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Fetal exposure to placental corticotropin-releasing hormone is associated with child self-reported internalizing symptoms

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ABSTRACT

Objective: Fetal exposure to maternal prenatal stress hormones such as cortisol exerts influences on the developing nervous system that persist and include risk for internalizing symptoms later in life. Placental corticotropin-releasing hormone (pCRH) is a feto-placental stress signal that also shapes fetal neurodevelopment and may be a more direct indicator of the fetal experience than maternal stress hormones. The programming effects of pCRH on child development are unknown. The current investigation examined associations between prenatal maternal and placental stress hormone exposures (maternal cortisol and pCRH) and child self-reported internalizing symptoms at age 5.
Method: Maternal plasma cortisol and pCRH levels were measured at 15, 19, 25, 31, and 36 weeks' gestation in a sample of 83 women and their 91 children (8 sibling pairs from separate pregnancies), who were born full-term. Child self-reported internalizing symptoms at age 5 were obtained using scales of the Berkeley Puppet Interview.
Results: Placental CRH profiles (including elevations in mid-gestation) were associated with higher levels of internalizing symptoms at age 5. This effect was not explained by critical prenatal or postnatal influences, including obstetric risk, concurrent maternal psychological state, and family socio-economic status. Prenatal maternal cortisol was not significantly associated with child self-reported internalizing symptoms.
Conclusions: Findings suggest that elevated exposures to the feto-placental stress signal pCRH exert programming effects on the developing fetal central nervous system, with lasting consequences for child mental health.

1. Introduction

The maternal endocrine stress system is profoundly altered during the course of human pregnancy. The maternal pituitary gland doubles in size, and the synthesis and release of stress peptides and hormones from the maternal hypothalamic–pituitary–adrenal (HPA) axis into the maternal circulation increases several-fold. However, it is the growth and development of a new transient endocrine organ, the placenta, that primarily is responsible for the profound changes in the maternal and fetal stress systems as gestation progresses. As early as 7–8 weeks' gestation, the placenta begins to synthesize the stress hormone corticotropin-releasing hormone (CRH), and this active peptide is released into both the maternal and fetal circulation (Gitau et al., 2004; Goland et al., 1988; Karteris et al., 2001; Mastorakos and Ilias, 2003). Placental CRH (pCRH) is identical in structure and activity to hypothalamic CRH (hCRH) and increases dramatically in the maternal circulation over the course of human pregnancy, reaching levels only present in the hypothalamic portal system during stress (Lowry, 1993). Concentrations of circulating maternal CRH are almost exclusively of placental origin, because the minute quantities of hCRH that are released into the maternal circulation are rapidly degraded and largely undetectable (Mesiano, 2014).

The feto-placental unit derives information from maternal physiological signals, including stress signals conveying a response to environmental threats or challenges, and adapts its developmental program accordingly (Gluckman and Hanson, 2004;

Abbreviation: pCRH, placental corticotropin-releasing hormone.

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Sandman and Davis, 2012). Placental CRH is responsive to a range of these stress signals, including increased norepinephrine and epinephrine, reduced uterine blood flow, and infection (Herrmann et al., 2001; Petraglia et al., 1989; Wadhwa et al., 2001). Further, in contrast to its negative feedback regulation of hCRH, maternal cortisol stimulates the synthesis and release of CRH in the placenta. Placental CRH penetrates the fetal blood–brain barrier and stimulates fetal adrenal cortisol production, which in turn further stimulates pCRH production (Kastin and Akerstrom, 2002; Mesiano, 2014). Thus, placental CRH represents an integrative pathway through which diverse prenatal stressors might inform the fetus of the state of its environment and shape fetal developmental trajectories (Charil et al., 2010; O'Donnell et al., 2009; Sandman et al., 2011).

Increasing evidence suggests that anxiety and mood disorders have origins in prenatal experiences (Baram et al., 2012; Sandman and Davis, 2012). Perhaps one of the most consistent neurobehavioral findings is that fetal exposure to elevations in stress hormones is associated with subsequent increased risk for internalizing problems (Bergman et al., 2007; Davis et al., 2005, 2007; Davis and Sandman, 2012; de Weerth et al., 2003). Most research examining the role of prenatal stress hormone exposures on the programming of offspring internalizing symptoms has focused on maternal cortisol, which increases two to four fold over human gestation. Evidence from rodent and non-human primate studies indicates that fetal exposure to elevated glucocorticoids is associated with increased fearful behavior, depression-like behavior, and stress reactivity (Abe et al., 2007; Kapoor et al., 2006; Kapoor and Matthews, 2005; Seckl, 2008). In humans, fetal exposure to elevated concentrations of maternal cortisol is associated with increased fetal and neonatal reactivity to stimulation (Davis et al., 2011; Glynn and Sandman, 2012), increased fearful behavior in infancy (Bergman et al., 2010; Davis et al., 2007; de Weerth et al., 2003), higher levels of internalizing behavior problems in children (Davis and Sandman, 2012), and alterations in brain regions association with internalizing problems (Buss et al., 2012; for a review, see Zijlmans et al., 2015).

