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CORTISOL: THE CULPRIT PRENATAL STRESS VARIABLE

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Elevated prenatal cortisol has been associated with several negative conditions including aborted fetuses, excessive fetal activity, delayed fetal growth and development, prematurity and low birthweight, attention and temperament problems in infancy, externalizing problems in childhood, and psychopathology and chronic illness in adulthood. Given that maternal prenatal cortisol crosses the placenta and influences other aspects of the prenatal environment, these effects on the fetus and later development are not surprising. Cortisol would appear to be a mediating variable, resulting from prenatal stress in several forms including depression, anxiety, anger, and daily hassles. Cortisol effects are further complicated by its interaction with neurotransmitters such as norepinephrine, which may itself

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cause premature birth via intrauterine growth deprivation related to uterine artery resistance. Recent research has suggested that cortisol-reducing therapies such as massage therapy can reduce the risk of perinatal complications including prematurity and low birthweight.

Keywords cortisol, depression, low birthweight, massage therapy, prematurity, prenatal stress

Maternal cortisol is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Perception of physical and psychological challenges prompts a stress response characterized by the activation of the HPA axis. HPA axis activation involves a cascade of events that starts with the release of corticotropin-releasing hormone (CRH) from the hypothalamus. This leads to the release of adrenocorticotropic hormone (ACTH) by the pituitary, resulting in adrenal cortex release of glucocorticoids (cortisol) and adrenal medulla release of norepinephrine and epinephrine (Becker et al., 2002; Mastorakos & Ilias, 2003).

Although short-term stress responses function to reestablish homeostasis, extreme and/or chronic HPA axis activation is maladaptive and can result in health problems. For example, chronic stress can lead to cardiovascular disease, ulcers, immunosuppression, neural degeneration, energy stores expenditure (resulting in fatigue myopathy and steroid diabetes), bone decalcification, and growth impairments (Becker et al., 2002). HPA axis hyperactivation has been associated with psychopathology. For example, severe stress often precedes the onset of psychopathology including anxiety, depression, PTSD, and schizophrenia (see de Kloet, 2003; Heim & Nemeroff, 2001; Nemeroff, 1998; Walker & Diforio, 1997 for reviews), and mothers exhibiting psychopathology are also more likely to experience increased stress during pregnancy (Zuckerman et al., 1989). Futhermore, depression and anxiety, which are often comorbid (Levine et al., 2001; Nemeroff, 2002), are accompanied by the biochemical pattern reflective of a stress response including both elevated cortisol and nonepinephrine (see Arborelius et al., 1999; de Kloet, 2003 for reviews).

MATERNAL CORTISOL DURING PREGNANCY

During pregnancy, maternal cortisol is also regulated by the placenta, deciduas, and fetal membranes. Over the course of pregnancy, the placenta secretes increasing amounts of CRH into the fetal and maternal bloodstreams, with levels

increasing exponentially from the eight week of gestation until delivery (Leung et al., 2001; Smith, 1998). The increasing unbound circulating placental CRH levels during pregnancy stimulate ACTH production in the pituitary leading to increased adrenal function. Placental CRH levels are, in turn, regulated by maternal neuroendocrine function with circulating glucocorticoid and norepinephrine levels stimulating placental CRH release and gene expression (Jones, Brooks & Challis, 1989; Mastorakos & Ilias, 2000; Petraglia et al., 1989). Maternal HPA activity (Leung et al., 2001; Mastorakos & Ilias, 2000; Smith & Thomson, 1991) and catecholamine levels rapidly rise from mid-gestation on to the end of pregnancy (Peleg et al., 1986).

Cortisol can be considered a culprit stress variable inasmuch as various immune and psychological challenges have been noted to increase its production (Altemus et al., 2001; Kanaley & Hartman, 2002; Padgett & Glaser, 2003). This may be particularly true during pregnancy, when several stress-related states including depression, anxiety and anger have been associated with elevated cortisol (Field et al., 2005a; Field et al., 2003).

MEASUREMENT OF CORTISOL

Although cortisol has been assayed in saliva, urine, and serum, some have suggested that saliva cortisol is a better indicator of hypothalamic-pituitary-adrenal (HPA) function than other body fluids because cortisol in saliva is present only in the unbound form (Obel et al., 2005). This is particularly true for pregnancy inasmuch as cortisol-binding proteins in plasma increase during pregnancy, suggesting that saliva cortisol may give a more accurate assessment of the biologically active hormone.

