This review of recent research on prenatal depression suggests that it is a strong predictor of postpartum depression and is more common than postpartum depression. Prenatal depression has been associated with excessive activity and growth delays in the fetus as well as prematurity, low birthweight, disorganized sleep and less responsiveness to stimulation in the neonate. Infants of depressed mothers have difficult temperament, and later in development attentional, emotional and behavioral problems have been noted during childhood and adolescence, as well as chronic illnesses in adulthood. Several variables have confounded the effects of prenatal depression including comorbid anxiety and anger as well as stressful life events. Potential mediating variables are low prenatal maternal dopamine and serotonin levels and elevated cortisol and norepinephrine. The associated intrauterine artery resistance may limit blood flow, oxygen and nutrients to the fetus. Some studies also suggest the heritability of developmental problems for the children of prenatally depressed mothers, including ADHD and antisocial behavior. Multivariate, longitudinal research is needed to disentangle these confounding and mediating variables.
Postpartum depression has received significant attention in the literature for its negative effects on child development (Field, 1998; Murray & Cooper, 1997). In contrast, there are very few prenatal depression effects studies, even though discussions of these effects date back to the time of Hippocrates (Huijzink, Mulder, & Buitelaar, 2004). Some have speculated that prenatal depression was not recognized because depressed mood was the expected correlate of normal hormonal changes such as increased cortisol across pregnancy (Field et al., 2004a). Others have cited the complexity of disentangling prenatal depression effects from those of postpartum depression. Still others have addressed some of the confounding prenatal variables such as the comorbidity of anxiety and depression, the use of medications as treatments for those mood disturbances and the excessive use of alcohol, illicit drugs, nicotine and even caffeine (Diego, Field, Hernandez-Reif, Vera, & Gil, 2007; Field, Hernandez-Reif, & Diego, 2006c). With the primary focus having been on postpartum depression, much of the early research on prenatal depression focused on its ability to predict postpartum depression.

Despite the inherent problems of studying prenatal depression effects on early development, some researchers have, nonetheless, attempted to control for potentially confounding prenatal variables and for the postpartum depression variable and have shown the negative effects of prenatal depression (Deave, Heron, Evans, & Emond, 2008; Luoma et al., 2001). Others have implied long-term effects of prenatal depression from perinatal outcomes that are known to predict long-term problems. For example, the risk of preterm delivery is significantly enhanced by prenatal depression, and preterm delivery, in turn, contributes to significant behavioral, cognitive and emotional problems in children (Li, Liu, & Odıoulı, 2009). Another example is that prenatal depression results in elevated neonatal cortisol levels (Field et al., 2004b; Lundy et al., 1999) which, in turn, influence infant temperament and childhood psychopathology (Davis et al., 2007). Still another example is that prenatal depression leads to neonatal fussiness and sleep problems (Field et al., 2004a) which are the most common concerns reported by parents to pediatricians and are linked to subsequent behavioral and physiological disturbances (Gregory et al., 2005; O’Connor et al., 2007).

This paper reviews the relatively sparse literature on prenatal depression effects on early development. The prevalence data on prenatal depression and prenatal versus postpartum depression are given as well as research showing the predictive validity of prenatal depression for postpartum depression. Risk factors for prenatal depression as well as confounding and comorbid variables are reviewed including stressful life events and anxiety which are also thought to affect early development. Effects on the fetus and newborn include growth and developmental delays followed by emotional and behavior problems in childhood and chronic illness in later development. Data are also reviewed on potential mediating biochemical variables including cortisol, norepinephrine, dopamine and serotonin. Finally, methodological limitations of the literature are summarized, and suggestions are made for future research.

2. Prevalence of prenatal depression

Prenatal depression, referred to as antenatal depression in many parts of the world, has ranged in incidence/prevalence from 6% to 38% in the published literature. These figures have varied by the state or country where the research occurred and the type of reporting. For example, in one study from the U.S., groups were separated by those women who experienced depression only during the antepartum period (that figure being a very low 6%) versus chronic depression (7%) and postpartum depression (9%) (Mora et al., 2009). Even within cultures such as the British culture, variations in prenatal depression rates have been noted such as 20% in Canada (Bowen & Muñajarine, 2006) and 31% in England (Hay, Pawlby, Waters, & Sharp, 2008). In most studies, the prevalence has hovered somewhere between 30% and 40%, such as 30% in Italy (with 12% being major depression and 18% being minor depression) (Marchesi, Bertoni, & Maggini, 2009) to 37% in Hong Kong (Lee et al., 2007) and to 38% in the U.S. (Records & Rice, 2007) (USA).

When prenatal and postpartum depression figures have been compared, generally speaking, prenatal or antenatal depression has been more frequent. For example, in one study prenatal depression was almost twice that of postpartum depression (29% vs. 17%) (Andersson, Sundström-Poromaa, Wulff, Aström, & Bixo, 2006), and at least a statistically significant greater incidence of prenatal depression was noted in another study (30% vs. 23%) (Edwards, Galletly, Semmler-Booth, & Dekker, 2008). The one exception was a recent study in which the prevalence was similar for the prepartum
and postnatal periods (9% vs. 8%) (Milgrom et al., 2008). The relatively greater incidence of prenatal depression is striking, especially given that the lion’s share of the research has been focused on postnatal versus prenatal depression. It is also somewhat surprising that postpartum depression has been assumed to have greater effects on development than the combination of prenatal environmental effects and a genetic predisposition that would be implied by prenatal depression effects.

