal cortisol may affect fetal growth by both changing the placental environment and by directly crossing the placenta (Jones, Brooks & Challis, 1989; Petraglia, Sutton & Vale, 1989). Elevated placental CRH can also induce vasodilatation, resulting in uterine artery constriction and reduced blood flow to the fetus (Clifton et al., 1994). Reduced blood flow to the fetus may, in turn, restrict oxygen and nutrient delivery and has been associated with birth complications including prematurity (Tchirikov, Rybakowski, Huneke, Schoder & Schroder, 2002).

By midgestation, the release of placental CRH results in elevated maternal cortisol and elevated fetal cortisol by directly crossing the placenta into the fetus (Gitau, Fisk, Teixeira, Cameron & Glover, 2001; Liu & Matthews, 1999). Fetal exposure to elevated maternal cortisol may affect fetal growth by dysregulating fetal autonomic nervous system activity (Omer, 1986) and mobilizing fetal energy stores via glycogenolysis (the conversion of glycogen to glucose), resulting in a high degree of calorie expenditure. This process may be further affected by the prolonged exposure to cortisol, leading to fetal HPA axis reprogramming and its effect on nervous system development (Liu & Matthews, 2001; Weinstock, 2001).

This pathway is supported by the strong association between maternal and fetal cortisol (Gitau, Cameron, Fisk & Glover, 1998; Gitau Fisk & Glover, 2004), and by the relation between elevated maternal cortisol and both preeclampsia (Hobel, Dunkel-Schetter, Roesch, Castro & Arora, 1999; Perkins et al., 1995) and premature delivery (Hobel et al., 1999; Leung et al., 1999; Wadhwa, Porto, Garite, Chic-DeMet, & Sandman, 1998). Research also suggests that corticosteroid infusions to the mother result in up to a 25% reduction in fetal weight and associated reductions in biparietal diameter, abdominal circumference and femur length (Jobe, Newnham, Willet, Sly & Ikegami, 1998). As already mentioned, prenatally depressed mothers also have fetuses with elevated heart rates (Allister et al., 2001) and with greater activity levels (Dieter et al., 2001), suggesting both physiological and physical hyperactivity.

A second potential pathway involves sympathoadrenal hyperactivation leading to the release of catecholamines including norepinephrine. Unlike cortisol, norepinephrine has not yet been shown to cross the placenta (Giannakouloupoulos, Teixeira, Fisk, & Glover, 1999). However, norepinephrine may affect the prenatal environment via its effects on the cardiovascular system. Norepinephrine infusions, for example, result in increased arterial pressure and uterine artery resistance and decreased uterine blood flow and fetal oxygenation (Clark, Irion & Mack, 1990; Stevens & Lumbers, 1995). Norepinephrine is also related to uterine artery contractions (Stjernquist & Owman, 1990) which restrict the flow of oxygen and nutrients to the fetus and result in fetal growth deprivation (Copper et al., 1996; Omer, 1986).

## 8. Caveats or confounding variables

These prenatal depression data are confounded by moods that are comorbid with depression. Other prenatal moods or emotions have been noted to differentially affect fetal and infant development including different types of depression called withdrawn versus intrusive depression, prenatal anxiety, prenatal anger and even combined optimism and pessimism. Because many of these are comorbid with prenatal depression, the depression effects would appear to be confounded.

Infants of withdrawn mothers are noted to perform less optimally on the Bayley scales at one year (Jones et al., 1997). Their mothers' prenatal profiles are different, as are their infants' profiles. In a study conducted by our group (Field et al., 2001), depressed mothers who could be classified as withdrawn or intrusive were compared with nondepressed

mothers on their prenatal cortisol and catecholamine levels and on fetal activity and neonatal outcome variables. The data suggested that the withdrawn mothers had lower dopamine levels during pregnancy, and their infants had lower Brazelton scale scores. The infants of withdrawn mothers also had the highest cortisol levels and the lowest dopamine and serotonin levels as well as asymmetrical EEG patterns.