Because cortisol can be affected by confounding variables including circadian rhythms, physical activity, various foods, smoking, caffeine, and alcohol, participants are typically asked to collect their samples early in the morning (Nepomnaschy et al., 2006). Others disagree, saying that evening cortisol measures may be more sensitive to the influence of chronic stress, inasmuch as morning values are at their peak, and it would take a major event to raise the already elevated levels (Grossi et al., 2001; Powell et al., 2002). Some have suggested that multiple measurements should be collected at different times and be aggregated.

PRENATAL CORTISOL EFFECTS ON THE FETUS

Miscarriage or spontaneous abortion has been associated with elevated cortisol, particularly in the first month following conception. In a recent study, pregnancies associated with elevated maternal cortisol were 2.7 times more likely to be unsuccessful (Nepomnaschy et al., 2006). Whereas 90% of the elevated cortisol pregnancies resulted in spontaneous abortions, only 33% of the normal cortisol pregnancies were lost. As the authors suggested, the association between increased maternal cortisol and higher risk of miscarriage within the first month of conception, together with the failure of previous research to find such an association during later gestation, suggested that pregnancy may be particularly sensitive to elevated cortisol during the placentation period.

Although the cortisol response to stress is adaptive in the face of challenging external stimuli, and although pregnancy cortisol is necessary for normal fetal growth and the preparation of the fetus for extrauterine life (Challis et al., 2001; McEwen, 2000), excessive cortisol appears to have negative influences on fetal development (Hansen et al., 2000; Obel et al., 2005). Fetal activity and fetal behavior have been notably affected by both elevated cortisol and elevated corticotropin-releasing hormone (CRH) (Rotmensch et al., 1999; Sandman et al., 1999a). These have included the failure of the fetus to show habituation to an acoustic stimulus (Sandman et al., 1999a) and an attenuated startle response in fetuses age 24–34 weeks after receiving synthetic glucocorticoids (Rotmensch et al., 1999).

Fetal activity and fetal weight have been associated with prenatal cortisol in one of the present authors' studies (Field et al., 2005a). Pregnant women were recruited between 20 and 28 weeks gestation and urine samples were assayed for cortisol, norepinephrine, epinephrine, dopamine, and serotonin. Ultrasound sessions were videotaped and coded for fetal activity and estimated fetal weight. Regression analyses were then conducted with fetal activity and fetal weight as outcome variables. Gestational age entered both analyses as the first variable followed by: (1) prenatal cortisol as a significant predictor of fetal activity (see Table 1); and (2) prenatal cortisol as a significant predictor of estimated fetal weight (see Table 2).

That gestational age explained a significant amount of the variance in fetal activity was not surprising inasmuch as the authors have noted fetal activity to increase significantly from 5 to 7 months gestational age (the time span covered in the study) and then decrease at 8 months (Dieter et al., 2001) (see Figure 1). That cortisol explained additional variance is a novel but, again, perhaps not surprising finding given that cortisol is highly correlated with depression and

Table 1. Model summary on fetal activity (Field et al., 2005a)

Model	*R*	*R square*	*df*	*F*	*t*	*p*
1	0.236	0.055	1	7.58		.007
Gestational Age					2.750	.007
2	0.351	0.123	6	2.90		.011
Gestational Age					2.840	.005
Cortisol					2.230	.028
Norepinephrine					0.122	.903
Epinephrine					1.000	.317
Dopamine					0.566	.572
Serotonin					0.675	.501

anxiety and, in turn, with fetal activity, as previously noted (Dieter et al., 2005). In contrast, the relationship between cortisol and estimated fetal weight was not expected even though many animal studies show a relationship between fetal weight/growth and corticosteroids. Rather, norepinephrine was expected to contribute to the variance on fetal weight based on the findings of Glover et al. (1999) and the present authors' data (Field et al., 2004a). In the path analysis of the Field et al. (2004a) study, norepinephrine predicted low birthweight and cortisol predicted prematurity. Although these findings are inconsistent, the authors' earlier study (Field et al., 2004a) had used birthweight as the outcome, and their more recent study (Field et al., 2005a) used fetal weight as the outcome variable. These two variables, norepinephrine and cortisol, may have different effects on the growth of the fetus depending on the gestational age. These data, thus, highlight the significance of prenatal maternal cortisol as a significant

Table 2. Model summary on estimated fetal weight (Field et al., 2005a)

Model	*R*	*R square*	*df*	*F*	*t*	*p*
1	0.982	0.964	1	1218.24		.000
Gestational Age					34.90	.000
2	0.987	0.974	6	245.30		.000
Gestational Age					36.90	.000
Cortisol					3.01	.004
Norepinephrine					0.55	.586
Epinephrine					0.59	.558
Dopamine					0.04	.971
Serotonin					1.11	.273

