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The Timing of Prenatal Exposure to Maternal Cortisol and Psychosocial Stress is Associated with Human Infant Cognitive Development

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Abstract

The consequences of prenatal maternal stress for infant mental and motor development were examined in 125 full term infants at 3, 6 and12 months of age. Maternal cortisol and psychological state were evaluated five times during pregnancy and at 3, 6 and 12 months postpartum. Exposure to elevated concentrations of cortisol early in gestation was associated with a slower rate of development over the first postnatal year and lower scores on the mental development index of the Bayley Scales of Infant Development (BSID) at 12 months. Elevated levels of maternal cortisol late in gestation, however, were associated with accelerated development over the first year and higher scores on the BSID at 12 months. Elevated levels of maternal pregnancy specific anxiety early in pregnancy were independently associated with lower scores on the BSID at 12 months. These associations could not be explained by postnatal maternal psychological stress, stress related to parenting, prenatal medical history, socioeconomic factors or child race, sex or birth order. These data suggest that maternal cortisol and pregnancy specific anxiety have programming influences on the developing fetus. Prenatal exposure to the same signal, cortisol, had opposite associations with infant development based on the timing of exposure.

Keywords

pregnancy; cortisol; stress; infant development; cognition; prenatal; depression; anxiety; fetal programming

The prenatal period is a time of rapid change during which fetal organs and organ systems are forming and are vulnerable to both organizing and disorganizing influences. These influences on the fetus have been described as programming; the process by which a stimulus or insult during a vulnerable developmental period has a long-lasting or permanent effect. The effects of programming are dependent on the timing of the exposure and on the developmental stage of organ systems. There is convincing support for fetal programming of adult health outcomes, however, the evidence comes primarily from retrospective studies that rely on birth phenotype (e.g., small size at birth or preterm delivery) as an index of fetal development (Barker, 1998, 2002). It is unlikely, however, that birth phenotype alone is the cause of subsequent health outcomes. Birth phenotype, instead, reflects fetal adaptation to exposures that shape the structure and function of physiological systems that underlie health and disease risk (Gluckman & Hanson, 2004; Morley, Blair, Dwyer, & Owens, 2002). One emerging risk factor for health outcomes resulting from fetal programming is prenatal exposure to maternal stress signals. The

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purpose of the present study was to investigate the programming influence of biological and psychosocial indicators of prenatal maternal stress for fetal development and to evaluate the effects of timing of exposure to stress on infant development.

Fetal Programming: The Role of Glucocorticoids (GCs)

For a number of reasons GCs have been proposed as a primary candidate for fetal programming. Glucocorticoids, cortisol in humans, are steroid hormones that play a critical role in normal development and are the end product of the hypothalamic-pituitary-adrenal (HPA) axis, one of the body's major stress responsive systems. HPA axis activity is regulated by the release of hypothalamic corticotrophin-releasing hormone (CRH) which stimulates the biosynthesis and release of adrenocorticotropic hormone (ACTH). Release of ACTH from the pituitary into the blood stream triggers cortisol production and release from the adrenal cortex. Cortisol is released into the general circulation and has effects on nearly every organ and tissue in the body (Munck, Guyre, & Holbrook, 1984). In human pregnancy, regulation of the HPA axis changes dramatically with the production and release of CRH from the placenta. In contrast to the role of cortisol in the negative feedback regulation of the HPA axis, cortisol stimulates placental CRH production resulting in a positive feedback loop that allows for the simultaneous increase of CRH, ACTH, and cortisol in the maternal and fetal compartments over the course of gestation (King, Nicholson, & Smith, 2001; Petraglia, Florio, Nappi, & Genazzani, 1996).

Maternal cortisol increases two- to four-fold over the course of normal gestation (Mastorakos & Ilias, 2003; Sandman et al., 2006). Fetal exposure to the increasing concentrations of maternal cortisol is regulated by a placental enzyme, 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which oxidizes cortisol to its inactive form cortisone (Beitens, Bayard, Ances, Kowarski, & Migeon, 1973; Brown et al., 1996). Levels of placental 11β-HSD2 also rise as pregnancy advances, providing partial protection for the fetus from maternal cortisol during critical stages of development. Towards the end of pregnancy, however, levels of the placental enzyme drop allowing a larger proportion of maternal cortisol to reach the fetus (Giannopoulos, Jackson, & Tulchinsky, 1982; Murphy, Smith, Giles, & Clifton, 2006). The normal increase in maternal cortisol during gestation and the decrease in placental 11β-HSD2 at the end of pregnancy ensure that the fetus is exposed to sufficient levels of cortisol during the third trimester, which are important for maturation of the fetal lungs and for preparation of the fetus for delivery (Austin & Leader, 2000; Hacking, Watkins, Fraser, Wolfe, & Nolan, 2001). Because placental 11β-HSD2 is only a partial barrier, active maternal cortisol passes through the placenta, and fetal cortisol levels are significantly correlated with maternal levels throughout gestation (Gitau, Cameron, Fisk, & Glover, 1998; Gitau, Fisk, Teixerira, Cameron, & Glover, 2001). Glucocorticoid receptors are present throughout the central nervous system (Diorio, Viau, & Meaney, 1993; Jacobson & Sapolsky, 1991; Sanchez, Young, Plotsky, & Insel, 2000) and GCs easily pass through the blood-brain barrier (Zarrow, Philpott, & Denenberg, 1970). Glucocorticoids play a critical role in normal brain development, which provides further evidence for GCs as a mechanism for programming the fetus (Matthews, 2000; Trejo, Cuchillo, Machin, & Rua, 2000; Welberg & Seckl, 2001).

Glucocorticoids shape the development of the neural systems involved in the regulation of emotion and cognitive function. Furthermore, moderate increases in GCs have salutary effects on both brain development and behavioral regulation (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006) For example, rodents exposed in the early postnatal period to moderate increases in GCs display decreased physiological and behavioral stress responses, persisting improvements on cognitive tasks assessing learning and memory, and increased neural plasticity (Catalani et al., 2002; Scaccianoce, Catalani, Lombardo, Consoli, & Angelucci, 2001; Trejo et al., 2000). Exposure to excess GCs, however, particularly during vulnerable periods, appears to be neurotoxic (Uno et al., 1994; Uno et al., 1990). Animal models have

demonstrated that prenatal exposure to administration of high levels of synthetic GCs has profound and lasting consequences for offspring including increased stress reactivity (Coe & Lubach, 2005; Hauser et al., 2007), poorer performance on cognitive tasks (Brabham et al., 2000) and impaired brain development, particularly in terms of reduced hippocampal volume (Bruschettini, van den Hove, Gazzolo, Steinbusch, & Blanco, 2006; Coe & Lubach, 2005; Uno et al., 1994). The few studies that have assessed the effects of prenatal treatment with a high dose of synthetic GCs in humans (given to women at risk of preterm delivery for maturation of fetal lungs) have documented consequences for emotional disturbances in early childhood (French, Hagan, Evans, Godfrey, & Newnham, 1999), dysregulated stress responses in infancy (Davis, Townsend et al., 2004; Davis et al., 2006), impaired memory in school aged children (MacArthur, Howie, Dezoete, & Elkins, 1982) and neurodevelopmental delays in toddlers (Spinillo et al., 2004; Wapner et al., 2007).