Another confounding factor is that prenatal anxiety is often comorbid with depression. Anxiety during mid-pregnancy has predicted lower mental and motor development scores at 8 months (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003). In this study, cortisol levels in late pregnancy were negatively related to both mental and motor development at three months and motor development at 8 months. In a study by the same group (Gutteling et al., 2005) in the Netherlands, pregnancy stress was a predictor of restless/disruptive temperament and externalizing behavior in 2-year-olds. High maternal anxiety levels during late pregnancy have also been associated with lower mental development scores at the age of 2 years by another group in the Netherlands (Brouwers, van Baar, & Pop, 2001).

In a prenatal anxiety study by our group, one hundred sixty-six women were classified as experiencing high or low anxiety during the second trimester of pregnancy (Field et al., 2003). The high anxiety women also had high scores on depression and anger scales. In a follow-up across pregnancy, the fetuses of the high anxiety women were noted to be more active and to experience growth delays. The high anxiety mothers' high prenatal norepinephrine and low dopamine levels were followed by their neonates having low dopamine and serotonin levels. The high anxiety mothers' newborns also had greater relative right frontal EEG activation and lower vagal tone. Finally, the newborns of high anxiety mothers spent more time in deep sleep and less time in quiet and active alert states and showed more state changes and less optimal performance on the Brazelton neonatal behavior assessment scale (motor maturity, autonomic stability and withdrawal).

In a data analysis on the same sample, the one-hundred and sixty-six women were classified as experiencing high or low anger during the second trimester of pregnancy (Field et al., 2002a). The high-anger women also had high scores on depression and anxiety scales. In a follow-up across pregnancy, the fetuses of the high-anger women were noted to be more active and to experience growth delays. The high-anger mothers' high prenatal cortisol and epinephrine and low dopamine and serotonin levels were mimicked by their neonates' high cortisol and low dopamine levels. The high-anger mothers and infants were also similar on their greater relative right frontal EEG activation and their lower vagal tone. The newborns of high-anger mothers had disorganized sleep patterns (greater indeterminate sleep and more state changes) and less optimal performance on the Brazelton assessment (orientation, motor maturity and depression scales).

Prenatal optimism–pessimism combined also seems to be a factor (Devincent, 2002). Recent research suggests that adverse effects of chronic prenatal maternal stress on birth outcomes may be due to underlying dispositions such as optimism and pessimism that are associated with stress. In this large sample study ( $N=332$ ), women high in both optimism and pessimism were more likely to deliver preterm infants than women who were high in optimism but low in pessimism. Possessing simultaneously positive and negative outlooks may have resulted in a state of cognitive dissonance that led to negative emotional and physiological states.

Ethnicity also appears to have differential effects on the fetus. For example, African–Americans are noted to deliver prematurely more than any other ethnic group. In a comparison between African–American and Hispanic pregnancies (Field et al., 2002b), the Hispanic mothers were older, had a higher socioeconomic status (SES) and had higher prenatal norepinephrine levels. Their fetuses were also more active. At the neonatal period they had higher anger scores, but also higher serotonin levels, and their infants had higher dopamine and lower cortisol levels, and they spent less time in deep and indeterminate sleep. A comparison in the same sample by middle/lower socioeconomic status (SES) revealed that the middle SES group was older, had more social support and showed less depressed affect, but had higher norepinephrine levels prenatally. At the postnatal period, the middle SES mothers had lower depression, anxiety and anger scores and lower norepinephrine levels. Their infants also had lower norepinephrine levels, fewer postnatal complications and were less excitable on the scale.

## 9. Prenatal interventions

Interventions are, of course, needed to help depressed mothers reduce their depression, anxiety and anger and to provide medical, economic and social support. Psychotropic medications have been tried with mixed results. A very large literature has debated the efficacy of psychotropic medications for prenatal depression. Although some have concluded no efficacy (Gentile, 2005; Misri et al., 2004), others have reported negative effects on the neonates including lower Apgar scores and lower Bayley developmental scores (Casper et al., 2003).