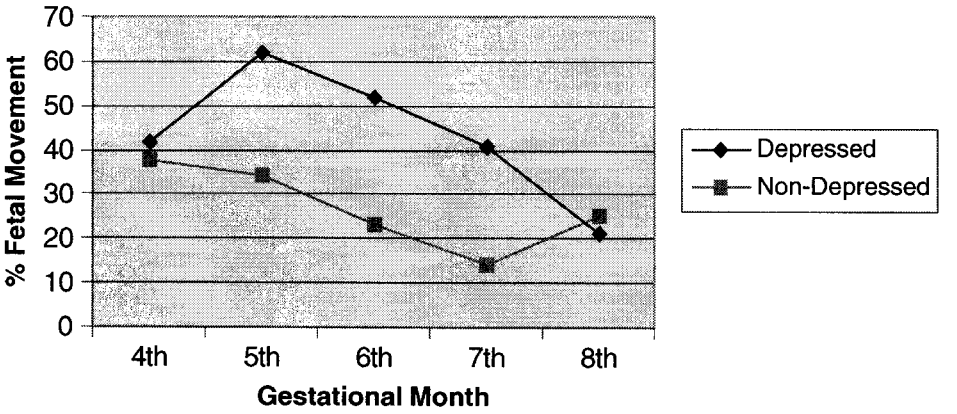

Figure 1. Fetal activity across gestation in fetuses of depressed and non-depressed mothers (Dieter et al., 2003).

predictor for both fetal activity and estimated fetal weight. In a future study, fetal and neonatal outcomes should be assessed in the same sample.

STABILITY OF PRENATAL CORTISOL

In at least two studies the present authors have documented the within subject stability of cortisol across pregnancy and from pregnancy to the newborn period. In a large sample study, pregnant women were recruited during their second trimester of pregnancy ($M = 20$ weeks gestation), and they were given a second assessment at approximately 32 weeks gestation. (Field et al., 2008). For both of these assessments, the pregnant women completed self-report measures including the Center for Epidemiological Studies-Depression Scale (CES-D) (Radloff, 1977), the State Anxiety Inventory (STAI) (Spielberger et al., 1970), and the State Anger Inventory (STAXI) (Spielberger, 1999), and their urines were assayed for cortisol, catecholamines (norepinephrine, epinephrine, and dopamine), and serotonin. Stability was noted for both the self-reported mood states and for the biochemistry across the 20- to 32-week gestational age period. Cortisol was significantly related to depression and to anxiety, all of which were significantly stable at 20 and 32 weeks. Cortisol at 20 weeks was correlated with cortisol at 32 weeks and was also correlated with depression and anxiety as well as leg pain and sleep disturbances.

In another study, the authors explored (1) the relationship between the mothers' prenatal and postnatal cortisol levels to determine continuity and (2) the relationship between the mothers' prenatal cortisol and the newborns' postnatal cortisol (Field et al., 2004c). In this sample, urines of depressed and

Table 3. Regression analysis on mothers' postnatal cortisol as dependent measure and prenatal biochemistry as predictors (Field et al., 2004c)

Prenatal variables	Beta coefficients	*t*	*p*
Cortisol	0.26	2.43	.02
Norepinephrine	0.03	0.32	NS
Epinephrine	0.18	1.73	.09
Dopamine	−0.20	−1.78	.08
5-HIAA (Serotonin)	0.05	0.46	NS

$R^2 = .19$; $p < .003$; NS = not significant.

non-depressed mothers were collected at the prenatal ultrasound clinic between 20 and 28 weeks gestation ($M = 24$ weeks). Their urines were again collected along with their newborns' urines within 24 h after delivery. Although cortisol levels are noted to increase across pregnancy, the cortisol levels decreased from the prenatal period (24 weeks) to the postpartum period. Depressed mothers versus non-depressed mothers, not surprisingly, had higher cortisol levels at both the prenatal and postpartum periods. In a regression analysis, the mothers' prenatal cortisol was a significant predictor of the mothers' postpartum cortisol (see Table 3). The newborns' cortisol levels were significantly higher than their mothers' prenatal cortisol levels, and the regression analysis on the mothers' prenatal cortisol and newborns' cortisol levels suggested that the mothers' prenatal cortisol was a significant predictor of the newborns' cortisol levels (see Table 4).