There are only a handful of studies that have evaluated the role that endogenous maternal cortisol plays in shaping human fetal development. Prenatal exposure to elevated maternal cortisol has been shown to predict increased fussiness, negative behavior and fearfulness in infancy (Davis et al., 2007; de Weerth, van Hees, & Buitelaar, 2003) and greater cortisol reactivity in childhood (Gutteling, de Weerth, & Buitelaar, 2005). Only one group has evaluated the effects of endogenous maternal cortisol during pregnancy on infant cognitive and motor development. Huizink and colleagues (2003) have shown that elevated prenatal maternal cortisol during the third trimester was associated with delays in mental development at 3 months and motor development at 3 and 8 months. A limitation of these studies with humans is that it is difficult to separate shared genetic effects on emotion and stress regulation from direct effects of maternal cortisol. However, in conjunction with animal models where random assignment is possible, and human studies involving synthetic GC administration, these studies suggest that prenatal exposure to endogenous maternal cortisol has a programming influence on the developing nervous system.

Fetal Programming: The Role of Maternal Psychosocial Stress

During pregnancy maternal psychosocial stress threatens the fetal nervous system and shortens the length of gestation. In humans, the most well documented effects of exposure to maternal stress is on birth outcomes including preterm delivery (Copper et al., 1996; Dole et al., 2003; Glynn, Wadhwa, Dunkel Schetter, & Sandman, 2001; Glynn, Dunkel Schetter, Hobel, & Sandman, 2008; Hobel & Culhane, 2003). Less is known about the consequences of prenatal maternal stress for human development independent of birth outcome. Numerous studies with rodent models have shown pervasive detrimental effects of exposure to prenatal maternal stress for the offspring (Dickerson, Lally, Gunnel, Birkle, & Salm, 2005; Maccari & Morley-Fletcher, 2007; Van den Hove et al., 2005; Weinstock, 2001). Similarly, exposure of non-human pregnant primates to behavioral stressors during the prenatal period is associated with enhanced stress reactivity (Clarke, Wittwer, Abbott, & Schneider, 1994), compromised neuromotor development (Schneider & Coe, 1993; Schneider, Coe, & Lubach, 1992), irritable temperament (Schneider, 1992), poor attention regulation (Schneider, Roughton, Koehler, & Lubach, 1999) and impaired brain development, specifically reduced neurogenesis in the dentate gyrus (Coe et al., 2003). Stress early in gestation had more serious consequences for offspring than later gestational stress (Mueller & Bale, 2007; Schneider et al., 1999), although not all studies have found an effect of timing of exposure (Coe et al., 2003). The ability to generalize to humans from animal models is limited by the vast differences in reproductive physiology, even in closely related species, such as humans and non-human primates (Power et al., 2006) and by the significant differences in the type of prenatal stress employed with different species (e.g., physical restraint in rodents vs. report of stress in humans).

A small but growing literature with human populations has established that prenatal exposure to elevated levels of maternal stress is associated with behavioral and emotional disturbances during infancy and childhood, after controlling for postpartum maternal psychological distress, including postpartum depression (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Davis et al., 2007; Davis, Snidman et al., 2004; Gutteling et al., 2005; Huizink, De Medina, Mulder, Visser, & Buitelaar, 2002; O'Connor, Heron, & Glover, 2002). Effects of prenatal maternal stress on cognitive and motor development are less clear. There is evidence that maternal self report of elevated stress and anxiety during the prenatal period is associated with delayed infant cognitive and neuromotor development (Brouwers, van Baar, & Pop, 2001; Huizink et al., 2003) and that these deficits may persist into adolescence (Mennes, Stiers, Lagae, & Van den Bergh, 2006). However, not all studies have demonstrated such an association (Brouwers et al., 2001; DiPietro, Novak, Costigan, Atela, & Ruesing, 2006; Van den Bergh, 1990) and is possible that generalized self-report measures of psychological distress do not adequately characterize stress that is unique during pregnancy. Evidence is emerging that measures of pregnancy specific stress are better than measures of generalized psychological distress for predicting developmental outcomes including preterm delivery (DiPietro, Ghera, Costigan, & Hawkins, 2004; Roesch, Dunkel-Schetter, Woo, & Hobel, 2004), fetal behavior (DiPietro, Hilton, Hawkins, Costigan, & Pressman, 2002), infant cognitive and motor development (DiPietro et al., 2006; Huizink et al., 2003) and infant emotional regulation (DiPietro et al., 2006).

Summary

During the prenatal period maternal signals of stress have a programming influence on the developing fetus and it is possible that these signals have different consequences as gestation advances. There are, however, few prospective studies with humans that have addressed this question. Given the vast changes in both maternal physiology and fetal development during the prenatal period, characterization of the effects of prenatal maternal cortisol and psychosocial stress for development requires multiple longitudinal assessments during gestation. The goals of the current study were to determine first, whether maternal cortisol maternal and psychological stress during pregnancy were associated with cognitive and motor development in the offspring independent of postpartum influences, and second, whether there was a sensitive period for these effects on development.

Methods

Participants

Study participants included mother-infant pairs from an ongoing longitudinal study of prenatal stress and development. Women with singleton pregnancies less than 16 weeks gestational age were recruited from obstetric clinics in Southern California and followed longitudinally from early pregnancy to 12 months postpartum. Women who were English speaking, non smokers, over the age of 18, did not take steroid medication, and for whom there was no evidence for drug or alcohol use during pregnancy were eligible for participation in this study. The current sample included the first 125 full term infants (60 girls and 65 boys) and their mothers to complete the 12 month assessment. Women gave informed consent for all aspects of the protocol, which was approved by the Institutional Review Board for protection of human subjects. Descriptive information for the study sample is shown in Table 1. All infants were full term at birth (M gestational age = 39.2 weeks, SD = 1.1 weeks; M weight = 3436 grams, SD = 447 grams). Infants in this sample were stable at the time of delivery and had a median 5-minute Apgar score of 9 (range = 8 to 10).

Procedures

Maternal saliva samples were collected for cortisol analyses and maternal psychological state (state anxiety, perceived stress and pregnancy specific anxiety) was assessed at five intervals during pregnancy (Time 1: 15.1 ± 0.89, Time 2: 19.1 ± 0.93, Time 3: 25.4 ± .95, Time 4: 30.8 ± 0.69; Time 5: 36.6 ± 0.61 weeks of gestation). Maternal depression was assessed at the first four visits. Infant mental and psychomotor development was evaluated at three (M = 3.1; SD = 0.27), six (M = 6.2; SD = 0.3) and twelve (M = 11.9; SD = 0.3) months of age. At the three postnatal assessments maternal state anxiety, perceived stress, depression and parenting specific stress were measured. The postpartum assessments of maternal psychological state were included to control for the potential influence of maternal affect during the postnatal period on infant development. Additionally, prenatal medical history and obstetric risk was obtained from an extensive medical interview conducted by a research nurse and through review of prenatal and hospital medical records.

Measures

Salivary Cortisol Assessment—Saliva samples were collected in the early afternoon, at least one hour after the participant had eaten, (time of day ranged from 13:19 to 13:30 across the five assessment intervals) using a Salivette sampling device (Sarstedt, Numbrecht, Germany). Within this restricted range of sample collection time, time of day was not associated with cortisol levels (all r's < 0 .15, all p's > 0.10).