3. Risk factors

3.1. Prenatal depression as a predictor of postpartum depression

Antenatal depression has been noted to significantly predict postpartum depression. For example, in one study, antenatal depression along with a prior history of depression and a low level of partner support were the strongest predictors of postnatal depression (Milgrom et al., 2008). Similarly, in another study, women who had antenatal depression were significantly more likely to be depressed postnatally (Edwards et al., 2008). In still another study, both antenatal anxiety and depression during the first, the second and third trimesters increased the risk of postpartum depression (Lee et al., 2007). Thus, the primary question that has been addressed in the literature has been answered in the positive, namely that prepartum depression increases the likelihood of postpartum depression. This has clinical significance because of the long-term effects of postpartum depression on the infant. Insofar as prenatal depression predicts postpartum depression and postpartum depression predicts developmental problems, prenatal depression would be at least indirectly related to less optimal child and adolescent development.

Negative effects of postpartum depression have been noted for infant psychological and physiological development (Civic & Holt, 2000; Field, 1998; Miller, 2002). Postpartum depression has also predicted behavioral/emotional problems in children in a number of clinical and community samples (Field, 1992; Goodman & Gotlib, 1999; Murray & Cooper, 1997). These findings, of course, do not suggest that these effects on child development are primarily postnatal depression effects inasmuch as many of these women likely experienced antenatal depression as well.

3.2. Predictors of antenatal depression

A recent review of the literature on predictors of prenatal depression suggested that antenatal depression may go undiagnosed because the symptoms of depression are attributed to the physical and hormonal changes that are typically associated with pregnancy (Bowen & Muhajarine, 2006). These authors cite several other risk factors including a history of depression, a lack of a partner, marital difficulties, a lack of social support, poverty, increased life stress, substance abuse, a history of previous abortions, unplanned pregnancy, ambivalence toward the pregnancy and anxiety about the fetus. Different studies have focused on different factors as well as the timing of those factors. For example, in one study, 46% of the variance of third trimester depressive symptoms was due to brief and intermittent negative mood states that occurred primarily during the first trimester and a lack of marital satisfaction and social support (Records & Rice, 2007).

In a study from Lithuania, risk factors were differentiated according to the trimester of their occurrence. In the first trimester, a greater prevalence of depression was independently associated with unplanned and unwanted pregnancy, high neuroticism, low education and a previous history of depression (Bunevicius et al., 2009). In the second trimester, the risk factors were unplanned and unwanted pregnancy and high neuroticism. And in the third trimester, unplanned and unwanted pregnancy, high neuroticism and the occurrence of psychosocial stressors during the last year were the greatest predictors. Interestingly, as in other studies in the literature, the greatest prevalence of depression was found in the first and last trimesters and the lowest in mid-pregnancy.

Others have differentiated the risk factors by major versus minor depression (Marchesi et al., 2009). In the Marchesi et al. (2009) study, the risk of developing major depression was predicted at the beginning of pregnancy by the presence of previous depressive episodes and conflicts with the husband/partner, whereas the risk of developing minor depression was predicted by being a housewife, the presence of previous depressive episodes and whether the pregnancy was unwanted.

In a study from Spain, risk factors differed as a function of gender (Escribe-Aguir, Gonzalez-Galarzo, Barona-Vilar, & Artazcoz, 2008). In this study, the prevalence of prenatal depression was higher among women (10%) than among men (7%). In both sexes, the probability of depression during pregnancy was higher among those with marital dissatisfaction and a previous history of depression. Unplanned pregnancy, unlike the findings of other studies reviewed, did not increase the risk of prenatal depression either in women or men. Gender differences were found on the impact of social support and the partner’s depression. Among men, low affective social support and partner depression were associated with a higher probability of reporting depression. Neither of these variables was related to women’s depression.

Other psychological risk factors reported in a study from Australia included low self-esteem, prenatal anxiety, negative cognitive style, major life events, low income and history of abuse (Leigh & Milgrom, 2008). There is some overlap in these risk factors across studies, although there are also unique findings which may relate to cross-cultural differences. The factors that occurred across more than a few studies were life events stress, lack of social support, marital difficulties and unplanned or unwanted pregnancy.
In one of the first studies on prenatal depression effects on the fetus, our group showed that fetuses of depressed mothers spent a significantly greater percentage of time being active (44% vs. 28%) (Dieter et al., 2001) (see Fig. 1). A stepwise regression suggested that 29% of the variance in fetal activity was explained by prenatal depression scale scores, with anxiety scale scores adding 6% to that variance to total 35% of the variance. In a similar study, behavior and heart rate responsivity to vibratory stimulation were measured in mid-trimester fetuses using a habituation paradigm (Emory & Dieter, 2006). The fetuses of prenatally depressed women showed less total movement and a heart rate increase as opposed to the heart rate decrease shown by the fetuses of nondepressed women (a heart rate decrease typically being associated with attention to a stimulus).

Some have speculated that excessive fetal activity may lead to delayed fetal growth. To identify whether prenatal depression is a risk factor for fetal growth restriction, the estimated fetal weight and birthweight data were used to compute fetal growth rates (Diego et al., 2009). The depressed women had elevated prenatal cortisol levels, and their fetuses were smaller and had slower fetal growth rates as well as lower birthweight. The depressed women had a 13% greater incidence of premature delivery, and their neonates had a 15% greater incidence of low birthweight. Regression analyses revealed that maternal cortisol levels were potential mediators of the relationship between maternal depression symptoms and both the fetal growth rate and gestational age. After controlling for maternal demographic variables, prenatal maternal cortisol levels were associated with 14% of the variance in the rate of fetal growth and with 30% of the variance in gestational age.

