

Antenatal maternal stress and long-term effects on child neurodevelopment: how and why?

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We review a significant body of evidence from independent prospective studies that if a mother is stressed while pregnant, her child is substantially more likely to have emotional or cognitive problems, including an increased risk of attentional deficit/hyperactivity, anxiety, and language delay. These findings are independent of effects due to maternal postnatal depression and anxiety. We still do not know what forms of anxiety or stress are most detrimental, but research suggests that the relationship with the partner can be important in this respect. The magnitude of these effects is clinically significant, as the attributable load of emotional/behavioral problems due to antenatal stress and/or anxiety is approximately 15%. Animal models suggest that activity of the stress-responsive hypothalamic-pituitary-adrenal (HPA) axis and its hormonal end-product cortisol are involved in these effects in both mother and offspring. The fetal environment can be altered if stress in the mother changes her hormonal profile, and in humans, there is a strong correlation between maternal and fetal cortisol levels. However, many problems remain in understanding the mechanisms involved in this interaction. For example, maternal cortisol responses to stress decline over the course of pregnancy, and earlier in pregnancy, the link between maternal and fetal cortisol is less robust. It is possible that the effects of maternal anxiety and stress on the developing fetus and child are moderated by other factors such as a maternal diet (e.g., protein load). It is suggested that extra vigilance or anxiety, readily distracted attention, or a hyper-responsive HPA axis may have been adaptive in a stressful environment during evolution, but exists today at the cost of vulnerability to neurodevelopmental disorders. **Keywords:** Antenatal, prenatal, stress, anxiety, child neurodevelopment, attention deficit/hyperactivity, HPA axis, cortisol. **Abbreviations:** HPA: hypothalamic-pituitary-adrenal; PVN: paraventricular nucleus of the hypothalamus; CRH: corticotropin releasing hormone; ACTH: adrenocorticotropin; GR: glucocorticoid receptor; MR: mineralocorticoid receptor; 11 β HSD-2: 11 beta hydroxysteroid dehydrogenase-2; NBAS: Neonatal Behavioral Assessment Scale; ADHD: attention deficit hyperactivity disorder; MDI: Bayley Mental Development Index; PDI: Bayley Physical Development Index.

The enduring effects of events experienced during human prenatal development have long been known, perhaps best illustrated by the effects of teratogens on postnatal physical, cognitive, and social outcomes. Prenatal exposure to toxic agents, such as alcohol, radiation, environmental pollution, and maternal infections, can lead to a range of adverse developmental outcomes. The nature and severity of some of these effects appear to be influenced by the degree and timing of the exposure during gestation. For example, during an outbreak of German measles (rubella) in the mid-1960s, as many as 20,000 babies were born with significant birth defects in the United States (Eberhart-Phillips, Frederick, & Baron, 1993). Babies whose mothers were exposed during their first trimester, a period of generalized and rapid organ development, tended to display widespread, global effects including cognitive dysfunction, heart malformations, cataracts, and deafness, as well as genital and intestinal abnormalities.

In comparison, babies whose mothers were exposed during the second and third trimesters, periods of organ system refinement and somatic growth, tended to have low birth weights, experience hearing loss, and display skeletal abnormalities. Such observations strongly support the notion that prenatal development is characterized by sensitive periods, developmental windows when organisms are particularly vulnerable to the relatively persistent and unmodifiable effects of environmental events or stressors. The specific structures and systems vulnerable at any given point in time appear to be those undergoing rapid maturational change.

More recently, the concept of sensitive periods in relation to human prenatal development has been invoked to describe the fetal origins of adult disease, an idea since termed the 'Barker hypothesis'. Barker stated that 'Coronary heart disease, Type 2 diabetes, stroke and hypertension originate in developmental plasticity, in response to undernutrition during fetal life' (Barker et al., 1993). Indeed, lower birth weights (even those occurring within the normal range) have

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been shown to place individuals at risk for developing features of cardiovascular disease and metabolic disorders such as diabetes, in adulthood (Barker, 2002, 2004, 2005; Barker & Hanson, 2004). Mortality rates associated with these conditions similarly increase among individuals with lower birth weights and smaller neonatal head circumferences (Barker, Bull, Osmond, & Simmons, 1990). These relations remain significant even when potential confounding factors such as diet and socioeconomic status are taken into account. It has become clear that neonatal outcomes are often markers for future health, and these findings have stimulated many lines of research to explore the nature of fetal programming.

Fetal programming is a concept that describes the fetus' physiological adaptation to the characteristics of the intrauterine environment within which it is developing. Such adaptation may subsequently affect the set points of physiological systems of the body undergoing rapid structural and functional changes, including those that maintain homeostasis. If not optimally suited for the postnatal environment, the prenatal physiological adaptations may render the offspring vulnerable to the development of health problems later in life. For example, offspring of nutrient-restricted pregnant dams have atypically high percentages of body fat and weight at 9 months of age if they are allowed to feed *ad libitum* postnatally (Desai, Gayle, Babu, & Ross, 2005). However, when nutrient restriction continues into the postnatal months, body fat and weight at 9 months are typical and no different in comparison to offspring who were not nutritionally restricted during either the prenatal or postnatal periods. Although fetal programming has been primarily discussed in relation to negative outcomes, pathology is not inherent in this concept (Schwartz & Morrison, 2005). Prenatal programming effects, according to this perspective, are aspects of ontological development.

The aim of this paper is to review evidence for the effects of antenatal maternal psychosocial stress on child neurodevelopmental outcomes and discuss some possible mechanisms for these effects. In the review of human studies that follows (see Table 1), prenatal stress is often inferred from maternal exposure to traumatic events, the presence of mood disorder symptomatology, or self-reports of daily hassles and negative life events during pregnancy. The findings will be discussed with respect to the age at which postnatal outcomes were assessed, in order to discern the extent to which this prenatal experience persists into postnatal life.

Developmental consequences of prenatal stress on human behavior

Symptoms of anxiety and depression occur frequently during pregnancy. Indeed, they are more

common in late pregnancy than in the postpartum period (Heron, O'Connor, Evans, Golding, & Glover, 2004). As early as 400 B.C., Hippocrates was aware of the importance of emotions in influencing pregnancy outcomes. Additionally, more than a thousand years ago in China, awareness of the importance of prenatal attitudes led to the institution of the first antenatal clinic (Ferreira, 1965). However, it is only relatively recently that this idea has been substantiated by human behavioral research.

Neonatal outcomes

In general, studies point to a small, but reliable link between prenatal stress and pregnancy outcomes in humans. Maternal reports of daily hassles as well as depression and anxiety symptoms appear to be associated with both earlier delivery and smaller size at birth, which in turn, are risk factors for impaired cognitive and social developmental outcomes (Wadhwa, 2005; Wadhwa, Sandman, & Garite, 2001; Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993). Recent studies also suggest an association between antenatal stress and lower scores on neonatal neurobehavioral assessments.