Saliva samples were spun and stored at −70 degrees C until assayed. Thawed samples were centrifuged at 3000 rpm for 15 minutes before assay. Salivary cortisol levels were determined by a competitive luminescence immunoassay (LIA; IBL-America, Minneapolis, MN) with reported detection limits of 0.015 μg/dl. The cross reactivity of the assay was <2.5% with cortisone, prednisone and corticosterone and <0.1% with other naturally occurring steroids. The intra- and inter-assay coefficients of variance are 5.5% and 7.6%, respectively. Data reduction for the LIA assay was done by an automated four-parameter logistics computer program (software Mikro Win 2000; Berthold Microplate Luminometer). One maternal sample from the second prenatal visit was removed because it was more than 4 standard deviations above the mean. All samples were assayed in duplicate and averaged. A square root transformation was implemented to reduce skewedness. All values reported in the text, tables and graphs are raw μg/dL levels to facilitate interpretation.

Maternal Psychological Assessments—Generalized or non-specific stress was evaluated using the 12-item version of Cohen's Perceived Stress Scale (PSS, Cohen, Kamarck, & Mermelstein, 1983). The PSS evaluated participants' feelings about how they were able to handle day-to-day problems and hassles, how often they felt nervous and stressed and how often they felt things were going well. Responses were made on a 5-point Likert scale ranging from 1 (never) to 5 (almost always) and the final score could range from 12 to 60. This measure has been used extensively with non pregnant and pregnant samples (Culhane et al., 2001; Glynn et al., 2008) and been shown to have both good internal consistency (α = .80) and validity (Cohen et al., 1983).

The short form of the Center for Epidemiological Studies Depression Inventory was used to evaluate maternal depression (CES-D, Santor & Coyne, 1997). Responses to each of the 9 items in this measure were recorded on a four-point Likert scale with a range of 0 to 3. Anchor points, in terms of days per week, were "rarely or none of the time (less than 1 day)" to "most or all of the time (5−7 days)". The final score could range from 0 to 27, with a higher score indicating greater impairment. This measure has been extensively used and published studies demonstrate both internal consistency (α = .84) and validity of this measure (Santor & Coyne, 1997). The CES-D is a frequently used instrument for the study of depression in the general

population and has been validated in pregnant samples (Marcus, Flynn, Blow, & Barry, 2003). Scores on the CES-D during pregnancy are associated with birth outcome and infant development (Davis et al., 2007; Lundy et al., 1999).

The 10-item State Anxiety subscale of the State-Trait Personality Inventory (STAI, Speilberger, 1983) was used to measure state anxiety. The STAI assessed the degree to which participants had experienced anxiety-related symptoms or emotions. Responses were made using a 4-point Likert scale ranging from 1 (not at all) to 4 (very much) and scores could range from a minimum of 10 to a maximum of 40. The STAI has been used for research purposes with both pregnant (Glynn et al., 2008; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999) and non-pregnant samples. The STAI has good internal consistency with a Cronbach's alpha coefficient of .92 (Spielberger, 1983).

The 10-item Pregnancy Specific Anxiety (PSA) scale was used to measure a woman's feelings about her health during pregnancy, the health of her baby and her feelings about labor and delivery. Answers were given on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much) and included items such as: I am fearful regarding the health of my baby, I am concerned or worried about losing my baby, and I am concerned or worried about developing medical problems during my pregnancy. The final score on this measure could range from 10 to 40. This reliable measure was specifically developed for use in pregnancy research and has good internal consistency (α = .75−.85) (Glynn et al., 2008; Rini et al., 1999).

The 36-item Parenting Stress Index (PSI) is a measure designed to identify stress within the parent-child relationship. Responses were given on a 5-point Likert scale. This measure includes items such as: I find myself giving up more of my life to meet my children's needs than I ever expected and My child rarely does things for me that make me feel good. The total score could range from 36 to 180. The Parenting Stress Index has good internal consistence (α = .95) (Abidin, 1995).

Medical Risk and Obstetric History

An extensive structured medical interview was conducted by a research nurse at the participants' first prenatal visit to assess pregnancy history and to identify risk factors that might affect pregnancy outcome. At each subsequent visit, a follow-up interview was conducted by the research nurse to assess pregnancy related changes in maternal health. Maternal and infant medical records were reviewed to assess prenatal medical history and birth outcome. A binary score assessing the presence or absence of prenatal medical risk was derived. The risk factors considered were infection, hypertension, diabetes, oligohydramnios, polyhydramnios, preterm labor, vaginal bleeding, placenta previa and anemia, in the index pregnancy. Additionally, birth order, gestational age at birth, birth weight and Apgar scores were recorded.

Infant Development

Infant development was assessed using the Bayley Scales of Infant Development-Second Edition (BSID). Examiners were trained by a clinician with over 15 years of experience with the BSID and were directly supervised by a clinical psychologist. Videotaped assessments were reviewed monthly. Interrater reliability, calculated on 20% of the assessments at each age, was 95% at 3 and 6 months and 93% at 12 months. The BSID is a standardized developmental assessment (Bayley, 1993). Measures of development were obtained at each age using the Mental Developmental Index (MDI) and Psychomotor Development Index (PDI). Sample items from the MDI and PDI at each age are presented in Table 2. Reliability coefficients on the BSID were .83, .92, and .88 for MDI and .84, .84, and .84 for PDI at 3, 6 and 12 months of age respectively. Conventional scoring of the BSID created composite MDI and PDI scaled

scores by summing the total number of items achieved, corrected for basal effects. The raw scores were converted to scaled scores by reference to a developmental table. Mean score raw scores and scaled scores for the MDI and PDI are presented in Table 3.

Data Analysis

Preliminary analyses were performed using regressions and t-tests to identify sociodemographic (i.e., race/ethnicity, marital status, education, and household income), pregnancy-related (i.e., prenatal medical risk) and infant (i.e., gestational age at birth, sex, birth order and ever breastfed) variables that might influence infant cognitive or motor development. The factors associated with infant outcomes with a p value of 0.10 or less were gestational age at birth (MDI and PDI, $p < 0.01$), maternal race ($p < 0.10$), prenatal medical risk (MDI only, $p = 0.10$) and birth order (PDI only, $p < 0.01$). None of the assessments of postnatal maternal psychological state (state anxiety, depression or perceived stress) significantly predicted infant development (all p's > 0.2). Furthermore, maternal report of stress within the parent child relationship was not significantly associated with infant development (all p's > 0.2). All variables that were associated with MDI or PDI in preliminary analyses (infant gestational age at birth, maternal race, birth order, and prenatal medical risk) were modeled as covariates. Although postnatal measures of psychological distress were not significantly associated with infant MDI or PDI at 3, 6 or 12 months, models were tested with and without these measures. Adjusting for postnatal maternal psychological distress did not change the statistical significance of the results in any of the analyses described below.

Hierarchical linear modeling (HLM) growth curve analyses (Raudenbush & Bryk, 2002; Singer & Willett, 2003) were used to describe both the trajectory of the prenatal indicators of maternal stress (maternal cortisol and psychosocial measures) across pregnancy and the trajectory of infant development as assessed with the BSID. HLM models were used to determine whether the patterns of prenatal endocrine and psychosocial stress measures were associated with individual differences in infant development. HLM, when used with repeated measures, treats the data in a hierarchical fashion with observations nested within persons. This approach allows variance to be modeled at multiple levels and provides several advantages over OLS regression (Raudenbush & Bryk, 2002). First, standard regression or ANOVA models are limited to one component of variability, the deviation of the individual from the group mean. In contrast, HLM includes the within-person variability assessed over time. Second, estimates of goodness of fit in modeling each individual's data are derived and the most reliable data are given greater statistical weight. Third, HLM produces robust estimates despite missing values for the repeated dependent measure (Ninety-nine participants had complete data at all prenatal assessments. Twenty three participants were missing data from one visit and three participants were missing data from two visits. One hundred and twelve participants had complete data at all postnatal assessments. Eight participants were missing data from one visit and five participants were missing data from two visits. In HLM models cases with complete data are weighted more heavily, but all cases are included in the estimation of effects. Finally, HLM uses precise measures of timing (i.e. gestational week) of data collection rather than nominal estimates of assessment intervals.