In another study, we attempted to differentiate the effects of prenatal dysthymia (chronic) versus major (acute) depression on maternal cortisol and fetal growth (Field et al., 2008c). The women with major depression had more self-reported symptoms of depression, anxiety and anger, and they had more daily hassles than the women with dysthymia. However, the dysthymic group had higher prenatal cortisol levels and lower fetal growth measurements (estimated weight, femur length, abdominal circumference) as measured at their first ultrasound (mean = 18 weeks gestation) (see Fig. 2). Prenatal depression had significant effects on both fetal activity and fetal growth rate which, in turn, were related to shorter gestation

Fig. 1. Delayed growth (femur length) in fetuses of depressed versus those of non-depressed women at 17–20 weeks gestational age.

Fig. 2. Greater percent time in movement by fetuses of depressed versus those of non-depressed women from 5 to 7 months gestational age.
and lower birthweight. The elevated prenatal maternal cortisol levels could be mediating the effects of depression on these growth delays.

4.2. Prenatal depression effects on birth measures

As already mentioned, prenatal depression has resulted in shorter gestation and lower birthweight (Diego et al., 2009; Field et al., 2004a). Preterm delivery is the leading cause of infant mortality and morbidity as well as inflated hospital and medical costs that have been estimated at around $26 billion in the U.S. (Armstrong, 2007). The incidence of preterm delivery remains at about 14% in the U.S. and is still of unknown etiology. Various psychopathological factors are thought to be potentially important risk factors for preterm delivery (Alder, Fink, Bitzer, Hosli, & Holzgreve, 2007; Negrers, Goldberg, Cliver, & Hauth, 2006). Depression has been noted to increase placental hormones including corticotrophic releasing hormone (Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, & Sandman, 1996) and cortisol (Field et al., 2004b). In one study, women with CES-D scores greater than 16 had almost twice the risk of preterm delivery compared to women without depressive symptoms (Li et al., 2009). In that study, the risk of preterm delivery increased with the increasing severity of depression and, unlike many other studies, the relationship between prenatal depression and preterm delivery was not confounded by the use of antidepressants.

In studies in other countries, for example in France, prenatal depression has also been associated with preterm delivery, although the rate of preterm birth there is typically lower than in the U.S. (Dayan et al., 2006). In this French study, the rate of preterm delivery was significantly higher for women with high depression scores (10%) than for other women (4%). Depression and low birthweight have also been associated, for example in Italy (Maina et al., 2008) and in Pakistan (Rahman, Bunn, Lovel, & Creed, 2007).

In studies by our group, chronic prenatal depression was associated with both shorter gestational age and lower birth-weight (Field et al., 2008e). However, like many other studies, comorbid problems were prevalent including chronically high anxiety, anger, sleep disturbance and pain scores. In a follow-up on prenatal dysthymic versus major depression effects on the fetus, we reported that the newborns of dysthymic versus major depression mothers had a significantly shorter gestational age, lower birthweight, shorter birth length and more obstetric complications (Field, Diego, & Hernandez-Reif, 2008a). And, of course, being born prematurely itself has developmental challenges independent of maternal depression effects. Although, even full-term infants of prenatally depressed mothers have developmental problems including being less responsive to stimulation. And, the neonates of dysthymic mothers also had lower orientation and motor scale scores and more depressive symptoms on the Brazelton Neonatal Behavior Assessment scale. These findings were not surprising to us given the higher prenatal maternal cortisol levels and the inferior fetal measures including lower fetal weight, fetal length, femur length and abdominal circumference already noted in our earlier study on fetuses of dysthymic pregnant women (Field et al., 2008c).

4.3. Newborns of depressed mothers are less responsive to stimulation

In several studies that have been reviewed elsewhere full-term newborns of depressed mothers showed inferior perception of various stimuli including smooth versus nubby nipples, different weight objects (plastic vials with high and low numbers of pellets) and different temperature (warm and cool) tubes see (Field, Hernandez-Reif, & Diego, 2009c) for a review. In another review, we reported their lesser responsiveness to faces and voices, suggesting that infants of depressed mothers show less orienting to the live face/voice of the Brazelton scale examiner and to their own and other infants’ recorded cry sounds (Field, Diego, & Hernandez-Reif, 2009a). This lesser responsiveness was attributed to higher arousal, less attentiveness and less “empathy.” Delayed heart rate deceleration to instrumental and vocal music sounds by newborns of depressed mothers has also been attributed to their delayed attention and/or slower processing.

5. Prenatal depression effects on infants

5.1. Early interactions and temperament

At 3–6 months, the infants of prenatally depressed mothers showed less negative responding to their mother’s noncontingent and still-face behavior, suggesting that they were more accustomed to this behavior in their mothers (Field et al., 2009a). The less responsive behavior of the depressed mothers was further compounded by their comorbid mood states of anger and anxiety and their difficult interaction styles including withdrawn or intrusive interaction styles (Field et al., 2009a). The dysthymic mothers’ and infants’ interactions were inferior to those of mothers with major depression (Field, Diego, Hernandez-Reif, & Ascencio, 2009b). The dysthymic group mothers, for example, spent less time smiling, touching and imitating their infants. Their infants spent less time smiling and more time showing distress behaviors.