Table 4. Regression analysis on newborns' cortisol as dependent measure and prenatal biochemistry as predictors (Field et al., 2004c)

Prenatal variables	Beta coefficients	*t*	*p*
Cortisol	0.23	2.07	.04
Norepinephrine	0.32	3.03	.03
Epinephrine	0.19	1.80	.08
Dopamine	−0.10	−0.84	NS
5-HIAA (Serotonin)	−0.02	−0.2	NS

$R^2 = .30$; $p < .000$; NS = not significant.

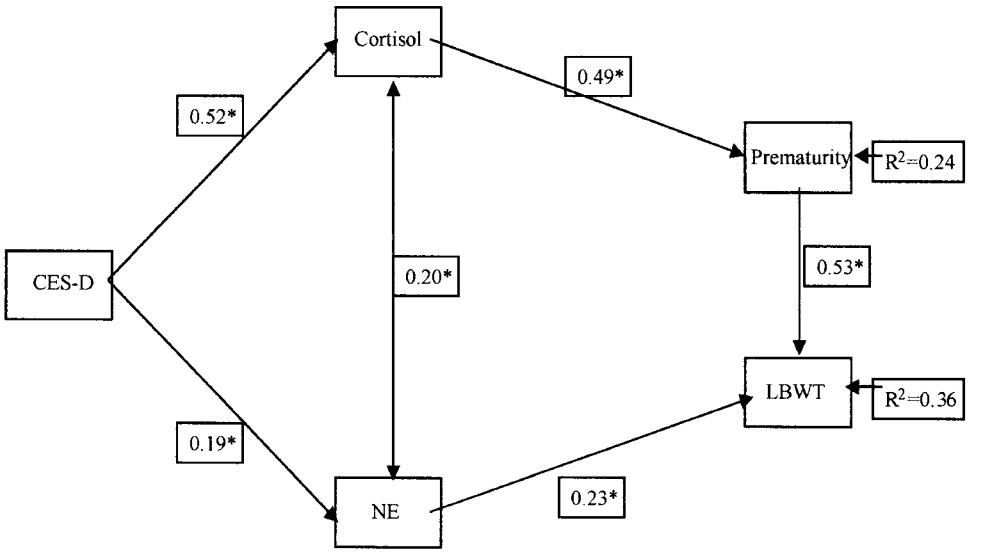

Figure 2. Path analysis of cortisol and NE (norepinephrine) contributions to prematurity and low birthweight, respectively (Field et al., 2004a).

PRENATAL CORTISOL PREDICTS PREMATURITY AND LOW BIRTHWEIGHT

Relationships have been consistently noted between prenatal maternal and fetal cortisol levels (Gitau et al., 1998; Glover et al., 1999). In an early retrospective study by the authors' group, it was noted that depressed women had higher cortisol levels during their last trimester of pregnancy, and their newborns subsequently showed the same pattern of elevated cortisol (Lundy et al., 1999). A more recent study by our group assessed biochemistry levels in depressed and non-depressed pregnant women during their second trimester of pregnancy and at the neonatal period (Field et al., 2004a). The mothers with depressive symptoms had higher prenatal cortisol levels, and they were also more likely to deliver prematurely and to have low birthweight babies. The newborns of mothers with depressive symptoms also had higher cortisol levels. In the path analysis, as predicted in the model proposed, prenatal depression was related to prepartum cortisol and norepinephrine levels, and the prenatal cortisol levels, in turn, were negatively related to prematurity, and the norepinephrine levels were related to low birth weight (see Figure 2). Thus, the elevated prenatal cortisol levels in this study were consistent with the elevated cortisol levels in depressed pregnant women in the Lundy et al. (1999) study.

According to Glover et al. (1999), and others, some 10–20% of the mothers' cortisol crosses the placenta. Just as norepinephrine was related to uterine artery

Table 5. Means for fetal activity and fetal growth measures taken at approximately 20 weeks gestation (Field et al., 2006)

	Cortisol level			
Measures	Low	High	*F*	*p*
Movement (% time)	33.81	41.40	3.81	.05
Femur length (mm)	3.59	3.54	1.02	.32
Head circumference (mm)	18.77	18.13	11.66	.001
Abdominal circumference (mm)	19.93	16.21	11.43	.001
Biparietal diameter (mm)	5.12	4.96	9.27	.003
Fetal weight (g)	535.20	485.89	5.36	.02

blood flow and fetal growth in the study by Glover et al. (1999), norepinephrine was related to fetal growth delays (low birthweight) in the present authors' study (Field et al., 2004a). Once again, in this sample, the mothers' prenatal cortisol levels were higher than their postnatal cortisol levels, and the infants' postnatal cortisol levels were significantly higher than both the mothers' prenatal and postnatal cortisol levels. In addition, in a multiple regression analysis, the mothers' prenatal cortisol predicted neonatal activity and the newborns' vagal activity.