Using HLM two sets of analyses were performed. The first analysis was implemented to examine whether prenatal maternal stress measures at a given prenatal assessment predicted the trajectory of infant development over the first postnatal year. In these analyses both mental and motor performance at a given age (3, 6 and 12 months) and developmental trajectories (slope) over the first postnatal year were assessed. To characterize developmental trajectories, raw data (rather than scaled scores) from the mental and psychomotor scales were used in these analyses. Data were modeled at the exact age in weeks that infants were tested to account for variability in assessment age. The second set of analyses assessed the profile or trajectory of

prenatal maternal stress measures that was associated with infant performance at 12 months using scaled scores determined based on developmental norms for the BSID.

1) Predicting Trajectories of Infant Development—To determine whether prenatal maternal stress measures predicted the trajectory of infant development across the first postnatal year two-level models were constructed. For these analyses raw data from the mental and psychomotor scales were used so that the trajectory of development could be assessed. Level 1 variables, or those evaluated longitudinally across the first postnatal year, included: infant mental and psychomotor development (raw data) and infant age in weeks entered as continuous variables. In all cases a linear model best fit the data. Maternal stress measures (cortisol, perceived stress, state anxiety, pregnancy specific anxiety and depression) measured at each of the five prenatal assessments and entered as continuous variables, were modeled at level 2. Prenatal predictors were assessed at each of the five prenatal assessment time points. Time invariant variables that reached criterion for inclusion as covariates [gestational age at birth, race/ethnicity (Hispanic: 0 = no, 1 = yes; white: 0 = no, 1 = yes), prenatal medical risk (MDI only; 0 = no, 1 = yes) and birth order (PDI only; 0 = firstborn, 1 = later born) were included at level 2. For each level 1 variable the models were tested for differences in slope and intercept at 3, 6, and 12 months of age.

2) Patterns of Maternal Biosocial Stress Associated with Infant Outcomes—At the infant ages where significant associations were found between predictor and outcome variables, a second set of analyses was performed to characterize the profile of maternal stress across pregnancy that was associated with infant outcomes at a given age. In all cases predictor and outcome variables were modeled as continuous variables. For these analyses, two-level models were constructed to evaluate maternal cortisol and psychosocial stress trajectories across pregnancy. Level 1 variables, or those evaluated longitudinally across the five prenatal assessment days, included: maternal cortisol, psychosocial measures (perceived stress, state anxiety, pregnancy specific anxiety and depression) and gestational week. A linear model was applied in all cases except for pregnancy specific anxiety where a quadratic function was a better fit ($\chi^2(3) = 12.1$, $p < .01$).

BSID scores (MDI and PDI), entered as continuous variables, were the outcomes of interest and were modeled at level 2. Time invariant variables that reached criterion for inclusion as covariates [gestational age at birth, race/ethnicity (Hispanic: 0 = no, 1 = yes; white: 0 = no, 1 = yes), prenatal medical risk (MDI only; 0 = no, 1 = yes), and birth order (PDI only; 0 = firstborn, 1 = later born) as well as postnatal measures of psychosocial distress were included at level 2. For each level 1 variable the model was tested for differences in slope and intercept at all time points within the range of actual endocrine and psychosocial assessments (13 to 38 weeks of gestation). Individual slope and intercept values were retained from significant models. The values that were most strongly associated with infant outcomes were entered into stepwise and hierarchical regression models to determine whether maternal psychosocial and endocrine stress measures jointly or independently predicted BSID scores.

Results

Infant Development

The unconditional growth model was significant indicating that mental ($t = 105.2$, $p < 0.001$) and psychomotor ($t = 108.3$, $p < 0.001$) performance (raw scores) improved across the first postnatal year (see Table3). As expected, scaled scores calculated with reference to developmental norms, did not increase ($p > 0.03$). Table 4 shows the correlation between mental and psychomotor development scaled scores across the three assessment time points. As

illustrated, modest stability is seen in BSID scores with a stronger association among temporally adjacent measures.

Maternal Cortisol

The unconditional growth model was significant indicating that, as expected, salivary cortisol levels increased across gestation ($t = 13.6$, $p < 0.001$). Salivary cortisol levels increased from 0.27 at 15 gestational weeks to 0.61 at 37 gestational weeks. Table 5 shows the correlation between cortisol measures across pregnancy. Moderate correlations were seen between temporally adjacent assessments.

Maternal Psychological State

Maternal perceived stress (means ranged from 20.1 to 21.6), depression (means ranged from 13.7 to 15.1) and state anxiety (means ranged from 17.7 to 18.6) did not significantly change over the course of pregnancy (p's ranged from 0.06 to 0.30). Pregnancy specific anxiety changed significantly across gestation ($t = 3.4$, $p < 0.01$). Levels were highest early in pregnancy and decreased through mid gestation. Mean pregnancy specific anxiety scores ranged from 17.3 to 18.7.

Each of the four psychosocial measures was stable over pregnancy. Within each measure intercorrelations ranged from 0.51 to 0.75 during pregnancy. Not only were scores on the psychosocial measures stable during the prenatal period, but as expected, concurrent measures of state anxiety, perceived stress and depression were intercorrelated (average r's = 0.66, p's < .001). The associations between these measures and pregnancy specific anxiety were lower, but also significant (average r's = 0.41, p's < .001).

During the postnatal period, levels of state anxiety (means ranged from 16.8 to17.5), perceived stress (means ranged from 20.1 to 21.1) and depression (means ranged from 12.8 to 12.9) were relatively stable (r's ranged from 0.45 to 0.68) and concurrent measures were intercorrelated (average r's = 0.67). Mean levels of parenting stress ranged from 64.2 to 66.6 and parenting stress was relatively stable over the first postnatal year (r's ranged from 0.48 to 0.67).

Prenatal Maternal Cortisol and Maternal Psychological state

Data indicate that maternal cortisol was not significantly associated with maternal anxiety, depression or pregnancy specific anxiety at any of the five prenatal assessment time points (all r's < 0.18). Prenatal maternal perceived stress was not associated with maternal cortisol at any of the prenatal assessment time points (all r's < 0.13) with the exception of the 36+ weeks' GA assessment. At this time point maternal cortisol was negatively associated with perceived stress levels [$r(119) = -.21$, $p < .05$].

Maternal Prenatal Stress Measures and Trajectories of Infant Development

We first examined whether the rate of infant development over the first postnatal year was associated with prenatal cortisol at each assessment interval, 15 weeks, 19 weeks, 25 weeks, 31 weeks and 37 weeks. For these analyses raw scores (rather than scaled scores) were used so that developmental changes could be evaluated. Data indicate that the level of maternal cortisol both early and late in gestation predicted infant mental development. Lower maternal cortisol at the first prenatal assessment (15 weeks) predicted accelerated infant mental development (steeper slope of raw scores) across the first postnatal year ($t = -2.5$, $p < 0.01$) resulting in enhanced cognitive functioning at 12 months of age ($t = 2.4$, $p < 0.05$). Furthermore, higher maternal cortisol late in gestation (37 weeks) additionally predicted accelerated infant development (a steeper slope of raw MDI scores) over the first postnatal year ($t = 1.9$, $p < 0.05$) resulting in a tendency for higher mental development raw scores at 12 months ($t = 1.6$, $p =$

0.10). Maternal prenatal cortisol at 19, 25 and 31 week assessments did not predict the trajectory of infant development assessed using mental development raw scores. No measure of maternal cortisol at anty time period predicted psychomotor development raw scores. None of the measures of maternal psychological distress (perceived stress, state anxiety, pregnancy specific anxiety and depression) were significantly associated with infant development using raw mental or psychomotor scores. These data suggest that the pattern of maternal cortisol during gestation predicts the trajectory of infant mental development over the first postnatal year resulting in significant differences in performance only at 12 months.