Stress reduction therapies for depressed pregnant women have led to lower depression scores, less negative affect and lower cortisol levels (Urizar et al., 2004). Other therapies that have been effective include massage therapy (Field et al., 2004d) and acupuncture (Manber, Schnyer, Allen, Rush & Blassey, 2004). Following acupuncture treatments, depression scores were reduced in pregnant women. Following massage therapy provided by the pregnant woman's significant other, the women had lower levels of anxiety and depressed mood and less leg and back pain (Field et al., 2004d). In addition, by the end of the study, they had higher dopamine and serotonin levels and lower levels of cortisol and norepinephrine. These changes may have contributed to the reduced fetal activity and the better neonatal outcome for the massage group. Fewer infants were born prematurely (0% in the massage group versus 17% in the control group), fewer were born low birthweight and the massage group newborns had better performance on the Brazelton.

## 10. Summary

A review of the research on prenatal depression effects on the fetus and newborn suggest that many prenatal, perinatal and postnatal complications occur. In addition, fetal activity is elevated, prenatal growth is delayed, and the incidence of prematurity and low birthweight are greater. Elevated prenatal maternal cortisol is the strongest predictor of these neonatal outcomes. Newborns of depressed mothers show a biochemical and physiological profile that mimics their mothers' prenatal biochemical/physiological profile including elevated cortisol, lower levels of dopamine and serotonin, greater relative right frontal EEG activation and lower vagal tone. Other mood states including anxiety and anger compound these effects. But little is known about the cause of the anxiety, anger, and depression which could differentially affect the neuroendocrine response to prenatal stress. Genetic factors and gene-environment interactions also need to be studied for their effects. Although moderate pressure massage can alleviate these effects including reducing prematurity and low birthweight, potential underlying mechanisms need to be further explored.

## Acknowledgements

We would like to thank the parents and infants who participated in these studies. This research was supported by a merit award (MH # 46586), Research Scientist Awards (MH # 00331 and AT# 001585) and March of Dimes Grant (# 12-FYO3-48) to Tiffany Field and funding from Johnson & Johnson Pediatric Institute to the Touch Research Institutes.

## References

- Abrams, S. M., Field, T., Scafidi, F., & Prodromidis, M. (1995). Newborns of depressed mothers. *Infant Mental Health Journal*, *16*, 233–239.
- Allister, L., Lester, B. M., Carr, S., & Liu, J. (2001). The effects of maternal depression on fetal heart rate response to vibroacoustic stimulation. *Developmental Neuropsychology*, *20*, 639–651.
- Anderson, L., Sundstrom-Poromaa, I., Wulff, M., Astrom, M., & Bixo, M. (2004). Implications of antenatal depression and anxiety for obstetric outcome. *Obstetric Gynecology*, *104*, 467–476.
- Anderson, L., Sundstrom-Poromaa, I., Wulff, M., Astrom, M., & Bixo, M. (2003). Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. *American Journal of Obstetric Gynecology*, *189*, 148–154.
- Bassett, J. M., & Hanson, C. (1998). Catecholamines inhibit growth in fetal sheep in the absence of hypoxemia. *American Journal of Physiology*, *274*, R1536–R1545.
- Bernstein, I., & Gabbe, S. G. (1996). Intrauterine growth restriction. In S. G. Gabbe, J. R. Niebyl, J. L. Simpson, & G. J. Annas, et al. (Eds.), *Obstetrics: normal and problem pregnancies* (3rd ed., pp. 863–886). New York: Churchill Livingstone.
- Brouwers, E. P., van Baar, A. L., & Pop, V. J. (2001). Does the Edinburgh postnatal depression scale measure anxiety? *Journal of Psychosomatic Research*, *51*, 659–663.
- Buitelaar, J. K., Huizink, A. C., Mulder, E. J., de Medina, P. G., & Visser, G. H. (2003). Prenatal stress and cognitive development and temperament in infants. *Neurobiology Aging*, *24*, 53–60.
- Casper, R. C., Fleisher, B. E., Lee-Ancajas, J. C., Gilles, A., Gaylord, E., DeBattista, A., & Hoyme, H. E. (2003). Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *Journal of Pediatrics*, *142*, 402–408.
- Chung, T. K., Lau, T. K., Yip, A. S., Chiu, H. F., & Lee, D. T. (2001). Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. *Psychosomatic Medicine*, *63*(5), 830–834.
- Clark, K. E., Irion, G. L., & Mack, C. E. (1990). Differential responses of uterine and umbilical vasculatures to angiotensin II and norepinephrine. *American Journal of Physiological Heart Circulation Physiology*, *259*, 197–203.
- Clifton, V. L., Read, M. A., Leitch, I. M., Boura, A. L., Robinson, P. J., & Smith, R. (1994). Corticotropin-releasing hormone-induced vasodilatation in the human fetal placental circulation. *Journal of Clinical Endocrinology and Metabolism*, *79*, 666–669.
- Copper, R. L., Goldenberg, R. L., Das, A., Elder, N., Swain, M., Norman, G., et al. (1996). The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. *American Journal of Obstetrics and Gynecology*, *175*, 1286–1292.