In a subsequent study, depressed pregnant women recruited at approximately 20 weeks gestation were divided by a median split into high and low urinary cortisol level groups (Field et al., 2006). The high cortisol group mothers had fetuses that were more active, and they had smaller head circumference, abdominal circumference, biparietal diameter, and fetal weight (see Table 5). As neonates, the high cortisol group were shorter gestational age and lower birthweight (see Table 6), and they had lower Brazelton habituation and higher Brazelton reflex scores. Discriminant function analysis suggested that cortisol levels more accurately classified the short gestation and low birthweight groups than the mothers' CES-D depression scores. In this study, a significant number of preterm infants were predicted by their cortisol levels (83%). In a similar study on pregnant women, hierarchical stepwise multiple regression analysis was conducted to evaluate the relation between maternal depression, anxiety, stress, cortisol, norepinephrine, and estimated fetal weight (Diego et al., 2006). While controlling for gestational age and fetal gender, the analysis revealed that only cortisol was a significant predictor of estimated fetal weight, suggesting that the effects of maternal depression on fetal growth were mediated by cortisol. Further, mothers with high cortisol levels were at risk for having fetuses with below average estimated fetal weight.

Table 6. Means for neonatal growth measures (Field et al., 2006)

	Cortisol level			
Measures	Low	High	*F*	*P*
Gestational age (weeks) ($R = 35–41$)	38.77	37.15	10.85	.001
Birthweight (g) ($R = 2807–3619$)	3392.87	3073.09	10.64	.001
Birth length (mm)	50.27	48.27	2.29	.14
Head circumference (mm)	34.00	33.45	0.92	.34

Prenatal cortisol levels have been noted to predict preterm birth at an even earlier gestational age ($M = 15$ weeks gestation) (Sandman et al., 2006), In this study, cortisol levels were higher at 15 weeks gestation and at 19 weeks gestation in women who later delivered preterm. The authors suggested that based on their hierarchical regression, maternal cortisol in early pregnancy was mediated by its influence on placental CRH (corticotropin hormone) at 31 weeks via the detection of stress by the placenta, which stimulated the subsequent release of CRH and, in turn, led to the preterm delivery. The authors further suggested that early exposure to cortisol may prime the placental clock and accelerate placental synthesis and the release of corticotrophic releasing hormone. The Field et al. (2004a, 2006) and the Sandman et al. (2006) studies highlight the importance of elevated cortisol predicting to premature delivery and, in turn, to the long-term developmental consequences of preterm delivery (Peterson et al., 2000).

PRETERM MATERNAL CORTISOL AND INFANT DEVELOPMENT

As already mentioned, many newborn behaviors measured by The Brazelton Neonatal Behavior Assessment Scale were negatively affected by elevated prenatal maternal cortisol including habituation, orientation, motor behavior, and autonomic stability (Field et al., 2004a, 2006). In addition, elevated neonatal activity and irritability were noted. Thus, it is not surprising that those infants of high prenatal cortisol mothers have shown temperamental difficulties such as crying and fussing. In a study in which bedtime behaviors were observed at 1 to 3, 5 to 7, and 18 to 20 weeks, crying, fussing and negative facial expressions were noted more frequently in the infants of high cortisol mothers (de Weerth et al., 2003). Maternal reports on temperament also suggested that these infants

have more difficult behavior particularly at the younger ages (weeks 1–7). Similarly, Graham et al. (1999) reported that infants of depressed mothers who had higher neonatal cortisol levels were notably more irritable, and had growth delays. Motor and cognitive development were delayed in these infants until at least three years. In another study on prenatal cortisol effects, high early morning cortisol levels in late pregnancy (37–38 weeks gestation) were related to lower Bayley Mental Development Index scores at three months of age and lower Psychomotor Development Index scores at both three and eight months of age.

PRENATAL CORTISOL EFFECTS ON LATER DEVELOPMENT

Maternal prenatal stress has been related to over activity and/or dysregulation of the HPAC-system in the mothers' offspring. These effects have been reported as responses to novel situations. In a recent study, responses to the first day of school were assessed including the children's cortisol levels (Gutteling et al., 2005). Prenatal cortisol was related to the children's cortisol levels as a reaction to the first day of school. Children whose mothers had higher levels of morning cortisol during pregnancy showed higher levels of cortisol both during the first and second school days. Cortisol circadian rhythms on school days also appeared to have a steeper slope as compared to those of weekend days.