The relation between prenatal stress and neonatal outcomes appears to depend, in part, upon the nature of the stressful experience as well as the specific outcome under investigation. This may explain why studies of women exposed to traumatic events, for example, have yielded somewhat equivocal results. In one study, women who were pregnant during the 6.8 magnitude Northridge, CA earthquake delivered approximately one week earlier than expected given the date of their last menstrual cycle (Glynn, Wadhwa, Dunkel-Schetter, Chic-DeMet, & Sandman, 2001). Infants were not born prematurely, however, because mean gestational lengths were greater than 38 weeks. In contrast, no differences in gestational length or risk for premature labor were observed among expectant mothers who were present at or otherwise proximal to the World Trade Center during the September 11 terrorist attacks (Berkowitz et al., 2003). Infants proximal to the World Trade Center in utero, however, were nearly twice as likely to experience intrauterine growth restriction, having birth weights below the 10th percentile given their gestational age (OR = 1.90). Evidence from the animal literature suggests that these effects may be due at least in part to elevations in maternal cortisol concentrations, which have been associated with both lower birth weights and elevated glucocorticoid levels in offspring (Seckl & Meaney, 2004).

Epidemiological studies examining the effects of daily hassles, negative life events, and occupational stressors during pregnancy have generally yielded more consistent results with respect to neonatal

Table 1 Effects of antenatal stress on neurodevelopmental outcomes

Study	Design	Sample	Stressor	Timing*	Outcomes	Results
Neonatal outcomes						
Wadhwa et al. (1993)	prospective	N = 90 upper-middle class	life events, daily hassles (SRLE, PSS, DHQ)	28 and 30 weeks	birth outcomes	- associated with lower birth weight and shorter gestational length - controlled for biomedical risk
Lou et al. (1994)	prospective	N = 70 stressed, N = 50 comparison	life events (GHQ)	mid-gestation	birth outcomes, neurobehavioral development at 4-14 days	- smaller head circumference, lower birth weight and lower Prechtl scores associated with greater number of life events
Copper et al. (1996)	prospective	N = 2593 high risk	depression/anxiety symptoms (ASAPSP)	25-29 weeks	birth outcomes	- associated with increased risk for preterm birth (OR = 1.16) and low birth weight (OR = 1.08) no relation observed with IUGR - controlled for maternal age, education, marital status, substance use
Brett et al. (1997)	retrospective	N = 421 premature; N = 612 at term	occupational stress (JCS)	6 mo postpartum	gestational length	- high strain (high demand/low control) full-time jobs associated with preterm birth (OR = 1.4) - controlled for race, SES, maternal health
Glynn et al. (2001)	retrospective	N = 40	earthquake	variable	gestational length	- reduction in gestational length among women experiencing the earthquake during pregnancy, particularly during the first trimester - controlled for obstetric risk, maternal CRH levels
Berkowitz et al. (2003)	retrospective	N = 187; near WTC N = 2367 comparison	Sept. 11 (PTSDC)	variable	birth outcomes	- no reduction in gestational length - increased risk of intrauterine growth restriction (OR = 1.90) for women near WTC
Field et al. (2003)	prospective	N = 132 middle-income	depression/anxiety anger symptoms (CES-D; STAI; POMS)	20 weeks	birth outcomes EEG, vagal tone neurobehavioral	- high anxiety associated with lower birth weight and vagal tone development; higher right frontal EEG asymmetry, poorer performance on Brazelton
Dole et al. (2003)	prospective	N = 1962 high risk, low income	life events, pregnancy-specific anxiety (LES)	24-29 weeks	gestational length	- life events and pregnancy-specific anxiety associated with increased risk for preterm birth (OR = 1.8 and 2.1 respectively) - controlled for maternal tobacco and alcohol use, bacterial vaginosis infection
Infant & childhood outcomes: social/emotional						
O'Connor et al. (2002)	prospective	N = 7448 ALSPAC	depression/anxiety symptoms (EPDS; Crown-Crisp)	18, 32 weeks' gestation; 8 weeks, 8, 21, 33 months postnatal	behavioral problems	- higher levels of anxiety at either timepoint at 47 months predicted increased risk of emotional problems - boys more likely to display hyperactivity/attention problems - controlled for postnatal anxiety, depression, SES, parity, birth outcomes
Davis et al. (2004)	prospective	N = 22 low risk	depression/anxiety symptoms (CES-D; STAI)	third trimester	temperament at 4 mo	- higher levels of depression and anxiety predicted heightened response to novelty - controlled for postnatal depression & anxiety

Table 1 (Continued)

Study	Design	Sample	Stressor	Timing*	Outcomes	Results
Van den Bergh & Marcoen (2004)	prospective	N = 72 low risk	anxiety symptoms (STAI)	12-22, 23-31, 32-40 weeks' gestation; 8, 10, 28 weeks postnatal	behavioral problems at 8-9 years (CBCL)	- higher levels of anxiety predicted variation in externalizing problems and self-reported anxiety - controlled for postnatal anxiety, SES, gender
Van den Bergh et al. (2005)	prospective	N = 57 low risk	anxiety symptoms (STAI)	12-22, 23-31, & 32-40 weeks' gestation; 1, 10, 28 weeks, 8/9, 14/15 years postnatal	behavioral problems at 14-15 years	- higher anxiety, particularly between 12-22 weeks' gestation, predicted higher levels of impulsivity and lower scores on the WISC - controlled for postnatal maternal anxiety
Infant and childhood outcomes: cognitive						
Huizink et al. (2003)	prospective	N = 170 low risk	daily hassles, pregnancy-specific anxiety (EPL; PRAQ-R)	15-17, 27-28, & 37-38 weeks	Bayley scales at 3 and 8 mo	- daily hassles, especially between 15-17 weeks, predicted lower MDI scores at 8 months - controlled for postnatal depression, SES, obstetric complications
LaPlante et al. (2004)	retrospective	N = 58 upper-middle & upper class	Quebec ice storm (IES-R; researcher-constructed questionnaire)	variable	Bayley MDI, MCDI at 24 mo	- maternal anxiety predicted 11% and 12% in MDI and MacArthur vocabulary scores, respectively - controlled for postnatal depression, birth outcomes, and obstetric complications
Niederhofer & Reiter (2004)	prospective	N = 247 low risk	psychological distress (researcher-constructed questionnaire)	16-20 weeks	academic achievement at 6 years	- greater psychological distress associated with lower grades in school
DiPietro et al. (2006)	prospective	N = 94 low risk	depression, anxiety symptoms; pregnancy-specific anxiety (POMS; STAI; DSI; PES)	24, 28, or 32 weeks	Bayley Scales at 24 mo	- higher levels of anxiety and depression positively related to MDI and PDI scores - controlled for maternal education, fetal sex
Bergman et al. (unpublished)	prospective	N = 125	life events	17 weeks	Bayley scales at 18 mo	- greater number of antenatal negative life events associated with lower MDI scores - no association observed with postnatal life events, maternal age, smoking
Infant & childhood outcomes: laterality & other neurodevelopmental disorders						
Obel et al. (2003a)	prospective	N = 824	life events (GHQ; researcher-constructed questionnaire)	8-19 & 27-34 weeks	handedness at 36 mo	- life events, particularly those between the first and second assessments, predicted higher incidence of mixed-handedness - controlled for parent handedness
Glover et al. (2004)	prospective	N = 7431 ALSPAC	depression/anxiety symptoms (EPDS; Crown Crisp)	18, 32 weeks; 8 weeks postnatal	handedness at 42 months	- antenatal anxiety, but not depression, predicts increased likelihood of mixed-handedness (OR = 1.28) - controlled for maternal drug use and age, obstetric complications, SES, birth outcomes, postnatal anxiety and depression