- Davidson, R. J. (2000). Affective style, psychopathology, and resilience: brain mechanisms and plasticity. *American Psychologist*, *55*, 1196–1214.
- Dawson, G. (1994). Frontal electroencephalographic correlates of individual differences in emotion expression in infants: a brain systems perspective on emotion. In N.A. Fox (Ed.). *The development of emotion regulation: behavioral and biological considerations* (pp. 135–151). *Monographs of the Society for Research in Child Development*, *59*, (2–3, Serial No. 240).
- de Kloet, E. R. (2003). Hormones, brain and stress. *Endocrine Regulations*, *37*, 51–68.
- De Tychey, C., Spitz, E., Briancon, S., Ligezzolo, J., Girvan, F., Rosati, A., Thockler, A., & Vincent, S. (2005). Pre- and postnatal depression and coping: a comparative approach. *Journal of Affect Disorders*, *85*, 323–326.
- de Weerth, C., Zijl, R. H., & Buitelaar, J. K. (2003). Development of cortisol circadian rhythm in infancy. *Early Human Development*, *73*, 39–52.
- Diego, M.A. (2004). *Maternal Neuroendocrine Function and Fetal Development*. Doctoral Dissertation. Florida Atlantic University, Boca Raton, Florida.
- Diego, M. A., Field, T., Cullen, C., Hernandez-Reif, M., Schanberg, S., & Kuhn, C. (2004). Prepartum, postpartum and chronic depression effects on infants. *Infant Behavior & Development*, *28*, 155–164.
- Diego M.A., Jones N.A. & Field, T, Hernandez-Reif, M., Shanberg, S., Kuhn, C. & Gonzalez-Garcia, A. (2006). Maternal neuroendocrine function mediates the effects of maternal distress on fetal development. *Infant Behavior and Development*. In Review.
- Dieter, J. N. I., Field, T., Hernandez-Reif, M., Jones, N. A., LeCanuet, J. P., Salman, F. A., et al. (2001). Maternal depression and increased fetal activity. *Journal of Obstetrics and Gynaecology*, *21*, 468–473.
- Field, T. (1984). Early interactions between infants and their postpartum depressed mothers. *Infant Behavior and Development*, *7*, 517–522.
- Field, T. (1992). Infants of depressed mothers. *Development and Psychopathology*, *4*, 49–66.
- Field, T., Sandberg, D., Garcia, R., Vega-Lahr, N., Goldstein, S., & Guy, L. (1985). Pregnancy problems, postpartum depression and early mother-infant interactions. *Developmental Psychology*, *21*, 1152–1156.
- Field, T., Healy, B., Goldstein, S., Perry, S., Bendell, D., Schanberg, S., et al. (1988). Infants of depressed mothers show “depressed” behavior even with non-depressed adults. *Child Development*, *59*, 1569–1579.
- Field, T., Fox, N., Pickens, J., & Nawrocki, T. (1995). Relative right frontal EEG activation in 3- to 6-month-old infants of “depressed” mothers. *Developmental Psychology*, *31*, 358–363.
- Field, T., Pickens, J., Fox, N., Nawrocki, T., & Gonzalez, J. (1995). Vagal tone in infants of depressed mothers. *Development and Psychopathology*, *7*, 227–231.
- Field, T., Diego, M., Dieter, J., Hernandez-Reif, M., Schanberg, S., Kuhn, C., et al. (2001). Depressed withdrawn and intrusive mothers’ effects on their fetuses and neonates. *Infant Behavior and Development*, *24*, 27–39.
- Field, T., Diego, M., Hernandez-Reif, M., Salman, F., Schanberg, S., Kuhn, C., et al. (2002). Prenatal anger effects on the fetus and neonate. *Journal of Obstetrics and Gynecology*, *22*, 260–266.