Infants of depressed mothers also cry significantly more times a day based on 24-h diaries completed by their mothers when the infants were 3-month old (Milgrom, Westley, & McCloud, 1995). Another study examined prenatal variables that predicted the excessive crying of 3-month-old infants of depressed mothers (Van der Wal, van Eijsden, & Bonsel, 2007). In this follow-up study, prenatal depression, anxiety and job strain were associated with excessive infant crying.
Prenatal depression has also been related to difficult infant temperament in general. In one study, prenatally depressed mothers reported more difficult temperament in their infants at both 2 and 6 months postpartum (McGrath, Records, & Rice, 2008). These differences remained after controlling for prenatal anxiety which occurred more often in the depressed mothers. In a similar study, prenatal depression, but not postpartum depression, predicted the ratings of negative affect in infants at 6 months postpartum (Huot, Brennan, Stowe, Plotsky, & Walker, 2004).

5.2. Prenatal depression effects on infant sleep

Just as infants’ wakeful behaviors have been notably affected by prenatal depression, their sleep problems have also been associated with prenatal depression. Sleep problems are the most common concern reported to pediatricians, with a range of 20–30% of children being affected (Gaylor, Burnham, Goodlin-Jones, & Anders, 2005; Liu, Liu, Owens, & Kaplan, 2005). In turn, infant sleep problems are correlated with many childhood behavioral and physiological conditions including depression (O'Connor et al., 2007) and neurodevelopmental disorders such as Attention Deficit/Hyperactivity Disorder (Gruber, Sadeh, & Raviv, 2000; Stores, 2001).

Research from our lab has documented prenatal depression and postnatal depression effects on sleep disturbances, fussing and crying in neonates (Diego, Field, & Hernandez-Reif, 2005). In that study, infants of mothers with both prenatal and postnatal depression were the most sleep-disturbed. In a subsequent study, we showed that prenatally depressed women who had their own sleep disturbances had infants who spent less time in deep sleep, more time in disorganized sleep and more time fussing and crying (Field et al., 2007).

Prenatal depression has also contributed to sleep problems in later infancy and early childhood (O'Connor et al., 2007). Sleep disturbances in this study included refusing to go to bed, waking up early, having difficulty going to sleep, having nightmares, continuing to get up after being put to bed, waking in the night and getting up after only a few hours of sleep. Prenatal depression predicted sleep problems at both 18 and 30 months of age independent of postnatal mood and obstetric and psychosocial variables. The authors speculated, based on animal data, that the HPA axis (hypothalamic pituitary adrenal axis) was an underlying mechanism for the effects of prenatal depression on sleep problems (Ader, 1975). At least one study has reported a relationship between the diurnal pattern in cortisol and sleeping through the night in infancy (de Weerth, van Hees, & Buitelaar, 2003). We have also noted relationships between prenatal depression, sleep and cortisol levels (Field et al., 2004b) and the confounding effects of prenatal anxiety and anger, as already noted.

6. Prenatal depression effects on children

6.1. Physiological measures in infants and children

In several studies on prenatal depression effects on neonatal outcome, we have reported lower vagal tone (which is associated with lesser attentiveness) and greater relative right frontal EEG activation (which is associated with withdrawal behavior) (Field et al., 2004b; see Field & Diego, 2008 for a review). In all of this research, the depressed women had lower vagal tone and greater relative right frontal EEG activation. Their infants, in turn, mimicked these physiological profiles. In addition, these vagal tone and EEG profiles persisted from the neonatal stage to early infancy to the preschool years (see Field & Diego, 2008 for a review; Jones, Field, Davalos, & Pickens, 1997).

Another group in the Netherlands also measured the high frequency component of heart rate variability as an indicator of vagal tone in 14-month-old infants (Dierckx et al., 2009). In this study, prenatal depression symptoms were associated with a higher mean heart rate and a lower high frequency component of heart rate variability, meaning lower vagal tone, in the infants.

6.2. Developmental delays, emotional and behavioral problems

In the Avon Longitudinal Study of Parents and Children (ALSPAC) (that takes place in Avon, England), developmental delays were noted at 18 months for the offspring of prenatally depressed women (Deave et al., 2008). A similar longitudinal study in the Netherlands reported externalizing and internalizing behavior problems in children between 14 and 54 months of age from depressed mothers (de Bruij, van Bakel, & van Baar, 2009). Uniquely, first trimester prenatal depression was associated with internalizing behavior problems for boys, and third trimester prenatal depression was associated with internalizing as well as externalizing behavior problems for girls. These results are complex and difficult to interpret.

In still another longitudinal study from Finland, prenatal depression predicted behavior problems based on the Child Behavior Problem Checklist at both 4–5 and 8–9 years of age, with prenatal depression being assessed in the third trimester (Luoma et al., 2004, 2001). In these studies, only externalizing behaviors were predicted by prenatal depression. The lack of association between prenatal maternal depression and internalizing problems for the children was an unexpected finding. Similarly, prenatal depression has predicted major depression and conduct disorder in adolescence, although these findings were based on retrospective data (Allen, Lewinson, & Seeley, 1998).
7. Prenatal depression effects on adults

7.1. Health and immune function

Prenatally depressed women have poorer self-reported health and functioning than their non-depressed counterparts. This has been demonstrated in one of our studies in which a greater incidence of prenatally depressed women reported the use of antibiotics (Field et al., 2004b). In another study, using self-report measures, health problems were noted in prenatally depressed women along with limited functional status (activities of daily living) (Orr, Blazer, James, & Reiter 2007). These women had approximately twice the risk of poorer self-reported health and functional status than those with lower scores on the CES-D after adjustment for age, marital status, smoking, education, insurance, trimester of pregnancy and race.