Table 1 (Continued)

Study	Design	Sample	Stressor	Timing*	Outcomes	Results
Beversdorf et al. (2005)	retrospective	N = 188 autism N = 212; no neurodev. diagnosis	life events (SRRS)	0-40 weeks	incidence of autism	- life events, particularly between 25-28 weeks, was associated with increased incidence of autism
Adult outcomes Selten et al. (1999)	retrospective; archival	N = 2786 exposed; N = 14,778 non-exposed	flood (Netherlands)	variable	psychopathology	- offspring at increased risk of developing schizophrenia (OR = 1.8)
Watson et al. (1999)	retrospective; archival	N = 611 exposed; N = 604 non-exposed	earthquake (China)	variable	psychopathology	- offspring at increased risk of developing affective disorders
Van Os & Selten (1998)	retrospective; archival	N = 419 exposed; N = 1480 non-exposed	WWII (Netherlands)	variable	psychopathology	- offspring at increased risk of developing schizophrenia (OR = 1.15), particularly if exposed during the first trimester (OR = 1.28)

Key: ALSPAC: Avon Longitudinal Study of Parents and Children; ASAPSP: Abbreviated Scale for the Assessment of Psychosocial Status in Pregnancy; CES-D: Center for Epidemiologic Studies Depression Scale; CRH: Corticotropin-Releasing Hormone; DHQ: Daily Hassles Questionnaire; DSI: Daily Stress Inventory; EPDS: Edinburgh Postnatal Depression Scale; EPL: Everyday Problem List; GHQ: General Health Questionnaire; HSC: Hopkins Symptom Checklist; IES-R: Impact of Event Scale-Revised; IUGR: intrauterine growth retardation; JCS: Job Content Survey; LBW: Low Birth Weight; LES: Life Experiences Survey; MCDI: MacArthur Communicative Development Inventory; MDI: Mental Development Index (Bayley); PDI: Physical Development Index (Bayley); PES: Pregnancy Experiences Scale; POMS: Profile of Mood States; PRAQ-R: Pregnancy Related Anxieties Questionnaire-Revised; PSS: Perceived Stress Scale; PTSDC: Posttraumatic Stress Disorder Checklist; SRLE: Schedule of Recent Life Events; SRRS: Social Readjustment Rating Scale; STAI: State-Trait Anxiety Inventory for Adults; WISC: Wechsler Intelligence Scale for Children; WTC: World Trade Center.

outcomes. For instance, Dole and colleagues (2003) found that maternal perception of negative life events between 24 and 29 weeks' gestation was significantly related to increased risk of preterm birth (OR = 1.8). This effect was not influenced by obstetric health or maternal substance use. African-Americans displayed a higher incidence of premature labor, as is well documented in the literature, but no interactions were observed between prenatal stress and maternal race. The results of this study were corroborated by Copper et al. (1996), who used maternal self-reports of mood disorder symptoms as markers of prenatal stress. Nearly 3000 mothers completed anxiety and depression questionnaires at approximately 26 weeks' gestation, at which time demographic information and obstetric history was also obtained. Although maternal anxiety and depression scores were significantly associated with lower educational levels and substance use, they also uniquely predicted both premature birth (OR = 1.16) and low birth weight (OR = 1.08). Occupational stressors have also been associated with an increased risk of premature labor (OR = 1.4), although this effect appears to be carried by women experiencing high job strain for at least 30 weeks of their pregnancy (Brett, Strogatz, & Savitz, 1997).

In addition to gestational age and weight at birth, a few studies have also explored relations between prenatal stress and neurobehavioral outcomes during the neonatal period. For example, Field et al. (2003) reported that newborns of mothers with high levels of anxiety display greater right frontal brain activation, a physiological profile that has been associated with the display of negative affect from infancy to adulthood (Davidson, 1998). The infants also spent more time in deep sleep, less time in quiet and active alert states, and showed more state changes and less optimal performance on the Neonatal Behavioral Assessment Scale (NBAS), a standard neurobehavioral assessment of motor maturity and autonomic stability during the neonatal period. These findings extended those of Lou et al. (1994), who found that antenatal life events predicted lower scores on another neurodevelopmental assessment, the Pechtl scale, as well as smaller head circumference and lower birth weight.

It is often unclear whether maternal appraisals or the nature of the stressful experience are driving these effects, since self-reports were employed in the studies that conceptualized stress as responses to chronic, day-to-day events. Definitions of prematurity also vary across the studies. For example, Copper et al. (1996) characterized premature birth as delivery prior to 35 weeks' gestation, while the other studies used a criterion of 38 weeks. Assuming that maternal psychological stress results in a modest reduction in gestational length, such conservative criteria might artificially attenuate the magnitude of the associated odds ratios. This is particularly important with the recent emphasis in newborn

medicine on physical and cognitive morbidity in the near-term infant (born between 34 and 37 weeks postconceptional age). Additionally, because the results of these studies focused exclusively on pregnancies that led to live births, it remains unclear how prenatal stress influences the rates of spontaneous abortions.

Infant and childhood outcomes

There is now good evidence from many independent prospective studies that antenatal stress is associated with adverse neurobehavioral outcomes, including social/emotional and cognitive functioning during childhood. Despite the fact that different methods for measuring both antenatal stress and the postnatal outcomes of interest were employed across studies, the results were consistent in establishing a prospective association between antenatal stress and neurobehavioral development.

Infant and childhood outcomes: social/emotional. With respect to social development, the outcomes receiving the most attention have been temperament and behavior problems. The temperament work represents a relatively recent area of investigation and has been studied exclusively during infancy. For example, Davis et al. (2004) found that scores on depression and anxiety inventories obtained during the third trimester of pregnancy predicted 27% and 20% of the variance in infants' observed behavioral reactivity at 4 months, respectively. Specifically, infants of mothers reporting higher levels of depression and anxiety during pregnancy tended to display higher levels of negative affect and motor activity when presented with a series of novel toys. This behavioral profile in infancy, in turn, has been associated with shyness and anxiety disorders in later childhood (Kagan, Reznick, & Snidman, 1987). It is of note that maternal anxiety and depression scores did not fall within the clinical range. Additionally, postnatal measures of anxiety and depression were unrelated to the infant temperament. It is not known how prenatal stress is related to other aspects of temperament (e.g., exuberance), or the extent to which relations already demonstrated predict temperament later in infancy or beyond.

In contrast, studies of antenatal stress and social developmental outcomes during childhood have focused primarily on parent-reported behavioral problems. Four independent prospective studies have found associations between antenatal stress and social/emotional problems during childhood. The most consistently observed adverse outcome is attention deficit hyperactivity disorder (ADHD) symptoms, observed in children between 4 and 15 years of age (O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Van den Bergh et al., 2005). However, other effects have also been described, such as increases in anxiety symptoms (O'Connor et al., 2002) and

externalizing problems (Van den Bergh & Marcoen, 2004). It is of interest that in the non-human primate studies of prenatal stress, a consistent finding in the offspring has been deficits in attention (Schneider, Moore, Kraemer, Roberts, & DeJesus, 2002).