- Field, T., Diego, M., Hernandez-Reif, M., Schanberg, S., Kuhn, C., Yando, R., & Bendell, D. (2002). Prenatal depression effects on the foetus and neonate in different ethnic and socio-economic status groups. *Journal of Reproductive and Infant Psychology*, *20*, 149–157.
- Field, T., Diego, M., Hernandez-Reif, M., Schanberg, S., Kuhn, C., Yando, R., et al. (2003). Pregnancy anxiety and comorbid depression and anger effects on the fetus and neonate. *Depression and Anxiety*, *17*, 140–151.
- Field, T., Diego, M., Dieter, J., Hernandez-Reif, M., Schanberg, S., Kuhn, C., et al. (2004). Prenatal depression effects on the fetus and the newborn. *Infant Behavior and Development*, *27*, 216–229.
- Field, T., Diego, M., Hernandez-Reif, M., Gil, K., Vera, Y., Schanberg, S., et al. (2004). Prenatal maternal biochemistry predicts neonatal biochemistry. *International Journal of Neuroscience*, *114*, 933–945.
- Field, T., Diego, M., Hernandez-Reif, M., Vera, Y., Gil, K., Schanberg, S., et al. (2004). Prenatal predictors of maternal and newborn EEG. *Infant Behavior and Development*, *27*, 533–536.
- Field, T., Diego, M. A., Hernandez-Reif, M., Schanberg, S., & Kuhn, C. (2004). Massage therapy effects on depressed pregnant women. *Journal of Psychosomatic Obstetrics Gynaecology*, *25*(2), 115–122.
- Field, T., Hernandez-Reif, M., Diego, M., Figueiredo, B., Schanberg, S., & Kuhn, C. (2006). Prenatal cortisol, prematurity and low birthweight. *Infant Behavior and Development*, *29*, 268–275.
- Fox, N.A. (1994). Dynamic cerebral processes underlying emotion regulation. In N.A. Fox (Ed.). *The development of emotion regulation: Behavioral and biological considerations* (pp. 152–166). *Monographs of the Society for Research in Child Development*, *59*, (2–3, Serial No. 240).
- Gentile, S. (2005). The safety of newer antidepressants in pregnancy and breast feeding. *Drug Safety*, *28*, 137–152.
- Giannakouloupoulos, X., Teixeira, J., Fisk, N., & Glover, V. (1999). Human fetal and maternal noradrenaline responses to invasive procedures. *Pediatric Research*, *45*, 494–499.
- Gitau, R., Cameron, A., Fisk, N., & Glover, V. (1998). Fetal exposure to maternal cortisol. *The Lancet*, *352*, 707.
- Gitau, R., Fisk, N. M., & Glover, V. (2004). Human fetal and maternal corticotrophin releasing hormone responses to acute stress. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, *89*, F29–F32.
- Gitau, R., Fisk, N. M., Teixeira, J. M., Cameron, A., & Glover, V. (2001). Fetal hypothalamic-pituitary-adrenal stress responses to invasive procedures are independent of maternal responses. *Journal of Clinical Endocrinology and Metabolism*, *86*, 104–109.
- Gutteling, B. M., de Weerth, C., Willmesen-Swinkels, S. H., Huizink, A. C., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. (2005). The effects of prenatal stress on temperament and problem behavior of 27-month-old toddlers. *European Child Adolescent Psychiatry*, *14*, 41–51.
- Hobel, C. J., Dunkel-Schetter, C., Roesch, S. C., Castro, L. C., & Arora, C. P. (1999). Maternal plasma corticotropin releasing hormone associated with stress at 20 weeks’ gestation in pregnancies ending in preterm delivery. *American Journal of Obstetrics and Gynecology*, *180*, S257–S263.
- Hoffman, S., & Hatch, M. C. (2000). Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. *Health Psychology*, *19*(6), 535–543.