Prenatal origins of illnesses have also been documented, lending support for the phenomenon that diseases often have their origins during fetal development (Barker, 2002; Kajantie, 2006). Studies have reported, for example, associations between birth complications such as low birthweight and subsequent risk of disease in adult life including hypertension, coronary heart disease, diabetes, depression and other cognitive and affective disorders (Cannon, Jones, & Murray, 2002; Gluckman & Hanson, 2004). Others have presented data suggesting that the relationship between prenatal stress and adult diseases is not necessarily mediated by birth complications but may be directly related to prenatal maternal stress (Entringer et al., 2008). Still others reviewed data on immune cells with receptors for hormones associated with the hypothalamic pituitary adrenal axis and the sympathetic adrenal medullary axis (Glaser & Kiecolt-Glaser, 2005). These authors showed that during stress, there was a shift from the Th1 to the Th2 cytokine system that suppressed cellular immunity and was related to inflammation. This shift from the Th1 to the Th2 system may be related to changes in stress catecholamines (Elenkov & Chrousos, 1999). Possible mechanisms for how this occurs are: (1) maternal stress hormones crossing the placenta to the fetus; (2) the release of placental hormones that enter fetal circulation; and (3) physiological changes such as increased uterine artery resistance that limits blood flow and thus the provision of nutrients and oxygen to the fetus (Huizink et al., 2004).

As some have suggested, maternal stress during pregnancy may delay postpartum immune adaptation (Knackstedt, Hamelmann, & Arck, 2005). According to these authors, the immune system of the neonate is basically a Th2 system, and early in life, there is a natural shift from Th2 to Th1 immunity. But, increased production of Th2 cytokines such as IL-4 has been noted in newborns who later developed atopic disease. This happens because of the increased levels of IgA and the high numbers of eosinophils. Other cytokine-inducing problems are anxiety, depression and cognitive deficits. The immune system changes that follow from prenatal depression are thought to disrupt the communication between the immune system, endocrine system and central nervous system, making prenatally stressed individuals more vulnerable to these problems (Kohman, Tarr, Day, McLinden, & Boehm, 2008).

7.2. Prenatal depression in men

Prenatal depression has typically been more prevalent among women than men. For example, in one study, prenatal depression occurred in 10% of women and 7% of men (Escribe-Aguir et al., 2008). In men and women, the probability of depression was higher in those with marital dissatisfaction and among those with a previous history of depression. Two factors that were related to a higher probability of depression in men were low affective social support and partner depression. These variables did not affect women's depression. In a study we conducted, depressed men as compared to nondepressed men not only had higher depression scores but also higher anxiety and daily hassles scores (Field et al., 2006b). Although the pregnant women in general had lower anxiety, anger and daily hassles scores than the men, the scores on the depression measures for depressed fathers and depressed mothers did not differ. However, paternal depression had less effect than maternal depression on their partners' scores. Nonetheless, the similarities between the scores of depressed mothers and depressed fathers highlights the importance of screening for depression of fathers-to-be as well as mothers-to-be during pregnancy.

In another publication form the Avon Longitudinal Study of Parents and Children, prenatal depression was measured in fathers, and later behavioral/emotional and psychiatric problems were assessed in the children (at 3½ and 7 years) (Ramchandani et al., 2008). The children whose fathers were depressed had the highest risk for psychopathology as measured by behavior problems at age 3½ and a psychiatric diagnosis at 7 years of age. This was particularly true for the sons of depressed fathers.

In another study based on the Minnesota twin family study database, the investigators explored whether major depression and/or antisocial behavior tended to occur more frequently among partners of depressed mothers (compared to partners of nondepressed mothers) and to examine how these paternal disorders related to psychopathology in their offspring (Marmarstein, Malone, & Iacono, 2004). In that study, depressed mothers tended to have antisocial partners. Depression in the mothers and antisocial behavior in the fathers were both significantly and independently associated with depression and conduct disorder in the 17-year-old offspring.
8. Comorbid anxiety and developmental outcomes

Anxiety is often comorbid with depression. In many studies those born to women who have experienced comorbid depression and anxiety are at particularly high risk for later developmental and social-emotional problems (Field et al., 2004a; Wadhwa, 2005). Women with high depression and anxiety scores are more likely to deliver preterm infants who are small for gestational age and, in turn, have other developmental problems. For example, in one study, depression and anxiety scores obtained during the third trimester of pregnancy predicted 27% and 20% of the variance of an infant’s observed behavioral reactivity at 4 and at 9 months respectively (Davis et al., 2004). In a longer-term study, anxiety during pregnancy accounted for 22% of the variance in symptoms of ADHD in 8-year-old children (Van den Bergh & Marconen, 2004). Similarly, depressed women in the top 15% for symptoms of anxiety at 32 weeks gestation had double the risk of having children with behavior problems at 4 and at 7 years of age (O’Connor, Heron, Golding, Glover, & The ALSPAC Study Team, 2003). The risk for this group of women was greater for having children with ADHD, anxiety or depression and conduct disorder. Prenatal depression/anxiety has also been noted to predict childhood anxiety and depression as late as 10 years of age (Leech, Larkby, Day, & Day, 2006).

Some have suggested that maternal prenatal anxiety predicts child outcomes more strongly than depression. For example, in one study, although antenatal depression was associated with child behavior problems, the associated effect size was smaller for depression than for anxiety (O’Connor, Heron, Golding, Beveridge, & Glover, 2002). These authors noted that the association between prenatal anxiety and child behavior problems was separate and additive to the effects of prenatal depression.