Infant and childhood outcomes: cognitive. Other studies show an effect of prenatal stress on the cognitive development of the child, as assessed by scores on the Bayley Mental Developmental Index (MDI), language development measures, or by school grades. These studies are generally fewer in number and have focused primarily on infants and young children, although one study found an association between maternal antenatal stress and school marks at 6 years (Niederhofer & Reiter, 2004). In one study, Huizink, Robles de Medina, Mulder, Visser, and Buitelaar (2003) examined the association between maternal reports of daily hassles, pregnancy-related concerns, and performance on MDI of the Bayley Scales of Infant Development at 3 and 8 months of age. Higher levels of daily hassles during early gestation and pregnancy-specific anxiety during mid-gestation were associated with lower scores on the MDI. However, this relation was observed only at the 8-month assessment. One possible explanation for these findings is that performance on the Bayley at 8 months requires the activity of brain regions being that are coming 'on-line' during late infancy, such as the hippocampus, and that these same brain regions are particularly susceptible to prenatal insults. Research from the iron deficiency literature suggests that this is a viable hypothesis for explaining the relation between perinatal events and postnatal sequelae (Schmidt & Georgieff, 2006). Bergman, Sarkar, O'Connor, and Glover (unpublished observations) have also found that exposure to life events during pregnancy was associated with a significant reduction in MDI scores in children of 14–19 months; there was no such link with postnatal life events scores.

Maternal exposure to traumatic events during pregnancy has also been associated with children's cognitive outcomes. Toddlers whose mothers were pregnant during the 1998 ice storm in Quebec, a disaster that resulted in the loss of electricity and water for up to five weeks in some regions of the province, displayed lower MDI and language development scores compared to standardized norms (LaPlante et al., 2004). Additionally, maternal subjective appraisals of distress during the ice storm uniquely predicted 11% and 12% of the variance in toddlers' MDI and language development scores, respectively – even after obstetric complications, birth weight, children's gestational age at birth, and maternal postpartum depression were taken into account. Given the size of these effects as well as the relative dearth of research with respect to childhood cognitive outcomes, this represents a particularly fruitful area for future investigation.

It is important to note that although the MDI is a widely used standardized tool for the assessment of cognitive development in infants and young children, the predictive value of the MDI to cognitive functioning at later ages is not strong. Thus, establishing that these prenatal experiences are associated with cognitive functioning in middle childhood, a point at which individual differences in cognitive abilities are more differentiated and stable, is an important next step.

It is also of interest that in one recent study of financially and emotionally stable women, there was a small but significant positive association between antenatal stress and both the MDI and physical developmental index (PDI) of the Bayley (DiPietro, Novak, Costigan, Atella, & Reusing, 2006). The authors suggested that a small to moderate amount of antenatal stress may actually be helpful for the development of the child, and that perhaps the association between prenatal stress or arousal and child outcomes is best represented by a u-shaped curve.

Infant and childhood outcomes: laterality and other neurodevelopmental disorders. In addition to the social and cognitive developmental outcomes, some studies suggest that antenatal stress predicts alterations in another index of neurobehavioral organization, laterality (Weinstock, 2001; Kofman, 2002). Glover, O'Connor, Heron, and Golding (2004), for example, observed that maternal reports of anxiety (but not depression) at 18 weeks' gestation predicted an increased likelihood of mixed-handedness when children were 42 months of age (OR = 1.23). This finding was observed over and above the effects of parental handedness, obstetrical and other antenatal risks, and postnatal anxiety. In another large-scale prospective study, Obel, Hedegaard, Henriksen, Secher, and Olsen (2003a) also showed that antenatal life events were associated with a higher prevalence of mixed-handedness during childhood. However, unlike Obel et al. (2003a), these investigators found that maternal reports of life events later in pregnancy (greater than 30 weeks' gestation) had greater predictive power than reports given earlier in pregnancy (less than 12 weeks' gestation). Despite this difference, the findings from both studies were similar in that they demonstrated links with mixed- as opposed to left-handedness.

Examination of such outcomes may be a particularly fruitful area for future research, as atypical laterality has been observed in children with autism, learning disabilities, and other psychiatric conditions, including problems with attention and schizophrenia (Glover et al., 2004). Indeed, a recent study has shown that prenatal stress, especially at 25–28 weeks' gestation, is associated with an increased risk of autism (Beverdorf et al., 2005). It is an interesting possibility that many of these symptoms or disorders, which share neurodevelopmental

components such as mixed-handedness, may be exacerbated by antenatal maternal stress.

Adult outcomes

Antenatal stress has also been associated with altered adult outcomes, although here, studies have focused almost exclusively on psychopathology. Maternal exposure to traumatic events during pregnancy, for example, has been associated with increased lifetime risk of developing psychiatric disorders. In a retrospective cohort study, Van Os and Selten (1998) demonstrated that the offspring of women who were pregnant during the German invasion of the Netherlands in 1940 were at a significantly increased risk for developing schizophrenia in adulthood (OR = 1.5). These results were replicated among a sample of Dutch adults whose mothers were pregnant during a devastating flood in 1953 (Selten, van der Graaf, van Duursen, Gispens-de Weid, & Kahn, 1999). Comparison samples in these studies included cohorts of individuals born prior to and following the disastrous event, in order to control for its subsequent effects on socioeconomic status and other large-scale societal changes. Additionally, a higher incidence of affective disorders was observed among a sample of Chinese adults whose mothers were pregnant during a severe earthquake in 1976 (Watson, Mednick, Huttunen, & Wang, 1999). These studies, however, may underestimate the magnitude of the relation between prenatal stressors and adult psychopathology because the incidence of the disorders was obtained from government hospital records and analyses were performed on the most severely affected individuals in the selected populations.

Magnitude of effects of antenatal stress on child neurodevelopment

The size of the effects found in many of these studies is considerable. Van den Bergh and Marcoen (2004) found that maternal anxiety during pregnancy accounted for 22% of the variance in symptoms of ADHD in 8–9-year-old children. In addition, exposure to stressful events doubled the risk for ADHD problems in a study by Obel et al. (2003b). Huizink and colleagues (2003) found a smaller effect, with 3–8% of the variance in mental and motor development at 8 months explained by anxiety during pregnancy. LaPlante et al. (2004) showed that the level of prenatal stress exposure accounted for 11% and 12% of the variance in the toddlers' Bayley MDI and productive language abilities respectively, and accounted for 17% of the variance of their receptive language abilities. Bergman, O'Connor, and Glover (in preparation) also observed an effect of antenatal life events at 18 months of age, accounting for 22% of the variance in Bayley MDI scores.

O'Connor et al. (2002) and O'Connor, Heron, Golding, and Glover (2003) found that women in the top 15% for symptoms of anxiety at 32 weeks' gestation had double the risk of having children with behavioral problems at 4 and 7 years of age, even after allowing for multiple covariates. It raised the risk for a child from this group of women having symptoms of ADHD, anxiety or depression, or conduct disorder from 5% to 10%. This implies that the attributable load in behavioral problems due to antenatal anxiety is of the order of 15%. If we were able to substantially reduce stress in pregnant women, such findings suggest that this may have an important effect on social and cognitive developmental outcomes.