- Huot, R. L., Brennan, P. A., Stowe, Z. N., Plotsky, P. M., & Walker, E. F. (2004). Negative affect in offspring of depressed mothers is predicted by infant cortisol levels at 6 months and maternal depression during pregnancy, but not postpartum. *Abdominal Aortic Aneurysm: Genetics, Pathophysiology, and Molecular Biology*, 1032, 234–236.
- Jablesky, A. V., Morgan, V., Zubrick, S. R., Bower, C., & Yellachich, L. A. (2005). Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. *American Journal of Psychiatry*, 162, 79–91.
- Jensen, C. B., Storgaard, H., Dela, F., Holst, J. J., Madsbad, S., & Vaag, A. A. (2002). Early differential defects of insulin secretion and action in 19-year-old Caucasian men who had low birth weight. *Diabetes*, 51, 1271–1280.
- Jesse, D. E., Seaver, W., & Wallace, D. C. (2003). Maternal psychosocial risks predict preterm birth in a group of women from Appalachia. *Midwifery*, 19, 191–202.
- Jobe, A. H., Newnham, J., Willet, K., Sly, P., & Ikegami, M. (1998). Fetal versus maternal and gestational age effects of repetitive antenatal glucocorticoids. *Pediatrics*, 102, 1116–1125.
- Jones, N. A., Field, T., Fox, N. A., Davalos, M., Lundy, B., & Hart, S. (1998). Newborns of mothers with depressive symptoms are physiologically less developed. *Infant Behavior and Development*, 21, 537–541.
- Jones, N. A., Field, T., Fox, N. A., Davalos, M., Malphurs, J., Carraway, K., et al. (1997). Infants of intrusive and withdrawn mothers. *Infant Behavior and Development*, 20, 177–189.
- Jones, S. A., Brooks, A. N., & Challis, J. R. G. (1989). Steroids modulate corticotropin-releasing hormone production in human fetal membranes and placenta. *Journal of Clinical Endocrinology and Metabolism*, 68, 825–830.
- Kaaja, R. J., Moore, M. P., Yandle, T. G., Ylikorkala, O., Frampton, C. M., & Nicholls, M. G. (1999). Blood pressure and vasoactive hormones in mild preeclampsia and normal pregnancy. *Hypertension Pregnancy*, 18, 173–187.
- Kurki, T., Hiilesmaa, V., Raitasalo, R., Mattila, H., & Ylikorkala, O. (2000). Depression and anxiety in early pregnancy and risk for preeclampsia. *Obstetrics and Gynecology*, 95, 487–490.
- Kutzler, M. A., Ruane, E. K., Coksaygan, T., Vincent, S. E., & Nathanielsz, P. W. (2004). Effects of three courses of maternally administered dexamethasone at 0.7, 0.75, and 0.8 of gestation on prenatal and postnatal growth in sheep. *Pediatrics*, 113, 313–319.
- Leung, T. N., Chung, T. K., Madsen, G., McLean, M., Chang, A. M., & Smith, R. (1999). Elevated mid-trimester maternal corticotrophin-releasing hormone levels in pregnancies that delivered before 34 weeks. *British Journal of Obstetrics and Gynecology*, 106, 1041–1046.
- Liu, L., & Matthews, S. G. (1999). Adrenocortical response profiles to corticotrophin-releasing hormone and adrenocorticotrophin challenge in the chronically catheterized adult guinea-pig. *Experimental Physiology*, 84, 971–977.
- Liu, L., & Matthews, S. G. (2001). Maternal glucocorticoid treatment programs HPA regulation in adult offspring: sex-specific effects. *American Journal of Physiological Endocrinology and Metabolism*, 280, E729–E739.
- Lundy, B., Field, T., & Pickens, J. (1997). Newborns of mothers with depressive symptoms are less expressive. *Infant Behavior & Development*, 19, 419–424.