Patterns of Maternal Cortisol Associated with Infant Development

A second set of analyses were performed to identify the pattern of maternal cortisol that predicted optimal performance at 12 months. For these analyses the scaled scores were used to allow for comparison to developmental norms. These models offer the additional advantage of assessing the slope or trajectory of maternal cortisol across gestation. As in the previous analyses, cortisol and BSID scores were modeled as continuous variables. As shown in Figure 1, infants scoring higher on the 12 month MDI were exposed to (i) lower maternal cortisol before 18 weeks gestational age (GA) (t's ranged from −2.1 to −2.7, p's < 0.05), (ii) an accelerated increase in maternal cortisol across gestation ($t = 3.7$, $p < 0.001$), and (iii) higher maternal cortisol after 30 weeks GA (t's ranged from 2.0 to 2.9, p's < 0.05). Interestingly, this profile of maternal cortisol additionally predicted whether or not 12 month old infants received a score that would be categorized as delayed using standardized cut offs on the BSID (p's < 0.05). Because the intercepts that were the strongest predictors of a low MDI score were high maternal cortisol at 13 weeks GA and low maternal cortisol at 38 weeks GA, a stepwise regression model was implemented to determine whether early and late cortisol jointly or independently predicted MDI. The stepwise model indicated that, after entering covariates into the model, early and late cortisol independently predicted infant MDI (13 week GA intercept: $\Delta R^2 = 0.05$, Beta = −0.23, $t = -2.5$, $p < 0.01$; 38 week GA intercept: $\Delta R^2 = 0.03$, Beta = 0.17, $t = 2.0$, $p < 0.05$). Together early and late maternal cortisol accounted for 8% of the variance in infant cognitive performance, as assessed with the MDI. At 13 weeks of gestation a 0.1 μg/dl increase in cortisol was associated with a 4 point decrease in MDI. At 38 weeks of gestation a 0.1 μg/dl increase in cortisol was associated with a 2 point increase in MDI. PDI was not significantly associated with maternal cortisol levels (p's > 0.3).

To determine whether there was a profile of prenatal maternal cortisol that predicted infant cognitive development, the slope of maternal cortisol across gestation was calculated for each woman. When the slope of maternal cortisol across pregnancy was added to the model it was demonstrated that cortisol slope was a stronger predictor of infant MDI ($\Delta R^2 = 0.06$, Beta = 0.24, $t = 2.8$, $p < 0.01$) than either early or late cortisol levels. Furthermore, after cortisol slope was entered into the model the effects of maternal cortisol early and late in pregnancy (intercepts at 13 or 38 weeks GA) were no longer significant (p's > 0.3). These data suggest that it is the profile of maternal cortisol across gestation that best predicts infant development.

Maternal Psychosocial Stress and Infant Development

A second set of HLM models were computed to examine associations between psychosocial indicators of maternal stress and infant development. Among all the measures of maternal distress (perceived stress, state anxiety, pregnancy specific anxiety and depression) only pregnancy specific anxiety was significantly associated with infant development. Infant performance on the MDI was associated with both pregnancy specific anxiety early in gestation and overall rate of change (shape of the curve) of pregnancy specific anxiety across gestation ($t = 2.4$, $p < 0.05$). As shown in Figure 2, infants scoring low on the MDI had mothers with the profile of (i) high pregnancy specific anxiety before 16 weeks GA (t's ranged from −2.6 to −1.9, p's < 0.05) and (ii) a steeper decline in pregnancy specific anxiety through mid gestation

(t's for rate of acceleration or instantaneous slope ranged from 2.1 to 2.9, p's < 0.05), such that no differences in level of pregnancy specific anxiety were detected beyond 16 weeks of gestation. Maternal pregnancy specific anxiety did not significantly predict whether infants were categorized as delayed using BSID criteria (p's > 0.17). Thirteen weeks GA was the time point at which level of pregnancy specific anxiety most strongly predicted infant cognitive development. At 13 gestational weeks a 5 point increase in pregnancy specific anxiety was associated with a 2 point decrease on the MDI. A stepwise regression was implemented to determine whether levels of pregnancy specific anxiety at 13 weeks GA or the rate of change of pregnancy specific anxiety over gestation best predicted infant scores on the MDI. After adjusting for covariates, overall rate of change of pregnancy specific anxiety was a stronger predictor of MDI than the 13 week GA intercept ($\Delta R^2 = 0.05$, Beta = −0.21, $t = -2.4$, $p < .05$) and accounted for the variance associated with the 13 week GA intercept ($p = 0.24$).

Influence of Maternal Psychological and Endocrine Factors on Infant Development

A hierarchical regression model was implemented to determine whether psychosocial (pregnancy specific anxiety) and endocrine (cortisol) measures independently or jointly predicted portions of the variance in infant cognitive development. Furthermore, after adjusting for covariates, maternal cortisol measures (slope and intercepts, $\Delta R^2 = 0.07$, $p < .01$) and maternal pregnancy specific anxiety indicators (slope and intercept, $\Delta R^2 = 0.05$, $p < .05$) independently predicted MDI. Together these two measures accounted for 12% of the variance in infant performance on the MDI at 12 months of age.

Discussion

The current study provides further evidence that maternal cortisol and signals of maternal psychosocial stress play a role in the programming of the human fetus. Both maternal cortisol and maternal psychosocial stress (pregnancy specific anxiety) were associated with the trajectory of infant development and influenced cognitive functioning at one year of age among healthy full term infants. Furthermore, the consequences of prenatal maternal stress were determined by the gestational period during which the fetus was exposed.

Prenatal Maternal Cortisol Influences Development

The present study suggests that prenatal maternal cortisol exerts a programming effect on human infant development. Maternal cortisol influenced the trajectory of infant development over the first postnatal year resulting in differences in performance on the MDI at 12 months. Performance on the PDI was not associated with maternal cortisol.

As expected, maternal cortisol significantly increased across gestation. The pattern of prenatal maternal cortisol was associated with infant cognitive functioning. Prenatal maternal cortisol levels predicted the rate of infant cognitive development over the first postnatal year, resulting in significant differences in performance on the MDI at 12 months of age. Specifically, infants who scored high on the MDI at 12 months of age were exposed to (i) low concentrations of maternal cortisol in early pregnancy, (ii) an accelerated trajectory of cortisol across gestation, and (iii) high concentrations of cortisol towards the end of pregnancy. Thus, prenatal maternal cortisol had opposite effects on infant cognitive development depending on the timing of exposure. These findings are remarkably consistent with the role cortisol plays in the maturation of the human fetus. Early in pregnancy the fetus is protected from the naturally occurring increases in maternal cortisol by 11β-HSD2, an enzyme that converts cortisol into its inactive form. However, because 11β-HSD2 is only a partial barrier, excessive increases in maternal cortisol early in gestation will result in overexposure of the fetus with potentially detrimental consequences. In contrast, as pregnancy advances towards parturition exposure to elevated cortisol is necessary and beneficial for maturation of fetal organ systems, including

the fetal lungs (Hacking et al., 2001). Fetal exposure to increased cortisol during the third trimester is facilitated by the sharp drop in 11β-HSD2 which allows a greater proportion of maternal cortisol to cross the placental barrier (Giannopoulos et al., 1982; Murphy et al., 2006). The current data provide new evidence that the programming influence of maternal cortisol on the developing fetal nervous system is dependent on the timing of exposure. Exposure to elevated concentrations of cortisol early in gestation had deleterious effects on subsequent infant cognitive development, whereas exposure to elevated levels of maternal cortisol late in gestation was associated with enhanced performance on tasks assessing mental development. It is possible that effects were observed for the MDI and not PDI because areas of the brain that are critical for cognitive functioning such as the hippocampus and prefrontal cortex are more vulnerable to the effects of GCs (Lowy, 1994; Uno et al., 1994; Welberg et al., 2001).