Most of these are substantial effects, but there remains considerable variation across children. Bergman, for example, has found that although antenatal maternal stress increases the risk for both cognitive delay and elevations in anxiety, these do not necessarily occur in the same children (unpublished). It is likely that there are gene-environment interactions (Caspi et al., 2003) so that the effects of antenatal stress become apparent among those children who also have specific genetic vulnerabilities.

Is this fetal programming?

The studies described have all reported associations between antenatal stress and a range of negative sequelae in children. However, this in itself does not prove that fetal programming is occurring. There could be other maternal and child effects that account for these associations, ranging from shared genetic variance to indirect behavioral mechanisms of influence. For example, a mother who experiences anxiety during pregnancy may have manifested the same level of anxiety preconception. In this case, the mechanism of transmission would be the transfer of genetic susceptibility to psychopathology as opposed to exposure to prenatal stress.

Additionally, if a mother is stressed during pregnancy, she may also continue to be stressed during the postpartum period, thus affecting parenting quality. Stress in the pre- and postnatal period could also affect maternal perceptions of child behavior. Results from studies in which independent observations of child behavior, as opposed to maternal report, were found to be associated with prenatal stress provide some refutation of a maternal bias hypothesis (Brouwers et al., 2001; Field et al., 2002). There remain, however, a number of potential third variables that might explain the apparent association between prenatal stress and child outcomes, such as maternal use of cigarettes or alcohol during pregnancy. Most studies, although not all, have controlled for these influences, which also have a direct effect on the development of the fetus. The best evidence for an antenatal effect of psychological

stress comes from those studies in which the association between prenatal stress and child outcomes remains even after controlling for maternal postnatal anxiety or depression (O'Connor et al., 2002; Van den Bergh & Marcoen, 2004; Brouwers et al., 2001). Bergman, O'Connor, and Glover determined the frequency of both antenatal and postnatal life events, and found that the reduction in Bayley MDI scores was associated only with the antenatal life events (unpublished). These studies do provide some support for the concept of fetal programming. Recent work with rodents, however, suggests that long-term behavioral outcomes are determined by characteristics of both the pre- and postnatal environment (Francis, Szegda, Campbell, Martin, & Insel, 2003). The interactive effects of pre- and postnatal environmental influences have not yet been examined in human populations, but represent a very important area for future investigation.

Methodological problems and unanswered questions

Sample sizes vary considerably in these studies and have predictable effects on the methods used for assessment and analysis. Whereas larger studies have relied upon maternal reports for ratings of antenatal stress as well as the developmental outcome of interest, the smaller studies more frequently employ observational measures (LaPlante et al., 2004; Van den Bergh & Marcoen, 2004). Despite such variations in sample size and methodological approaches, the studies collectively suggest that maternal stress during pregnancy is a non-specific risk factor for negative outcomes during childhood.

Almost all studies in this literature have measured antenatal stress using self-reports. There is variation in the type of questionnaire administered, however, as some studies assessed daily hassles (Huizink et al., 2003), whereas others focused on life events (Lou et al., 1994; LaPlante et al., 2004; Obel et al., 2003a), perceived stress (Huizink et al., 2003; Rodriguez & Bohlin, 2005), or pregnancy-specific worries (DiPietro et al., 2006). However, these studies do suggest that developmental effects can be observed with relatively low levels of anxiety and/or chronic stress, at least for the kinds of social/emotional and cognitive outcomes investigated.

There is still much to learn about the types of antenatal emotional disturbance or stress that is most harmful for fetal and child development and the contexts in which such effects may be attenuated. None of the published studies have employed clinical interviews, and it is not known whether specific subtypes of maternal psychopathology (e.g., phobia, generalized anxiety disorder, post-traumatic stress disorder (PTSD)) differentially predict postnatal outcomes. This is important, as different biological profiles are associated with different types of psychopathology – particularly with respect to func-

tioning of the HPA axis, a system purported to explain relations between antenatal stress and the types of postnatal outcomes previously described (see next section). For example, lower concentrations of cortisol secretion have been associated with PTSD, whereas higher concentrations have been associated with generalized anxiety disorder as well as depression (Golier & Yehuda, 1998; Yehuda, Teicher, Trestman, Levengood, & Siever, 1996; Hoehn-Saric, McLeod, Lee, & Zimmerli, 1991). There is some evidence that levels of maternal self-reported anxiety predict child outcomes more strongly than depression. For example, O'Connor et al. (2002) found that although antenatal depression was associated with child behavioral problems in a similar way to prenatal anxiety, the associated effect size was smaller. The authors also found that the association between antenatal anxiety and child behavioral problems was separate and additive to the effects of postnatal depression (O'Connor, Heron, & Glover, 2002).

There is some indication that specific types of life events that occur during pregnancy predict effects on the developing child. For example, children of mothers who report undergoing a separation or divorce during pregnancy or experienced 'cruelty by the partner' were more likely to display lower scores on measures of cognitive development (Bergman, O'Connor, & Glover, unpublished). This finding is similar to an early study by Stott (1973), which suggested that continuing personal tensions (specifically marital discord) were a particular risk factor for 'neurological dysfunction, developmental delays and behavior disturbance' during childhood.

The extent to which antenatal stress differentially affects the development of male and female children is not clear, because few studies report results for each sex separately. The studies of O'Connor et al. (2002) and Van den Bergh and Marcoen (2004) did examine both sexes, however, and found a greater effect of antenatal anxiety on ADHD symptoms in boys than in girls at 4 years. However, in a follow-up study of these same children at age 7, the increased risk due to antenatal anxiety was similar for both sexes, suggesting an interactive effect of gender and development (O'Connor, Heron, Golding, & Glover, 2003). In another example, Catalano and colleagues (2005) reported that the fetal death sex ratio in California was increased for males over females 2 months after the September 11, 2001 attacks in New York City. Because sex ratios did not differ from expected values 9, 10, or 11 months following the attacks, decreases in conception rates do not appear to account for this finding. Nonetheless, given that antenatal stress is associated with risk for psychopathology, and that psychopathological outcomes are often characterized by skewed gender distributions, this represents an important consideration to explore in future investigations.

While mounting evidence points to an association between prenatal stress and postnatal developmen-

tal outcomes, there is currently little agreement about the gestational age most sensitive to such stress. Of the four studies that investigated symptoms of ADHD, for example, one found some evidence for greater sensitivity during the first trimester (Rodriguez & Bohlin, 2005), two during mid-gestation (Van den Bergh & Marcoen, 2004; Obel et al., 2003b) and one during late gestation. There are several possible reasons for these discrepancies. One is that the temporal boundaries of stressful experiences are, in many instances, difficult to quantify. For example, events that are acute in onset (e.g., natural disasters, death of a family member) often lead to enduring changes in the surrounding environment, which may be subsequently appraised as stressful. Additionally, maternal reports of anxiety and depression as well as daily hassles are characterized by their chronicity, rendering it difficult to quantify the onset and offset of the stressful experience. Also, studies differ in terms of the timing of the gestational assessments. In O'Connor et al. (2002), for example, anxiety was measured at 18 and 32 weeks' gestation, and the associations were stronger with the latter time point. It remains possible that the effects were actually maximal at mid-gestation, and this would concur with the findings of other studies. Moreover, smaller-scale studies may not have enough power to effectively examine the issue of sensitive periods during pregnancy with respect to stress. More research is clearly needed to address these issues.