The effects of prenatal cortisol on adult development have been inferred from studies on prenatal glucocorticoid effects on preterm delivery. It is presumed that chronic stress and the resultant prolonged activation of the HPA sympathetic nervous system induces disorders similar to those that are noted after prenatal glucocorticoid administration such as anxiety, depression, diabetes, alcoholism, smoking, and drug abuse (Charmandari et al., 2003; Seckl, 2001) together with immune dysfunction (Coe et al., 2002). Similarly, preterm delivery has been associated with long-term developmental consequences including motor delays (Knoches & Doyle, 1993). Further, low birthweight has been related to an increased incidence of cardiovascular and metabolic disorders in later development, including hypertension, coronary heart disease, type II diabetes, insulin resistance, and hyperlipidemia (Barker, 2002; Welberg & Seckl, 2001). Low birthweight has also been associated with psychopathology such as depression, schizophrenia, and autism (Welberg & Seckl, 2001; Weinstock, 2001).

The links between prenatal cortisol and later development led to the fetal programming or fetal origins hypothesis of adult disease, which suggests that

prenatal cortisol causes low birthweight, which, in turn, leads to vulnerability to diseases in later life. This may be mediated by alterations in the HPAC axis functioning inasmuch as low birthweight individuals have elevated morning cortisol levels in later life (Levitt et al., 2000; Phillips et al., 2000). Total urinary cortisol metabolite excretion (Levitt et al., 2000; Reynolds et al., 2001), elevated cortisol and abnormal regulation of the HPAC axis can also be found in generalized anxiety disorders and depression (Arborelius et al., 1999). Those individuals have higher concentrations of urinary and salivay cortisol (Nemeroff et al., 1984).

POTENTIAL UNDERLYING MECHANISMS

Maternal Neuroendocrine Function and Perinatal Outcomes

Although the mechanisms underlying the effects of cortisol on perinatal outcomes have yet to be determined, one potential pathway involves maternal cortisol directly affecting the fetus. Two other potential pathways involve maternal cortisol and norepinephrine levels regulating the prenatal environment via their effects on the placental clock and uterine artery vasoconstriction.

Direct Effects on the Fetus

Even though the placenta forms a structural and biochemical barrier to protect the fetus, cortisol can readily cross the placenta (Pepe & Albrecht, 1995; Petraglia et al., 1989). As such, it is not surprising that animal studies indicate that elevated maternal corticosteroid levels also result in elevated fetal corticosteroid levels (Koehl et al., 1999; Takahashi et al., 1998). This is supported in humans by the significant association between maternal and fetal cortisol levels (Gitau et al., 1998, 2004) and by research showing that by the beginning of midgestation, placental CRH can stimulate fetal ACTH secretion (Gitau et al., 2001; Liu & Matthews, 1999). As such, elevated maternal cortisol can result in elevated fetal cortisol by directly crossing the placenta into the fetus. The prolonged exposure of the fetus to cortisol can, in turn, negatively affect fetal growth and organ development (Kapoor et al., 2006; Weinstock, 2005).

Effects on the Placental Clock

Maternal cortisol and norepinephrine levels play a key role in regulating the prenatal environment. For example, placental CRH levels are regulated

by maternal neuroendocrine function with circulating glucocorticoid and norepinephrine levels stimulating the expression and release of placental CRH (Challis et al., 2000; Mastorakos & Ilias, 2000). This increase in placental CRH can, in turn, influence the timing and onset of delivery (Sandman et al., 1999a; Sandman et al., 2006) and be responsible for the high rates of premature delivery observed for depressed women (Field et al., 2004a; Orr et al., 2002).

Effects on Uterine Artery Vasoconstriction

Another potential mechanism for the effects of prenatal depression on perinatal outcomes may involve uterine artery vasoconstriction. Depression is a major risk factor for the development of cardiovascular disease, including hypertension (Plante, 2005), and hypertension during pregnancy is a leading cause of maternal and fetal morbidity and mortality including the development of preeclampsia, fetal growth retardation, and premature delivery (Frishman et al., 2005; Seely & Lindh, 2003). The elevated cortisol and norepinephrine levels associated with prenatal depression (Field et al., 2004a; Lommatzsch et al., 2006; Lundy et al., 1999) may underlie these effects by inducing uterine vasoconstriction. For example, both cortisol and norepinephrine are essential components of the mechanism regulating the structure and function of the cardiovascular system (Hadoke et al., 2006; Kandel et al., 2000), with the release of cortisol and norepinephrine into the blood stream eliciting vascular constriction (Girod & Brotman, 2004; Kandel et al., 2000). Cortisol and norepinephrine have also been shown to directly affect the intrauterine vasculature, with norepinephrine reliably inducing uterine artery vasoconstriction (Steele et al., 1993; Yousif et al., 2003) and cortisol increasing the density of uterine artery adrenoreceptors, thereby potentiating norepinephrine-mediated uterine artery contractions (Xiao et al., 2003).