Glucocorticoids, in addition to their critical role in lung maturation, also play an important role in normal brain development and have been implicated in neuronal maturation and survival (Drake, Tang, & Nyirenda, 2007; Scaccianoce et al., 2001; Trejo et al., 2000). The association between increased concentrations of cortisol during the third trimester and improved cognitive functioning at 12 months of age is highly plausible given the role that GCs have been shown to play in regulating brain development in animal models. Although excessive prenatal administration of GCs causes both neural degeneration and impaired performance on cognitive tasks (Coe & Lubach, 2005; Uno et al., 1994; Uno et al., 1990), moderate increases in GCs facilitate brain development resulting in enhanced cognitive functioning (Casolini et al., 1997; Catalani et al., 2000; Scaccianoce et al., 2001). The current findings emphasize that within physiological limits during the prenatal period, the level of GCs associated with optimal development will be determined by the gestational period. Optimal development was observed in infants of mothers with low levels of maternal cortisol early and high levels late in pregnancy.

One other group that examined the effect of prenatal exposure to endogenous maternal cortisol for human infant cognitive development reported that elevated maternal cortisol during the third trimester was associated with poor performance on the MDI at 3 months of age (Huizink et al., 2003). The reason for the discrepancy between this report and the current study, where third trimester maternal cortisol was unrelated to 3 month BSID performance and positively related to 12 month BSID performance is unclear. There are, however, differences in the design of the two studies. The current investigation included longitudinal assessments of infants across the first postnatal year allowing us to evaluate the trajectory of infant cognitive development. Furthermore, at 3 months of age, performance on the BSID is highly influenced by infant behavioral state and later MDI scores are more stable than earlier scores (Bayley, 1993). The current study included a large sample of 125 mother-infant pairs and serial assessments of prenatal maternal cortisol levels at five distinct gestational periods. In this large sample with precise measures of maternal cortisol over the course of pregnancy, our results indicated that poor performance on the MDI at 12 months was associated with elevations in maternal cortisol early in pregnancy and not during the third trimester.

Prenatal Maternal Psychosocial Stress Influences Infant Development

Among all of the measures of prenatal maternal psychological distress (perceived stress, state anxiety, pregnancy specific anxiety and depression), only pregnancy specific anxiety significantly predicted infant development. Maternal report of pregnancy specific anxiety was highest early in pregnancy and declined as gestation advanced. Furthermore, both the level of pregnancy specific anxiety early in gestation and the overall change in pregnancy specific anxiety significantly predicted infant performance on the MDI, but not PDI, at 12 months of age. Pregnancy specific anxiety was not associated with infant development at earlier ages. A low infant MDI score at 12 months of age was associated with the maternal profile of high

pregnancy specific anxiety before 16 weeks GA and a steeper decrease in pregnancy specific anxiety through mid gestation, at which point pregnancy specific anxiety was not associated with infant development. It may be surprising that a steeper decline in pregnancy specific anxiety was associated with poorer infant scores on the MDI. It is likely, however, that the steeper decline in pregnancy specific anxiety reflects higher initial values; levels of pregnancy specific anxiety did not differ later in gestation. It is not surprising that pregnancy relates stress changes across gestation. The stimuli that lead to pregnancy specific stress appraisals are different early in gestation (e.g., fear of miscarriage) as compared to late in gestation (e.g., concern about labor and delivery). Pregnancy anxiety was not measured prior to 13 weeks GA and thus it remains possible that pregnancy anxiety earlier in pregnancy would have a greater effect. Further research is needed to better understand the way that pregnancy specific stress changes across gestation as well as how pregnancy specific stress is different from other types of stress. Importantly, the mother's pregnancy specific anxiety predicted infant development even after controlling for actual medical risk and postnatal maternal stress. These data suggest that (i) signals of maternal psychosocial stress during the prenatal period may be transmitted to the fetus and have programming consequences for development, (ii) the fetus is more vulnerable to the effects of these signals early in gestation, and (iii) maternal stress related to pregnancy may have more profound implications for the fetus as compared to generalized maternal distress.

The finding that pregnancy specific anxiety and not generalized distress measures predicts infant outcomes suggests that stress related to events, beliefs or fears proximal to pregnancy are both novel and more relevant to the pregnant woman and therefore more consequential to the fetus and that this measure detects unique emotional distress. In contrast to the three generalized distress measures which evaluate stress related to generalized worry, daily hassles and negative mood, the pregnancy specific anxiety scale evaluates maternal stress that is directly related to her pregnancy including concern about the health of her baby, fear of miscarriage, and worry about the development of pregnancy related medical problems. Accumulating evidence indicates that that measures of pregnancy specific anxiety are better predictors of shortened gestation (Roesch et al., 2004), fetal behavior (DiPietro et al., 2002), and infant outcomes (DiPietro et al., 2006; Huizink et al., 2003) than measures of generalized maternal distress. Overall, our finding that pregnancy specific anxiety, but not generalized distress, was associated with impairments in infant cognitive development is consistent with these studies. The variability among studies relying on self report of generalized maternal stress (Brouwers et al., 2001; DiPietro et al., 2006; Huizink et al., 2003; Van den Bergh, 1990) may be due to fact that these measures do not capture maternal stress related to the well being of her developing fetus that is unique to pregnancy. Two published studies examined the association between pregnancy specific anxiety and infant cognitive development and found that elevated pregnancy specific anxiety during the third trimester predicted poorer performance on tasks assessing infant mental development (DiPietro et al., 2006; Huizink et al., 2003). Although the effect of timing differed between our study and the two other published studies, our findings are consistent with evidence that the fetus is more vulnerable to maternal stress early in gestation (Mueller & Bale, 2007; Schneider et al., 1999).

Prenatal Maternal Stress is Associated with the Trajectory of Infant Development

The current findings indicate that while prenatal exposure to maternal stress and stress hormones predict infant development, significant associations do not emerge until 12 months of age. Prenatal maternal cortisol levels were, however, associated with the trajectory of infant development over the first postnatal year. Individual patterns of low maternal cortisol early and high maternal cortisol late in pregnancy predicted an accelerated trajectory of infant cognitive development over the first postnatal year resulting in improved performance on the MDI at 12 months. It is not clear why significant differences in performance on the MDI did

not emerge until 12 months of age. During the prenatal period organs and organ systems are forming and thus are especially vulnerable to both organizing and disorganizing influences. Disruption at this early stage of development has the potential to alter developmental trajectories resulting in developmental impairments that only emerge as that capacity develops. Thus, as cognitive functions come 'on line' we may begin to detect delays that were not apparent previously. Consistent with this hypothesis there is evidence from experimental studies with rodents that exposure to early life stress can have consequences for cognitive functioning that are not observable until adulthood (Brunson et al., 2005) as well as from human observational studies associating size at birth with adult health outcomes (Barker, 1998; 2002). Alternatively, it is possible that the lack of differences at 3 and 6 months may be due to limitations in our ability to evaluate children at these young ages.