Prenatal anxiety has also been predictive of illnesses like asthma in childhood (Cookson, Granell, Joinson, Ben-Hlomo, & Henderson, 2009). After adjusting for postnatal anxiety and a number of other confounding variables, asthma at age 7½ years was more likely to occur in the group whose mothers were in the highest compared to the lowest quartile of prenatal anxiety. In at least two studies, prenatal anxiety was associated with elevated cortisol in the offspring later in childhood. In one study, prenatal anxiety was associated with elevated cortisol in 10-year-old children (O’Connor, Ben-Shlomo, Heron, Adams, & Glover, 2005). In another study, prenatal anxiety was associated with a flattened cortisol daytime profile which, in turn, was related to depressive symptoms (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008).

In most of these studies, depression and anxiety were confounded, as it is difficult to find samples of pregnant women who are high anxiety but not depressed. The incidence of comorbid depression and anxiety is very high, and it is virtually impossible to statistically control for these confounding variables. Thus, it can be assumed that findings related to prenatal depression may also be related to prenatal anxiety and vice versa.

Still other emotions may affect prenatal depression and the related physiological reactions and biochemical profiles. Anger has been noted to accompany both prenatal depression and anxiety (Field et al., 2002). And other kinds of emotions might also have negative effects such as guilt and insensitivity. Different types of depression style in the mothers, e.g. intrusion versus withdrawal, also differentially impact the fetus and newborn (Field, Diego, & Hernandez-Reif, 2006a).

8.2. Cortisol as a potential mediating variable

Maternal stress during pregnancy is noted to increase cortisol and corticotrophin releasing hormone levels in the mother and the fetus (Field et al., 2004b; Weinstock, 2008). Placental corticotrophic hormone is released into fetal circulation (Alder et al., 2007). In addition, elevated estrogen levels in pregnancy lead to a doubling of corticosteroid-binding globulin levels, resulting in a low breakdown of cortisol. This confounds the steady increase of cortisol levels across pregnancy, peaking in the third trimester at about two to three times the non-pregnant values. Fetal cortisol concentrations are linearly related to maternal concentrations (a maternal-fetal ratio of 12–1) (Gitau, Cameron, Fisk, & Glover, 1998). Although there is a substantial amount of maternal cortisol being inactivated in the placenta by 11beta-hydroxysteroid-dehydrogenase type 2, there is still a contribution of 10–20% of maternal cortisol (Challis et al., 2001). As these authors suggest, the second possible pathophysiological effect of prenatal depression and anxiety is via the effect of intrauterine artery blood flow. As already mentioned, increased uterine artery resistance limits uterine blood flow and therefore the supply of oxygen and nutrients to the fetus (Sjostrom, Valentin, Thelin, & Marsal, 1997; Teixeira, Fisk, & Glover, 1999). Elevated norepinephrine is thought to mediate the effects of prenatal depression on increased uterine artery resistance.

These hormones may contribute to behavior disorders in the offspring including attention and learning deficits, generalized anxiety and depression. Hypothalamic pituitary adrenal axis changes have been induced by prenatal stress in rats and non-human primates (Darmaudery & Maccari, 2008). Variables that affect these changes are the timing of the stress, its intensity and duration and the gender of the offspring. Structural changes occur in the hippocampal region, frontal cortex, the amygdala and the nucleus accumbens. During adulthood the animals exposed to these early stressors showed high anxiety levels and depression-like behavior as well as memory impairments on hippocampus-dependent functions like memory. These dysfunctions, however, appear to be reversible by environmental enrichment and anti-depression treatments.

Maternal stress not only increases corticosteroid levels in the fetal brain but also decreases fetal testosterone in males and alters catecholamine activity in female fetuses (Weinstock, 2007). Learning deficits related to neurogenesis and dendritic
spine density in the prefrontal cortex and hippocampus are more readily seen in prenatally stressed males, while anxiety, depression and an increased response of the HPA axis to stress are more prevalent in females.

In the human model, elevated mid-pregnancy corticotrophin releasing hormone has been associated with prenatal depression (Rich-Edwards et al., 2008). And elevated mid-pregnancy prenatal cortisol contributed to 24% of the variance in preterm delivery in our study (Field et al., 2004b) (see Fig. 3). In our comparison on pregnant women diagnosed with dysthymia versus major depression (Field et al., 2008b), the dysthymic group had higher prenatal cortisol levels and lower fetal growth measures including estimated weight, femur length and abdominal circumference as measured at the first ultrasound. Thus, elevated cortisol appears to contribute to delayed fetal growth and preterm delivery.

Fetal exposure to maternal cortisol is reputedly regulated by the placental hormone, 11beta-hydroxysteroid dehydrogenase type 2, which oxidizes cortisol to its inactive form cortisone. Although that hormone increases across gestation, it only partially protects the fetus from the effects of maternal cortisol (Seckl & Meaney, 2004). As already mentioned, as much as 10–20% of maternal cortisol passes through the placenta, and fetal cortisol levels are significantly correlated with maternal levels (Gitau, Fisk, Teixerira, Cameron, & Glover, 2001). As in the rat model, chronically high levels of cortisol can have negative effects on human brain structure and function (Hillshouse & Grammatopoulos, 2002).

Increased fussiness and negative behavior have, for example, been noted in the infants of at least two samples of mothers who had elevated prenatal cortisol (Davis et al., 2007; de Weerth et al., 2003). Elevated prenatal maternal cortisol at 30–32 weeks gestation was significantly associated with maternal reports of infant negative reactivity in one sample (Davis et al., 2007). Comorbid prenatal anxiety and depression predicted even more difficult infant temperament. The association between maternal cortisol and prenatal depression remained after controlling for postpartum depression. Although the negative infant temperament in this study was based on a self-report measure, difficult infant temperament was based on behavioral observations over the first 5 postnatal months in the second study (de Weerth et al., 2003). Higher levels of third trimester maternal cortisol predicted increased fussing, crying and negative facial expressions, particularly during the first two postnatal months. And, in turn, infants with negative temperament were more likely to become behaviorally inhibited as children in a longitudinal study (Pfeifer, Fisk, Teixerira, Cameron, & Glover, 2002).