- Lundy, B. L., Jones, N. A., Field, T., Nearing, G., Davalos, M., Pietro, P., et al. (1999). Prepartum depression effects on neonates. *Infant Behavior and Development*, 22, 121–137.
- Luoma, I., Kaukonen, P., Mantymaa, M., Puura, K., Tamminen, T., & Salmelin, R. (2004). A longitudinal study of maternal depressive symptoms, negative expectations and perceptions of child problems. *Child Psychiatry and Human Development*, 35, 37–53.
- Luoma, I., Tamminen, T., Kaukonen, P., Laippala, P., Puura, K., Salmelin, R., et al. (2001). Longitudinal study of maternal depressive symptoms and child well-being. *Journal of American Academy of Child and Adolescent Psychiatry*, 40(12), 1367–1374.
- Manber, R., Schnyer, R. N., Allen, J. J., Rush, A. J., & Blasse, C. M. (2004). Acupuncture: a promising treatment for depression during pregnancy. *Journal of Affect Disorder*, 83, 89–95.
- Marcus, S. M., Flynn, H. A., Blow, F. C., & Barry, K. L. (2004). Depressive symptoms among pregnant women screened in obstetrics settings. *Women's Health*, 12, 373–380.
- Misri, S., Oberlander, T. F., Fairbrother, N., Carter, D., Ryan, D., Kuan, A. J., et al. (2004). Relation between prenatal maternal mood and anxiety and neonatal health. *Canadian Journal of Psychiatry*, 49(10), 684–689.
- Moncuso, R. A., Schetter, C. D., Rini, C. M., Roesch, S. C., & Hobel, C. J. (2004). Maternal prenatal anxiety and corticotropin-releasing hormone associated with timing of delivery. *Psychosomatic Medicine*, 66(5), 762–769.
- Monk, C., Sloan, R. P., Myers, M. M., Ellman, L., Werner, E., Jeon, J., et al. (2004). Fetal heart rate reactivity differs by women's psychiatric status: an early marker for developmental risk? *Journal of the American Academy of Child and Adolescent Psychiatry*, 43, 283–290.
- Murray, L., & Cooper, P. J. (1997). *Postpartum depression and child development*. New York: Guilford Press.
- Nakano, Y., Oshima, M., Sugiura-Ogasawara, M., Aoki, K., Kitamura, T., & Furukawa, T. A. (2004). Psychosocial predictors of successful delivery after unexplained recurrent spontaneous abortions: a cohort study. *Acta Psychiatrica Scandinavica*, 109, 440–446.
- O'Connor, T. G., Heron, J., Glover, V., & ALSPAC Study Team. (2002). Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41, 1470–1477.
- O'Connor, T. G., Heron, J., Glover, V., Golding, J., & Beveridge, M. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *British Journal of Psychiatry*, 180, 502–508.
- O'Connor, T. G., Heron, J., Glover, V., Golding, J., & ALSPAC Study Team. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *Journal of Child Psychology and Psychiatry*, 44, 1025–1036.
- Omer, H. (1986). Possible psychophysiological mechanisms in premature labor. *Psychosomatics*, 27, 580–584.
- Orr, S. T., James, S. A., & Blackmore Prince, C. (2002). Maternal prenatal depressive symptoms and spontaneous preterm births among African-American women in Baltimore, Maryland. *American Journal of Epidemiology*, 156, 797–802.
- Patel, V., Rodrigues, M., & DeSouza, N. (2002). Gender, poverty, and postnatal depression: a study of mothers in Goa, India. *American Journal of Psychiatry*, 159, 1437–1438.