Postnatal Influences on Development

There is strong evidence across a wide range of species that early postnatal experiences influence the development of individual differences (Coplan et al., 1996; Dawson & Ashman, 2000; Levine, 1957). Maternal stress, anxiety, and depression during infancy have pervasive influences on development including enhanced stress reactivity, poor emotional regulation, and impaired cognitive development (Coghill, Caplan, Alexandra, Robson, & Kumar, 1986; Dawson & Ashman, 2000; Essex, Klein, Cho, & Kalin, 2002; Kaplan, Bachorowski, Smoski, & Hudenko, 2002). It is important to note the observed effects of prenatal exposure to maternal stress on infant development were independent of postnatal maternal psychological distress (anxiety, stress and depression) and parenting specific stress evaluated at 3, 6 or 12 months. Furthermore, the effects of prenatal stress were observed in our full term cohort and were not explained by sociodemographic factors including household income, maternal education, age, race or marital status or to maternal pregnancy related medical risk factors. Our findings that prenatal maternal stress measures were significantly associated with cognitive development in full term infants, and that this association was not mediated or moderated by relevant postnatal factors, add strong support to the argument that prenatal experiences and exposures have a significant role in shaping developmental outcomes.

Programming Influences of Prenatal Maternal Stress

The current findings in a healthy sample of full term infants, demonstrate that both psychological (pregnancy specific anxiety) and endocrine (cortisol) indicators of maternal stress are associated with poorer performance on the MDI of the BSID at one year of age. For both psychosocial and endocrine indicators of stress, timing of exposure was critical. Optimal performance on the MDI at 12 months of age was observed in infants of mothers with low levels of cortisol early in pregnancy and high levels near term. Despite the finding that fetal exposure early in pregnancy to maternal cortisol and pregnancy specific anxiety had similar effects on infant mental development, these two measures were not correlated and they exerted independent influences on development. This finding is consistent with the majority of published studies that have failed to discover a significant relation between maternal psychological state and maternal cortisol during pregnancy (Davis et al., 2007; de Weerth & Buitelaar, 2005; Mc Cool & Susman, 1994; Petraglia et al., 2001). Future research will have to examine other stress responsive hormones, as well as vascular or immune pathways that could be mechanisms by which increases in maternal psychosocial stress might affect the fetus.

Limitations

First, because this study relied on naturally occurring variations in maternal cortisol, rather than experimental manipulations, it is difficult to separate the effects of cortisol from the consequences of other factors that might contribute to this association such as components of the postnatal environment including postpartum depression or maternal stress or from shared

genetic effects. In the current study, however, postpartum psychological state was not associated with infant development and adjusting for postpartum maternal psychological state did not alter the relation between prenatal maternal stress measures and infant cognitive development, supporting our conclusion that prenatal exposures were responsible for this association. Furthermore, the current findings are consistent with animal models where random assignment is possible (e.g., Catalani et al., 2002; Weinstock, 2001) as well as recent human studies that have evaluated the consequences for development of randomly occurring stressful events, such as natural disasters (Laplante et al., 2004; Yehuda et al., 2005). Second, the current study included a low risk sample of women with healthy full-term pregnancies. It is probable that examination of women experiencing more severe stress or who have clinically significant psychopathology would reveal more profound programming influences on developmental outcomes. Third, maternal cortisol is an indirect measure of fetal exposure. However, there is evidence with human fetuses documenting that maternal and fetal cortisol levels are significantly correlated (Gitau et al., 1998; 2001).

Conclusions

Studies from animal models have demonstrated that early life environmental factors, including exposure to maternal stress and stress hormones, can cause structural and functional changes to the developing nervous system which persist throughout the lifespan. This study is among the first to evaluate the effects of endocrine and psychosocial indicators of prenatal maternal stress for infant development. Data indicate that both endocrine and pregnancy specific psychosocial indicators of stress changed over the course of gestation and both independently predicted infant cognitive development at one year of age. These effects were strongly dependent on the timing of exposure and could not be accounted for by postnatal indicators of maternal distress. Elevated levels of maternal psychosocial stress and maternal cortisol early in gestation were associated with poorer cognitive functioning at one year of age. In contrast, later in gestation elevated maternal cortisol was associated with improved performance on the MDI at one year. The current study provides new evidence that prenatal exposure to maternal cortisol and maternal psychosocial stress exerts programming effects on the fetus with persisting consequences for infant behavior. During the prenatal period the mother's physiology directly affects the fetus and has the opportunity to shape developmental trajectories. It may be for this reason that prenatal factors exerted a stronger influence on MDI performance at one year, as compared to more proximal maternal factors. It is our intention to continue to follow this cohort to determine if there is a persisting influence of prenatal stress on other domains of functioning including emotional regulation and whether these effects persist to later development.