The negative infant temperament findings are perhaps not surprising given that maternal depression and elevated prenatal cortisol levels have been associated with increased infant cortisol levels (Brennan et al., 2008; Field et al., 2004a). Comorbid depression/anxiety has also been related to infant cortisol reactivity at 6 months (Brennan et al., 2008). The problem, once again, was that this study did not have a large enough comparison group of depressed women without anxiety to assess its independent effects on infant cortisol levels. The comorbid depression/anxiety disorder mothers may have suffered from more severe depression than the noncomorbid group, and the increased severity of depression itself may have impacted infant cortisol levels.

Elevated prenatal cortisol has also been related to later emotional and cognitive development including the increased risk of anxiety and depression as well as attentional deficits/hyperactivity and language delays (Talge, Neal, Glover, & the Early Stress, Translational Research and Prevention Science Network, 2007). Although many of these findings are independent of the effects of postpartum depression and anxiety, understanding the mechanisms is complex given that the childhood problems may also be mediated by elevated cortisol. Elevated cortisol in infancy, for example, has been associated with childhood behavior problems, especially social withdrawal (Essex, Klein, Cho, & Kalin, 2002). Similarly, higher cortisol levels at preschool age have been associated with internalizing problems at kindergarten age (Goldsmith & Lemery, 2000).

Elevated cortisol is also associated with immune dysfunction including the dominance of the Th2 cytokine system which suppresses cellular immunity and activates humoral immunity (Glaser & Kiecolt-Glaser, 2005). Almost all immune cells have receptors for hormones that are associated with the HPA axis and the sympathetic-adrenal-medullary (SAM) axis (Glaser & Kiecolt-Glaser, 2005). This may explain the association between prenatal depression, preterm delivery and
other immune disorders such as asthma and allergies (Kajantie, 2006; Remes & Pekkanen, 2005). These may be mediated by the overproduction of interleukin-4 (IL-4), IL-6 and IL-10 following stress and elevated cortisol (Entringer et al., 2008).

In looking for cortisol-lowering interventions, the use of antidepressants by pregnant women lowered infant cortisol in at least one study (Brennan et al., 2008). Although this finding is controversial inasmuch as some researchers have failed to find negative effects of maternal antidepressants on child behavior and development (Nulman et al., 2002) while others have noted negative effects. Negative effects include selective serotonin reuptake inhibitors taken during pregnancy contributing to neonatal withdrawal syndrome (Sanz, De-las-Cuevas, Kiuru, Bate, & Edwards, 2005) and to infant pulmonary hypertension (Chambers et al., 2006).

8.3. Neurotransmitter effects

At least three neurotransmitters have been implicated in prenatal depression effects including elevated norepinephrine and low levels of dopamine and serotonin. In one study from our lab, elevated norepinephrine and low levels of dopamine and serotonin were noted in depressed pregnant women at 20 weeks gestation (Lundy et al., 1999). In a subsequent study, similarly high levels of norepinephrine and low levels of dopamine and serotonin were noted in pregnant women again at approximately 20 weeks gestation (Field et al., 2004b). In this study, the neonates of the depressed women had biochemical profiles that mimicked their mothers’ profiles including elevated norepinephrine and low levels of dopamine and serotonin. Elevated norepinephrine is a risk factor because of its association with intrauterine artery resistance and limited transport of oxygen and nutrients to the fetus (Teixeira et al., 1999).

In a subsequent study we divided a sample of depressed pregnant women into high and low prenatal maternal dopamine groups based on a tertile split on their dopamine levels at 20 weeks gestation (Field et al., 2008b). The low dopamine group had a higher depression scores and higher norepinephrine at the 20-week gestational age visit as well as lower dopamine and serotonin levels at both the 20 and 32 weeks gestational age visits. The neonates of the mothers with low versus high prenatal dopamine levels also had lower dopamine and serotonin levels as well as higher cortisol levels. Finally, the neonates in the low dopamine group had lower scores on the Brazelton autonomic stability and excitability scales. Thus, lower prenatal maternal dopamine levels associated with prenatal depression were related to low levels of neonatal dopamine and dysregulation in the neonate, although all of these effects were confounded by low serotonin levels. In another study, splitting the group of depressed women into high and low serotonin groups resulted in similar negative effects (Field et al., 2008d).

8.4. Other potential confounding variables

Although prenatal stress effects have been recorded since the time of Hippocrates and the origins of medicine, the variability in the definition and measurement of prenatal stress has made it difficult to group studies and perform meta-analyses (Huizink et al., 2004). In addition to the depression/anxiety comorbidity, cortisol and neurotransmitter confounds already mentioned, several other confounding variables have been studied for their negative effects on the fetus including stressful life events, daily hassles and other markers of stress (see Beydoun & Saftlas, 2008 for a review). Others have similarly noted the problem of misinterpreting the symptoms of depression (sleep problems, energy and appetite changes) as normative experiences of pregnancy rather than depression (Marcus, 2009). In this review, additional complications of pregnancy that were associated with depression included inadequate weight gain, under-utilization of prenatal care, poor health, lower SES and alcohol use.