- Perkins, A. V., Linton, E. A., Eben, F., Simpson, J., Wolfe, C. D., & Redman, C. W. (1995). Corticotrophin-releasing hormone and corticotrophin-releasing hormone binding protein in normal and pre-eclamptic human pregnancies. *British Journal of Obstetrics and Gynaecology*, *102*, 118–122.
- Petraglia, F., Sutton, S., & Vale, W. (1989). Neurotransmitters and peptides modulate the release of immunoreactive corticotropin releasing factor from cultured human placental cells. *American Journal of Obstetrics and Gynecology*, *160*, 247–251.
- Pickens, J. N., & Field, T. (1993). Facial expressivity in infants of “depressed” mothers. *Developmental Psychology*, *29*, 986–988.
- Pickens, J., & Field, T. (1995). Facial expressions and vagal tone of infants of depressed and nondepressed mothers. *Early Development and Parenting*, *4*, 83–89.
- Rahman, A., Iqbal, Z., Bunn, J., Lovel, H., & Harrington, R. (2003). Impact of maternal depression on infant nutritional status and illness: a cohort study. *Archives of General Psychiatry*, *61*, 946–952.
- Sondergaard, C., Olsen, J., Friss-Hasche, E., Dirdal, M., Thrane, N., & Sorensen, H. T. (2003). Psychosocial distress during pregnancy and the risk of infantile colic: a follow-up study. *Acta Paediatrica*, *92*, 811–816.
- Stevens, A. D., & Lumbers, E. R. (1995). Effects of intravenous infusions of noradrenaline into the pregnant ewe on uterine blood flow, fetal renal function, and lung liquid flow. *Canadian Journal of Physiology and Pharmacology*, *73*, 202–208.
- Stjernquist, M., & Owman, C. (1990). Adrenoceptors mediating contraction in the human uterine artery. *Human Reproduction*, *5*, 19–24.
- Stowe, Z. N., Hostetter, A. L., & Newport, D. J. (2005). The onset of postpartum depression: implications for clinical screening obstetrical and primary care. *American Journal of Obstetric Gynecology*, *192*, 522–526.
- Sugiura-Ogasawara, M., Furukawa, T. A., Nakano, Y., Hori, S., Aoki, K., & Kitamura, T. (2002). Depression as a potential causal factor in subsequent miscarriage in recurrent spontaneous aborters. *Human Reproduction*, *17*, 2580–2584.
- Tchirikov, M., Rybakowski, C., Huneke, B., Schoder, V., & Schroder, H. J. (2002). Umbilical vein blood volume flow rate and umbilical artery pulsatility as ‘venous-arterial index’ in the prediction of neonatal compromise. *Ultrasound Obstetrics and Gynecology*, *20*, 580–585.
- Teitebaum, M. A., Bourdon, K., & Locke, B. Z. (1990). Relationship between depressive symptomatology and birth outcome in respondents to the National Maternal and Infant Health Survey. In *Presented at the 118th Meeting of the American Public Health Association*.
- Urizar, G. G., Jr., Milazzo, M., Le, H. N., Delucchi, K., Sotelo, R., & Munoz, R. F. (2004). Impact of stress reduction instructions on stress and cortisol levels during pregnancy. *Biology Psychology*, *67*, 275–282.
- Wadhwa, P. D., Porto, M., Garite, T. J., Chicz-DeMet, A., & Sandman, C. A. (1998). Maternal corticotropin-releasing hormone levels in the early third trimester predict length of gestation in human pregnancy. *American Journal of Obstetrics & Gynecology*, *179*, 1079–1085.
- Weinstock, M. (2001). Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Progress in Neurobiology*, *65*, 427–451.