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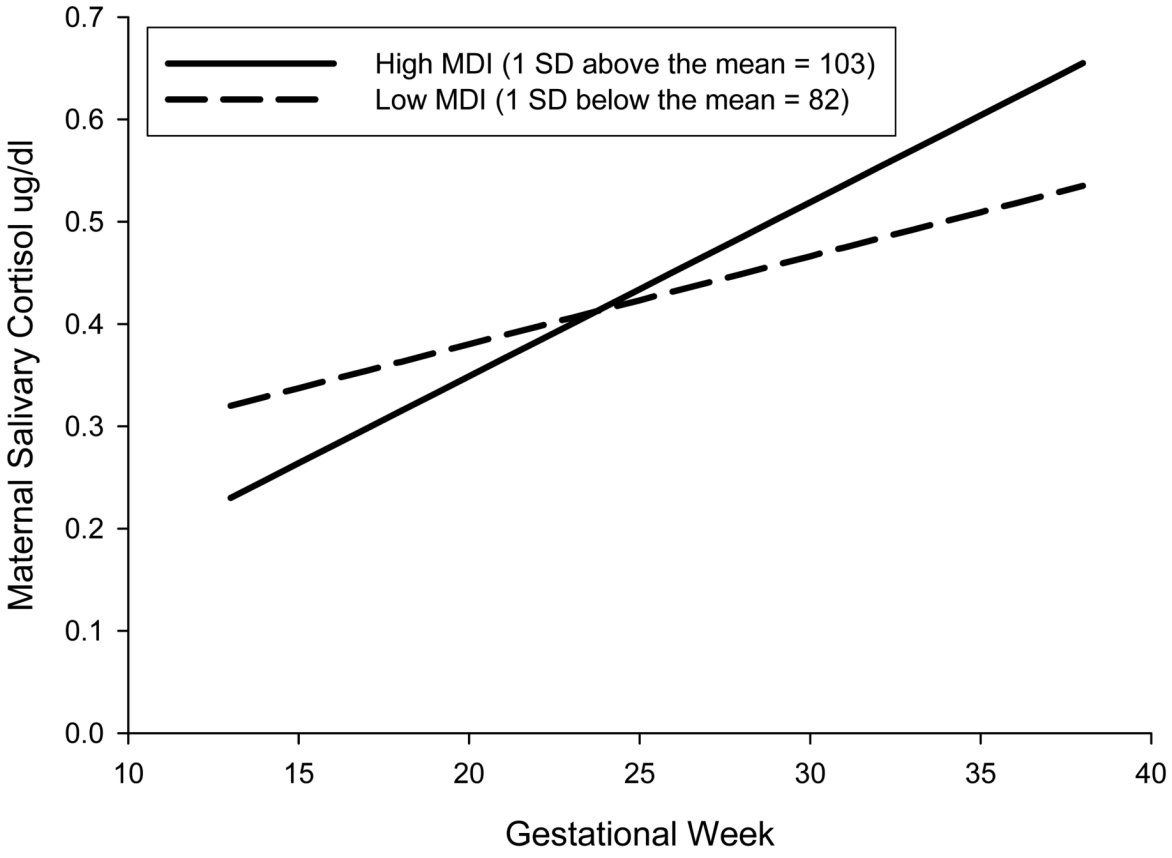
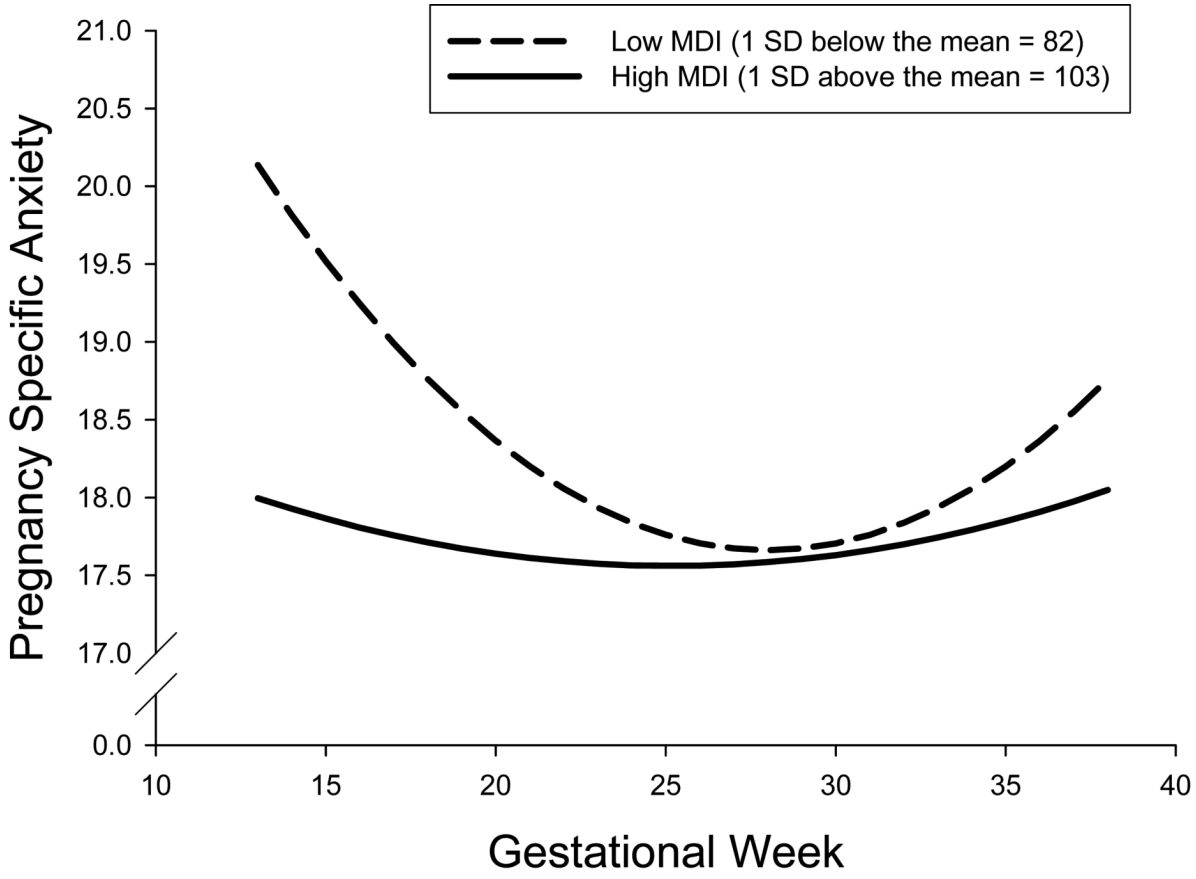


*Both maternal cortisol and MDI scores were analyzed as continuous variables. For graphing purposes we have displayed the cortisol trajectory for mothers of infants with MDI scores one SD above or below the mean.

Figure 1.
Infant performance on the MDI at 12 months of age is associated with the trajectory of maternal cortisol across gestation. The top and bottom SD for MDI are modeled with HLM.



*Both maternal pregnancy specific anxiety and MDI scores were analyzed as continuous variables. For graphing purposes we have displayed the trajectory of pregnancy specific anxiety for mothers of infants with MDI scores one SD above or below the mean.

Figure 2.
Elevated pregnancy specific anxiety early in gestation is associated with poorer performance on the MDI at 12 months of age. The top and bottom SD for MDI are modeled with HLM.

Table 1

Demographic information for the study sample

	Study Sample (N=125)
Maternal age at delivery	29.9*
Married	79%
Primiparous	48%
Education	
High school or equivalent	95%
College graduate	46%
Annual household income	
$0 to $30,000	17%
$30,001 and $60,000	26%
$60,001 and $100,000	33%
Over $100,000	24%
Race/Ethnicity	
Non-Hispanic white	50%
Hispanic	30%
Asian	10%

* (SD=5.3, range 19 to 41)

Table 2

Sample items from the mental and psychomotor scale

	Mental Scale	Psychomotor Scale
3 months	Discriminates novel visual pattern	Elevates self by arms
	Eyes follow rod	Sits with support
	Reaches for suspended ring	Balances head
6 months	Lifts inverted cup	Uses whole hand to grasp pellet
	Looks for fallen spoon	Sits alone
	Pulls string to secure ring	Turns from back to stomach
12 months	Puts one cube in cup	Walks alone
	Responds to spoken request	Throws ball
	Places one puzzle piece	Squats briefly

Table 3

Descriptive information (mean and standard deviation) for infant BSID scores

	Infant Age		
	3	6	12
Mental Development Raw Score	30.4 (3.3)	61.2 (4.3)	84.9 (4.3)
MDI Scaled Score	92.8 (5.9)	96.6 (8.8)	93.1 (10.3)
Psychomotor Development Raw Score	23.1 (2.8)	40.0 (4.2)	64.1 (4.3)
PDI Scaled Score	93.7 (8.6)	97.3 (12.9)	97.1 (16.8)

Table 4

Intercorrelations among MDI and PDI scaled scores across the first postnatal year

	3 mo MDI	3 mo PDI	6 mo MDI	6 mo PDI	12 mo MDI	12 mo PDI
3 mo MDI	-	.41**	.23*	.08	.06	.13
3 mo PDI	-	-	.16	.22*	.15	.26**
6 mo MDI	-	-	-	.61**	.27**	.40**
6 mo PDI	-	-	-	-	.37**	.55**
12 mo MDI	-	-	-	-	-	.43**

* $p < .05$

** $p < .01$

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Table 5

Intercorrelations among prenatal maternal cortisol samples

	Gestational Week			
	19	**25**	**31**	**37**
15 Wks GA	.21*	.34**	.03	.05
19 Wks GA	-	.22*	.11	.09
25 Wks GA	-	-	.07	.02
31 Wks GA	-	-	-	.39**

* $p < .05$

** $p < .01$