Underlying mechanisms: HPA axis and associated biological processes

Investigators have focused primarily on the hypothalamic-pituitary-adrenal (HPA) axis in both mother and child as the primary biological mechanisms underlying the long-term effects of prenatal stress. The HPA axis is linked with relevant behavioral outcomes (Gunnar, 2001) and much animal work has shown its susceptibility to the long-term effects of early developmental experience (Levine, 2005). Indeed, in several animal species, disruptions in early caregiving are associated with permanent alterations in the dynamics of this axis, a system that is critically involved in preserving physical health as well as mobilizing energy stores, promoting vigilance, and inhibiting inflammatory responses under conditions of stress and threat (Gunnar, 2003). Further, early postnatal experiences have been shown to affect the developing cortico-limbic circuits involved in the regulation of the HPA axis, thereby rendering animals more vulnerable to effects of subsequent stressors (Gunnar & Talge, in press). Specifically, the activation of the HPA axis is more pronounced and the response more prolonged. Moreover, a pattern of exhibiting heightened behavioral manifestations of anxiety in the response

to stressful stimuli persists into adulthood (e.g., bodily stilling or freezing). Such chronic activation of the axis can be related to the development of health problems, and mounting evidence points to an increased vulnerability to the development of psychopathology. Therefore, given the apparent relevance of early life experience to HPA and behavioral responses to stressors, a burgeoning program of research has examined the effects of prenatal stress in relation to this biological system as well as postnatal behavioral outcomes.

Evidence from animal models

In animal models, both rodent and non-human primate, the central role of the HPA axis in mediating prenatal stress effects in both mother and offspring is well established (Weinstock, 1996, 2001; Schneider, Coe, & Lubach, 1992), although of course many other neurocircuits, such as the dopaminergic and serotonergic systems, are also likely to be involved.

The most frequent techniques used to induce maternal stress in rats involve restraint (placing the pregnant rat inside a narrow, illuminated tube) or exposure to unpredictable bouts of loud noise. Both procedures produce reliable and significant increases in HPA activity in pregnant dams (Barbazanges, Piazza, Le Moal, & Maccari, 1996; Weinstock, Matlina, Maor, Rosen, & McEwen, 1992). Typically, these stress paradigms are administered 3–5 times during the last week of pregnancy, covering approximately 33% of fetal rat gestation. Comparison groups include dams who remain undisturbed during their pregnancies, and offspring who are cross-fostered to control for maternal postnatal behavior.

Elevations in maternal HPA activity caused by either restraint or noise stress during pregnancy have been associated with both short- and long-term effects on developing offspring. For example, this prenatal experience is consistently linked with smaller size and head circumference at birth (Weinstock, 1996). Prenatal stress exposure is also associated with altered HPA functioning and long-term behavioral outcomes in the offspring. For example, restraint stress during pregnancy predicts higher basal activity of the axis (Weinstock et al., 1992) as well as potentiated and prolonged HPA responses when the offspring undergo restraint stress on postnatal days 60 and 90 as adults (Weinstock et al., 1992, Vallee et al., 1997). These results are accompanied by the downregulation of glucocorticoid receptors (GRs) in the hippocampus and hypothalamus (Barbazanges et al., 1996). However, GRs and corticotropin-releasing-hormone (CRH) expression in the amygdala were upregulated, a neurobiological profile associated with anxiety-like behavior (Weinstock, 1996). Indeed, prenatally-stressed offspring display heightened behavioral responses to novelty, including freezing, decreased exploration, and

defecation (Vallee et al., 1997), behaviors that are also associated with post-stress serum concentrations of cortisol. Disturbances in spatial memory and other aspects of cognitive functioning have also been observed (Chapillon, Patin, Roy, Vincent, & Caston, 2002). Postnatal environmental enrichment, however, does appear to reverse the effects of prenatal stress at the behavioral (Vallee et al., 1997; Maccari et al., 1995) and cognitive level (Bredy, Humpart-zoomian, Cain, & Meaney, 2003). Thus, in rodents, the postnatal environment can influence the manifestation of prenatal stress effects.

In sum, the rodent literature suggests that prenatal stress is associated with many long-term effects in the offspring, including behavioral hyper-arousal and impaired cognitive functioning. These effects are in turn associated with altered function of the HPA axis, and its altered control by central glucocorticoids receptors (Figure 1). Postnatal environmental enrichment, however, can mitigate these effects.

A series of developmental studies with non-human primates has also provided convincing evidence that prenatal stress, and its associated increase in maternal HPA activity, is related to both short- and long-term negative sequelae in the offspring (Schneider et al., 2002; Clarke, Soto, Bergholz, & Schneider, 1996), including impairments in attention as well as heightened levels of anxiety. The central role of the maternal HPA axis has been demonstrated (Schneider et al., 1992) as these behavioral effects can be replicated by administering ACTH to the pregnant monkey and abolished by adrenalectomy. Prenatal stress manipulations in non-human primates typically involve removing pregnant rhesus monkeys from their cages and subsequently exposing them to uncontrollable, loud noise bursts. These exposures typically occur once per day, five days a week for approximately 25% of gestation, and are associated with elevations in HPA activity (Clarke et al., 1996). In several of these studies, prenatally stressed and control monkeys were reared together in a nursery, irrespective of their prenatal experience, to control for postnatal effects of maternal behavior.

In terms of neonatal outcomes in the primate, no group differences in gestational length were observed as a function of prenatal stress exposure, although neonates tended to be smaller at birth (Schneider et al., 2002). Effects with respect to neurobehavioral outcomes, which were measured during the first month of life, depended somewhat upon the timing of the manipulation during pregnancy. Specifically, monkeys who were exposed to stress early in gestation (days 45–90) often performed more poorly on measures of attention (e.g., visual orienting) and motor maturity (e.g., head posture) than monkeys exposed during mid- to late gestation (days 120–134) or the undisturbed controls (Schneider, Roughton, Koehler, & Lubach, 1999). Mid- to late gestational stress, however, was typically associated with poorer

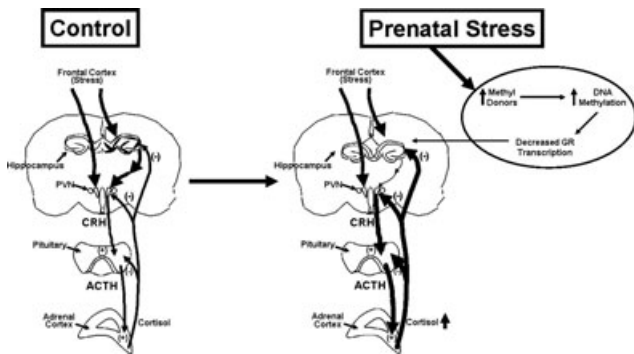


Figure 1 A model to show how antenatal stress may affect the function of the HPA axis, by a reduction in glucocorticoid receptors in the hippocampus, causing reduced negative feedback.