Uterine artery vasoconstriction is associated with preeclampsia (Knuist et al., 1998) and the development of other perinatal complications including fetal growth retardation (Copper et al., 1996; Dugoff et al., 2005) and premature delivery (Tchirikov et al., 2002). These outcomes are likely the result of reduced uterine blood flow resulting in placental hypoxia and the restriction of oxygen and nutrient delivery to the fetus. Uteroplacental circulation can be estimated using color Doppler ultrasound with pulsed wave methodology to derive the uterine artery resistance index (RI) from the ratio of peak systole and dystole measurements. Doppler ultrasound can also be used to derive the pulsatility index (PI). Both resistance index and pulsatility index values are inversely related to uterine artery blood flood. Doppler ultrasound velocimetry has been

used to estimate uterine artery blood flow in anxious women in at least three studies. These studies reveal that anxious women exhibit elevated uterine artery PI (Sjostrom et al., 1997) and uterine artery RI during the third trimester (Teixeira et al., 1999), but not during the second trimester of pregnancy (Kent et al., 2002).

The HPAC (hypothalamic-pituitary-adrenal-cortico) system has been located primarily in the hypothalamus and brainstem. The principal regulator of the system, corticotrophic-releasing hormone (CRH) located in the hypothalamus, is released into circulation together with arginine vasopressin in response to stress (Weinstock, 2005). CRH then releases adrenocorticotrophic hormone (ACTH) in the pituitary gland, and ACTH and CRH activate the adrenal gland to release cortisol and catecholomines (Chrousos & Gold, 1992). The noradrenergic, serotonergic, and dopaminergic systems are activated and, in turn, influence attention, mood, and motor behavior (Makino et al., 2002).

A recent review on studies of isolated placentas in rats, non-human primates, and humans led the authors to propose three principal mechanisms for the transference of cortisol from the pregnant woman to the fetus (Huizink et al., 2004). The first potential mechanism they proposed was that cortisol crosses the placenta. The second alternative was that placental CRH is released in response to stress and reaches the fetal circulation. The third was that the utero placental blood flow changes in response to maternal stress-induced secretion of cortisol and catecholomines.

Others (Wüst et al., 2005a) have suggested that genetic determinants could mediate the relationship between HPAC activity and low birthweight or short gestational age inasmuch as twin studies have shown high heritability of HPAC activity (Bartels et al., 2003; Federenko et al., 2004; Wüst et al., 2000). In this way, according to the authors, genetic factors may influence the cortisol levels that the fetus is exposed to and their severe impact on birthweight, length and gestational age. Still others have suggested that the increase in total cortisol could be due to a temporary decrease of hypothalamic-pituitary-sensitivity to cortisol feedback (Scott et al., 1990), to an increase in arginine vasopressin secretion, in turn, stimulating the release of ACTH and cortisol (Magiakou et al., 1996) and or to the anti-glucocorticoid action of rising circulating levels of progesterone (Allolio et al., 1990).

Even though fetal cortisol levels are reputedly lower than those of the mother (Gitau et al., 2001), high levels of maternal cortisol can double fetal concentrations (Gitau et al., 1998) inasmuch as 33–40% of the variance in fetal cortisol has been attributed to prenatal maternal cortisol levels (Gitau et al., 1998, 2001). Animal studies have suggested that although glucocorticoids are

important for normal maturation in regions of the developing nervous system, prenatal glucocorticoid administration tends to delay maturation of neurons, myelination, and vasculature (Huang et al., 2001a, 2001b), and exposure to glucocorticoids *in utero* affects synapse formation (Antonow-Schlorke et al., 2003) and may permanently alter brain structure (Mathews, 2000).

Although several have suggested that life-long programming of the HPAC system might explain the relationship between birthweight and adult diseases, the data are contradictory. In a recent study in Finland, elderly subjects with detailed birth records were studied to examine the relationship between birth measures and the adult HPAC system (Kanjanytie et al., 2002). Cortisol and the Ponderal Index were significantly related in both genders, but the association between fetal growth and cortisol levels differed as a function of gestational age. In those adults who had been born before 39 weeks gestation, prenatal cortisol was inversely related to birthweight and to birth length, whereas for those born after 40 weeks gestation, a positive correlation was noted between prenatal cortisol, birthweight and the Ponderal Index. Thus, the relationship between birthweight and cortisol in adult life appears to be different for subjects born at different gestational ages.