Additional risk factors are depression history, lack of a partner, marital difficulties, lack of social support, poverty, family violence, increased life stress, substance use, history of previous abortions, unplanned pregnancy, ambivalence towards the pregnancy and anxiety about the fetus (Bowen & Muhajarine, 2006). Prenatal alcohol exposure, for example, has contributed to externalizing (aggression) and internalizing (anxious/depressed) problems (Sood et al., 2001). And, alcohol exposure during the first and second trimesters has been related to childhood IQ as late as 10 years (Willford, Leech, & Day, 2006). Antidepressants are another potentially confounding factor. Reputedly, 13% of depressed pregnant women use antidepressants (Marcus & Flynn, 2008). Antidepressants are noted to have negative effects on the fetus and neonate including shorter gestational age and a greater rate of prematurity (14% versus 5%) (Suri et al., 2007).

8.5. Methodological limitations

Unfortunately, very few longitudinal, multivariate studies have been conducted on prenatal depression effects. Most of the data come from short-term univariate studies. For example, increased prenatal depression was related to increased cortisol which, in turn, predicted prematurity, as reported by our group (Field et al., 2004a). A separate group of investigators reported that prematurity predicted developmental problems. Thus, separate research groups have studied the relationships between depression, cortisol and prematurity and the relationships between prematurity and developmental problems. However, no long-term studies have been conducted on all factors in the same sample. In addition, not all elevated cortisol mothers have preterm infants. Only 24% of the variance in prematurity was explained by increased cortisol in our study (Field et al., 2004a). A similar point can be made about depression being associated with increased norepinephrine and increased norepinephrine being associated with premature delivery (Lundy et al., 1999). However, as has been noted, the effects of
Another example of this problem is the literature on comorbid depression/anxiety leading to long-term increases in cortisol or cortisol dysregulation, implying that increased cortisol is associated with prenatal depression and anxiety. However, in the long-term studies on increased cortisol and cortisol dysregulation, prenatal cortisol was not measured. Comorbid depression/anxiety has also been related to chronic illness in adults. The implied increase in cortisol makes sense inasmuch as increased cortisol decreases immune cells, most especially natural kill (NK) cells as well as NK cell activity. Then again, however, no long-term studies have been conducted that include prenatal depression, prenatal cortisol and follow-ups to long-term immune function and illness.

As was mentioned earlier, the problem of depression and anxiety being comorbid has confounded the prenatal depression effects, and attempts to unconfound them are difficult inasmuch as individuals with depression alone or with anxiety alone are difficult to find. Prenatal and postpartum depression are also confounded. Although long-term effects have been noted for postpartum depression (Hay et al., 2008; Murray & Cooper, 1997), postpartum depression effects may in fact be prenatal depression plus postpartum depression effects inasmuch as: (1) prenatal depression is the strongest predictor of postpartum depression; (2) a prenatal depression alone sample is difficult to find; (3) the additive effects of postpartum depression are difficult to control statistically; and (4) prenatal effects on neonatal outcome are difficult to separate into genetic and prenatal environmental determinants.

In addition, the studies have varied on diagnostic measures and definitions of depression. And none of the studies have explored the antecedent of depressive episodes as, for example, if the prenatal depression was ongoing from childhood or related to recent losses or traumas, pregnancy factors, illnesses, or family history. And, investigators did not ask about depression before pregnancy.

These, then, are some methodological limitations of the existing data. Nonetheless, the research suggests long-term effects of prenatal depression on both behavior problems and cognitive development on the offspring. Disentangling causal factors and mediating variables will require more sophisticated, multivariate, longitudinal research designs. The existing data also suggest the need for interventions to reduce prenatal depression and its associated biochemical and immunological effects.

8.6. Future research

Associations between prenatal environmental factors and childhood disease may be attributable to true prenatal environmental effects or to the “confounding” effects of a genetic predisposition that is shared by the mother and her offspring (Thapar et al., 2007). Studies have been conducted involving embryo transfer in animals, but genetic research designs have not been adequate for assessing these effects in humans. In the Thapar et al. (2007) study, genetically related offspring (in vitro fertilization/sperm donation) were compared to a group of offspring who were genetically unrelated to the woman who was pregnant (egg donation/embryo donation). This group of investigators used this model for studying the effects of prenatal smoking, which were found to reduce birthweight in both unrelated and related offspring (Rice et al., 2009). In contrast, the association between prenatal smoking and offspring antisocial behavior depended on inherited factors because that association was only present in mothers and their genetically related offspring. Similarly, the link between prenatal stress and offspring attention deficit hyperactivity disorder was only present in related mother–offspring pairs, therefore attributable to inherited factors as reported by the same group of investigators (Rice, Jones, & Thapar, 2007). This may be a model for future research that attempts to disentangle genetic from prenatal environment effects.

9. Summary

In summary, maternal prenatal depression is the strongest predictor of postpartum depression and is believed to be more common than postpartum depression. Prenatal depression has been associated with excessive activity and growth delays in the fetus as well as prematurity, low birthweight, disorganized sleep and less responsiveness to stimulation in the neonate. Infants of depressed mothers have difficult temperament, and attentional, emotional and behavioral problems have been noted in childhood and adolescence as well as chronic illness in adulthood. Several variables confound the effects of prenatal depression including comorbid anxiety effects and anger as well as stressful life events. And others not measured such as insensitivity and withdrawal may further confound these effects. Potential mediating variables are low prenatal maternal dopamine and serotonin levels and elevated cortisol and norepinephrine. The associated intrauterine artery resistance may limit blood flow, oxygen and nutrients to the fetus. Cross-fostering developmental studies also suggest the heritability of developmental problems including ADHD and antisocial behavior. Multivariate, longitudinal research is needed to disentangle these confounding and mediating variables.

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References


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