The HPA axis is an elaborate system of checks and balances that, beyond the maintenance of a circadian rhythm, allows mammals to adapt to changes in their environment. The system is geared to respond rapidly to stressful stimuli, and then return to the baseline state of homeostasis. Under stimulatory conditions neurons in the paraventricular nucleus of the hypothalamus (PVN) secrete corticotropin releasing hormone (CRH) into the hypophyseal portal circulation. In the anterior pituitary, CRH induces production of adrenocorticotropin (ACTH), which is released into the systemic circulation to stimulate formation and release of glucocorticoids from the adrenal cortex (cortisol in human and corticosterone in rat). Elevated serum glucocorticoids provide the physiologic milieu required for an adaptive stress response, but also immediately begin to interact with corticoid receptors to inhibit the stress response via negative feedback. Deleterious consequences of chronic exposure to stress or high levels of glucocorticoids are well characterized, including structural damage to key brain regions such as the hippocampus. Therefore, the HPA axis needs to not only respond swiftly to stress, but to terminate the stress response equally rapidly. Two steroid receptors mediate HPA negative feedback in the brain. The glucocorticoid receptor (GR) demonstrates low affinity binding of glucocorticoids operates within the range of the stress response. The mineralocorticoid receptor (MR) has higher affinity to glucocorticoids and is vital in controlling basal HPA tone and the circadian rhythm. While the PVN expresses predominantly GR, both receptors are particularly enriched in hippocampus, which has been implicated in mediating the neuronal aspects of glucocorticoid feedback on the brain. Therefore, it is reasonable to assume that dysfunction in either receptor system could severely affect the ability of an animal to adapt to its environment. In the model of epigenetic effects of prenatal stress on the hippocampal glucocorticoid receptors in the child proposed in this review, prenatal stress causes increased methylation for the promoter region of the glucocorticoid receptor in the hippocampus. This results in less transcription, fewer receptors, less feedback control and a greater cortisol response to stress. These effects may be modified by maternal prenatal diet or immune status

neurobehavioral outcomes than was observed in the undisturbed pregnancies.

The effects of stress have also been observed under conditions of subsequent challenge at older ages, particularly in response to social separation. Although the effects of gestational timing are mixed, prenatally stressed monkeys tend to display heightened ACTH, but not cortisol, responses to social isolation at 8 months of age. Additionally, these monkeys display more pronounced behavioral disturbances (e.g., stereotypies) during this period of isolation (Schneider et al., 2002). Prenatal stress also affects behavioral responses to reunion with peers, reflected by lower levels of locomotor activity, exploration, and play following their reintroduction into the group. These behavioral results were replicated when monkeys were 3–4 years of age, a period considered to be analogous to adolescence (Coe et al., 2003). Assessments at this stage have also demonstrated that prenatal stress, irrespective of the timing during gestation, was associated with decreased neurogenesis in the dentate gyrus as well as a 10–12% decrease in hippocampal volume (Coe et al., 2003). This demonstrates that prenatal stress results in relatively long-term effects on the brain as well as behavior, particularly under conditions of challenge.

Finally, prenatally stressed monkeys mount a more prolonged HPA response to a pharmacological challenge, suggesting impairment in the negative feedback regulation of the system (Coe et al., 2003). The pathophysiology of this finding has yet to be examined, though it is plausible that high circulating levels of maternal cortisol may down-regulate the expression of fetal hypothalamic glucocorticoid receptors as suggested by the rodent literature.

The HPA axis as mediating mechanism in humans

There is much less understanding of the mechanisms underlying the apparent effects of antenatal stress in humans, including the role of the HPA axis in mother or child. In one study, O'Connor et al. (2005) measured diurnal cortisol in 74 of the children of the ALSPAC longitudinal cohort at 10 years of age. Maternal antenatal anxiety at 32 weeks predicted children's morning cortisol concentrations after allowing for obstetric and socio-demographic factors. There were no links between children's cortisol and maternal anxiety or depression antenatally or postnatally. Huot, Brennan, Stowe, Plotzky, and Walker (2004) showed that maternal depression during pregnancy, but not postpartum, predicted the ratings of negative affect in the offspring. In addition, cortisol levels in response to a mild stressor at 6 months of age predicted negative affect in infants and toddlers. Both these studies are in agreement with animal findings.

In contrast to maternal depression, lower cortisol levels were observed among infants of mothers who developed PTSD in response to September 11

compared to infants of mothers who did not develop PTSD (Yehuda et al., 2005). Lower cortisol levels were most apparent in infants born to mothers exposed in their third trimesters. The authors state that 'effects of maternal PTSD related to cortisol can be observed very early in the life of the offspring and underscore the relevance of in utero contributors to putative biological risk for PTSD.' However, PTSD, unlike milder stress or anxiety, is typically associated with lower rather than higher cortisol levels.

There is evidence of a strong correlation between maternal plasma and fetal plasma cortisol levels (Gitau, Cameron, Fisk, & Glover, 1998; Gitau, Fisk, Teixeira, Cameron, & Glover, 2001), although fetal levels are about 10 fold lower than maternal levels. Thus, although the majority of maternal cortisol is metabolized as it crosses the placenta, it appears that enough crosses into the fetal compartment to have a clinically significant effect on fetal brain development. Clearly, the correlation between maternal and fetal cortisol levels in plasma does not prove that the mechanism by which prenatal stress affects the fetus is via maternal cortisol. Other explanations for this correlation, such as a joint stimulation of cortisol production in both mother and fetus by placental CRH, are plausible. Recent results (Sarkar, Bergman O'Connor, Fisk, & Glover, unpublished) demonstrate that the correlation between maternal and fetal cortisol only becomes significant by mid-gestation. Thus, if maternal cortisol has an effect on fetal development earlier in gestation, the mechanism remains obscure.

Higher levels of self-reported stress have been found to be significantly associated with elevated maternal ACTH and cortisol concentrations at 28 weeks' gestation (Wadhwa et al., 2001), even after controlling for obstetric complications. Combined with such demographic information as SES and race, stress appraisals accounted for approximately 36% and 13% of the variance in maternal ACTH and cortisol, respectively. In contrast, higher levels of perceived social support have been found to be associated with lower maternal levels of both ACTH and cortisol (Wadhwa, Dunkel-Schetter, Chicz-De-Met, Porto, & Sandman, 1996; Wadhwa et al., 2001). This raises the intriguing possibility that social support, and the behavioral coping that it facilitates, buffers the maternal HPA axis (at least at the pituitary and adrenal levels) from activation in response to stressful events.

Maternal stress during pregnancy has also been associated with alterations to the characteristic diurnal rhythm of salivary cortisol. In one study, maternal reports of negative life events were compared to morning and evening samples of cortisol that were collected at 14 and 30 weeks' gestation. Results indicated that lower morning and higher evening values of cortisol were observed if mothers reported experiencing one or more negative life

events, irrespective of the timing during gestation (Obel et al., 2005).