INTERVENTIONS TO LOWER PRENATAL MATERNAL CORTISOL

Given all of the aforementioned negative effects of prenatal maternal cortisol, and given the relationship between elevated prenatal cortisol levels and premature birth (Field et al., 2004a; McCool et al., 1994; Ponirakis et al., 1997), interventions are needed for lowering cortisol levels. Although the anti-depressant literature is mixed, as few as 1% of pregnant women take antidepressants, highlighting the need to find alternative therapies for reducing cortisol. In a recent study, pregnant women were assigned to a stress reduction or a non-stress reduction condition (Urizar et al., 2004). In the stress reduction condition, the women were asked to follow the instruction "eliminate things that are stressful and/or participate in things that are relaxing on a daily basis for the rest of the study." Content analysis of the activities selected by the women for stress reduction were household activities (58%), outdoor activities (51%), and interaction with others (35%). The analysis also indicated a significant decrease in morning cortisol levels for the stress reduction group. Participants in the first trimester of pregnancy also had significant decreases in evening cortisol levels. The effects of the stress reduction program may have been mediated by exercise-induced reductions in cortisol. Stimulation of pressure

receptors, as in exercise, typically leads to an increase in vagal activity and an associated decrease in cortisol (Field et al., 1996).

Possibly by a similar mechanism, massage therapy has been noted to decrease cortisol in many stress conditions (Field et al., 2005b). The present authors have noted, for example, a significant decrease in cortisol following pregnancy massage (Field et al., 2004b). In this study, pregnant women were recruited during their second trimester of pregnancy and randomly assigned to a massage therapy group, a progressive muscle relaxation group or a control group who received prenatal care alone. The massage therapy group participants received two 20-min sessions by their significant others each week for 16 weeks of pregnancy starting during their second trimester. Immediately after the massage sessions on the first and last days, they reported lower levels of anxiety and depressed mood as well as less leg and back pain. The massage group, by the end of study, had lower cortisol and norepinephrine levels and higher dopamine and serotonin levels. These biochemical changes may have contributed to the reduced fetal activity (which is often excessively high in depressed pregnant women) and the better neonatal outcome for the massage group including a lesser incidence of prematurity and low birthweight as well as better performance on the Brazelton Neonatal Behavior Assessment Scale. Lower cortisol levels may have also contributed to the lesser incidence of obstetric complications including abortion, preeclamsia, preterm labor, and a lesser incidence of pregnancy infection (Field et al., 2004c).

Similar effects have been noted for rat pups in neonatal handling paradigms. Short periods of handling rat pups (50 min per day) during the first two weeks of life permanently increases hippocampal glucocorticoid receptor levels (Meaney et al., 1992). This reputedly potentiates the HPAC axis sensitivity to glucocorticoid-negative feedback and lowers plasma glucocorticoid levels throughout life. Meaney and his colleagues have called this state "compatible with a good adjustment to environmental stress." Inasmuch as neonatal handling enhances mother care-related behavior, the handling that the rat pups receive from the mother reputedly stimulates pressure receptors in the rat pups, leading to very similar effects as those from massage in the human infants (Schanberg & Field, 1987).

SUMMARY AND FUTURE DIRECTIONS

In summary, future research is needed to assess the more complex interactions that occur between cortisol and catecholamines (norepinephrine, epinephrine, dopamine) and serotonin. Although these may be too complex to study in

human models, they are likely the more critical underlying mechanisms. Further research is also needed on cortisol-lowering interventions to prevent prematurity and low birthweight and the lifelong problems that have followed these birth conditions. Elevated prenatal cortisol has been associated with several negative conditions including aborted fetuses, excessive fetal activity, delayed fetal growth and development, prematurity and low birthweight, attention and temperament problems in infancy, externalizing problems in childhood and psychopathology and chronic illness in adulthood. Given that as much as 10–20% of the mother's prenatal cortisol crosses the placenta, these effects on the fetus and later development are perhaps not surprising. Cortisol would appear to be the mediating variable resulting from prenatal stress in several forms including depression, anxiety, and daily hassles. Cortisol effects are further complicated by its interaction with neurotransmitters such as norepinephrine which may, itself, cause premature birth and intrauterine growth deprivation via uterine artery resistance. Recent research suggests that cortisol-reducing therapy such as massage therapy can at least prevent some of the negative effects including prematurity and low birthweight.

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