Based on the animal literature, one would hypothesize that if the mother is stressed, her cortisol rises and this in turn crosses the placenta in sufficient concentrations to affect fetal development. However, some problems remain with this proposed mechanism in humans. For example, maternal cortisol responses to stress decrease markedly across gestation, such that by late pregnancy, the maternal HPA axis can be quite unresponsive. This has been shown in response to a pharmacological challenge (Schulte, Weisner, & Allolio, 1990), a physical challenge such as the cold pressor test (Kammerer, Adams, Castelberg, & Glover, 2002), and to the psychological stress of awaiting amniocentesis (Sarkar, Bergman, Fisk, & Glover, 2006). Thus, at the time in pregnancy when there appears to be the strongest link between maternal and fetal cortisol, the maternal HPA axis becomes less sensitive to stress. It remains possible that at around mid-gestation, the maternal HPA axis is still responsive and there is passage of cortisol from mother to fetus. However, maternal cortisol is metabolized in the placenta by 11 β HSD-2, an enzyme that converts cortisol to its biologically inactive form, cortisone. As a result, elevations in maternal cortisol are regulated by concentrations of this enzyme, and consequently limit the fetus' exposure to this hormone.

As discussed earlier, there is little agreement in the literature about the period of gestation in which maternal stress is most harmful for the fetus. It is also possible that some women and their infants escape the desensitization of the HPA axis that normally occurs with the progression of pregnancy through differences in their genetic make-up and psychological vulnerabilities. It is known that there are polymorphisms in the glucocorticoid receptor that are associated with different patterns of cortisol response to the same stressor (Wust, Federenko, van Rossum, Koper, & Hellhammer, 2005). It will be interesting to examine these polymorphisms in both mothers and children who appear vulnerable to antenatal stress.

Other possible mechanisms

This review has focused on the potential role of the HPA axis in mediating the link between maternal antenatal stress and an adverse neurodevelopmental outcome for the child. However, other mediating mechanisms are possible; they just have not been studied in humans. For example, stress and anxiety cause substantial activation of the sympathetic-adrenal system and this could also be important. Noradrenaline does not appear to cross the placenta (Giannakouloupoloulos, Teixeira, Fisk, & Glover, 1999), but could affect the fetus indirectly by acting to cause contractions of the myometrium or by reducing uterine blood flow by affecting trophoblastic

invasion. There certainly appear to be rapid mechanisms linking maternal emotional state and fetal behavioral and heart rate responses (e.g., Monk, Myers, Sloan, Ellman, & Fifer, 2003) which cannot be explained by the slower responses of the HPA axis. Additionally, given that the HPA axis functions in concert with other biological systems of the body (e.g., sympathetic-adrenal axis), antenatal stress effects are likely mediated by the dynamic interaction among these systems.

Epigenetic mechanisms and possible influence of diet

Epigenetic mechanisms underlying the long-term effects of perinatal stress have been studied in postnatal rats. Meaney and colleagues have established a model showing the long-term effects of different patterns of early maternal caregiving. Mothers that carry out more nursing and licking have adult offspring who are less anxious in behavioral tests and also have smaller and briefer HPA responses to novel stressors (Zhang, Parent, Weaver, & Meaney, 2004; Caldji, Diorio, & Meaney, 2000). Recently, this group (Weaver et al., 2004) has shown that this increased nurturing is associated with less methylation of the promoter region of the GR gene in the hippocampus. Methylation blocks transcription and decreased methylation results in expression of more GR receptors, more feedback control of the HPA axis, less corticosterone response to stress, and less anxious behavior. It is interesting to note that modifications in methylation were highly specific for both gene and brain region. It is likely that similar epigenetic modifications occur in the fetal brains of prenatally stressed animals and humans, but this remains to be determined.

Weaver et al. (2005) have also shown that one can increase the methylation of the promoter region of the hippocampal GR receptor in this model by direct infusion of methionine, reversing the effect of 'good mothering' and making offspring behaviorally hyperaroused. It is suggested that methionine, a major methyl donor normally supplied by protein, especially in meat, may be modified by diet, altering the effects of perinatal stress.

The hypothesis that diet may impact fetal programming is supported by studies of cardiovascular function in rodent models. Results from several studies demonstrate that if a pregnant rat is fed a diet low in protein, her adult offspring have altered cardiovascular function and raised blood pressure (Langley & Jackson, 1994; Petry, Ozanne, Wang, & Hales, 1997; Brawley, Poston, & Hanson, 2003). Of special relevance to the possible influence of diet on the effects of prenatal stress are the experiments of Bertram, Trowern, Copin, Jackson, and Whorwood (2001). These authors showed that a low protein maternal antenatal diet decreased the expression of 11 β HSD-2 in the placenta. This could potentially

result in the fetus being exposed to higher levels of cortisol. A low-protein maternal diet also induces increased expression of GRs in the lung and kidney of the offspring, thus potentiating the peripheral effects of HPA activity.

Predictive adaptive response and evolutionary significance

Gluckman and Hanson (2005) have put forward the concept of the 'predictive adaptive response' to explain the evolutionary purpose of epigenetic fetal changes in utero to prepare the offspring for the particular environment in which it will find itself. Such changes can be much more rapid in response to a changing environment than the natural selection method based on genetic variation.

They suggest that early life responses occur in a single generation to increase the chance of survival of the individual to reproductive fitness. These changes occur early in development when the individual is most plastic. In mammals, this is primarily during embryonic and fetal life. Hanson and Gluckman discuss the example of the large fluctuations in population numbers of snowshoe hares in North America. When food is scarce, for example after a late spring, the population declines and many die of starvation. The fewer numbers mean that the remaining animals are more likely to be killed by their natural predators such as the lynx or coyote. The remaining hares must be extremely vigilant. Because the female hares are stressed, they have high cortisol levels during pregnancy; this in turn alters the function of the HPA axis of the offspring making them more vigilant and aware of the potential threat from potential predators. This will help them to survive until food supplies increase and population numbers can increase.

This type of fetal adaptive response to stressful surroundings has presumably developed in primates, including humans, also. We can speculate that extra vigilance and rapid shifts in attention could be adaptive in an environment full of danger or predators. In our own civilization, with no predators, and in which great premium is put in education on focus and concentration, extra vigilance and rapid shifts in attention can be maladaptive, and result in unnecessary anxiety and problems with attention.

Future research

There are many important ways in which this area of research can and should be developed. All the existing studies linking antenatal maternal stress and adverse child neurodevelopmental outcomes have been carried out in Europe and North America. The stress experienced by women in their everyday lives in the developing world may be much harsher

and the outcomes for their children deserve study. The effects of other stresses such as war and political conflict on pregnant women and their future children are also likely to be severe and need to be understood. Based on the fact that similar levels of prenatal stress result in a variety of behavioral outcomes, we know that antenatal stress does not affect all children in the same way. It is important to understand more about genetic and other vulnerability factors as well as the protective effects of prenatal and postnatal environments, and also mechanisms of resilience. The implication of the existing research is that intervention during pregnancy to reduce stress or anxiety during pregnancy should reduce the incidence of emotional and cognitive problems in the child and later adult. The potential efficacy of different types of such interventions still needs to be explored.

We also need to understand much more about the hormonal and other mechanisms underlying these effects and the gestational ages of vulnerability. This will help to design the timing of effective antenatal interventions and help researchers better characterize the biological and hormonal milieu within which the fetus is developing. There can be a dissociation between self-reports of psychological distress and changes in levels of hormones such as cortisol. It would also be of interest to use other approaches to examine fetal and neonatal development such as MRI, which may both show effects of prenatal stress and be used to demonstrate the efficacy of intervention. It is quite possible that the effects of prenatal stress are moderated by other aspects of the environment such as maternal diet and immune status, and this has yet to be studied.

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