However, because the placenta is responsive to a variety of stress signals, including cortisol of both maternal and fetal origin (Mesiano, 2014), levels of circulating pCRH may be a more direct indicator of fetal exposure and response to stressors than maternal cortisol alone. In the only published study that evaluated the consequences of pCRH on the development of internalizing symptoms in humans, elevated pCRH levels at 25 weeks' gestation predicted increased mother-reported infant fear and distress (Davis et al., 2005). Further, compelling evidence from experimental animal models indicates that exposure to stress-induced elevations in CRH or exogenous CRH early in life may alter the structure and function of brain regions involved in internalizing symptoms (Avishai-Eliner et al., 2002; Chen et al., 2010; Maras and Baram, 2012). These findings encourage further investigation of the role of pCRH in the programming of offspring internalizing symptoms.

Mid-gestation is a period of rapid acceleration in maternal cortisol and pCRH trajectories (Sandman et al., 2006) and appears to be a sensitive window for effects on the fetal central nervous system (Sandman et al., 2015). Elevations in mid-gestational pCRH are linked to increased infant fear and distress (Davis et al., 2005), as well as a variety of other fetal and infant developmental outcomes related to maturation and body composition (Class et al., 2008; Ellman et al., 2008; Sandman et al., 2006; Stout et al., 2015 Stout et al., 2015). The fetal brain is rapidly developing at mid-gestation, such that it might be particularly susceptible to organizing and disorganizing programming influences at this time.

The aim of the current study is to test the hypothesis that accelerated prenatal trajectories of pCRH and maternal cortisol during mid-gestation are associated with child self-reported internalizing symptoms at age 5 in a sample of typically developing children born at full term. We chose to assess internalizing symptoms early in childhood because rates of depressive and anxious disorders begin to accelerate at this age (Luby et al., 2002; Merikangas et al., 2010), and because early childhood symptoms are predictive of symptom trajectories and later psychiatric diagnosis (Ialongo et al., 2001). Unlike the vast majority of studies that have relied on parental report to examine the association between prenatal exposures and child temperament, we eliminated possible maternal bias and obtained unique insight into children's symptoms by directly assessing child self-report of internalizing child behavior (Ialongo et al., 2001; Luby et al., 2007; Najman et al., 2001).

2. Method

2.1. Study overview

Study participants were mother–child pairs from a prospective, longitudinal study of prenatal psychobiological risk and development. Women with intrauterine, singleton pregnancies less than 16 weeks' gestational age were recruited at a large university medical center in Southern California and assessed over the course of gestation. Mother–child pairs were assessed when the child was 5 years of age.

2.2. Participants

The sample comprised 83 mothers and their 91 five-year-old, typically developing children (M_{age} = 5.13, 53% female). Eight of these women participated in the study twice for two separate pregnancies, with both children included in the study.[1] At recruitment, inclusion criteria were English-speaking, adult (>18 years old) women with intrauterine, singleton pregnancies. Exclusion criteria at recruitment were the presence of uterine or cervical abnormalities; conditions such as endocrine, hepatic or renal disorders or use of corticosteroid medication; and self-reported abuse of tobacco, alcohol, or recreational drugs in pregnancy. Additional inclusion criteria for the current study were delivery of a full-term infant (gestational age at delivery ≥37 weeks; M = 39.64 weeks, SD = 1.14 weeks), maternal completion of at least 3 of 5 prenatal hormone assessments, and child completion of the internalizing symptoms scales of the Berkley Puppet Interview. Mothers were primarily Caucasian, non-Hispanic and Hispanic; had received greater than a high school level of education; and were cohabiting with the child's father at the time of child assessment (see Table 1 for sample descriptives). Mothers provided written informed consent for all aspects of the protocol, which was approved by the university's Institutional Review Board for protection of human subjects.

2.3. Procedures

Maternal blood plasma samples were obtained for cortisol and pCRH analysis at 15 (M = 15.45 ± .93), 19 (M = 19.63 ± 1.10), 25 (M = 25.86 ± 1.03), 31 (M = 31.14 ± .93), and 36 (M = 36.78 ± .87) weeks' gestation. Obstetric risk information was collected by detailed medical interviews at each prenatal visit, along with comprehensive examination of prenatal and delivery medical records. Child self-reported internalizing symptoms and maternal depressive symptoms were evaluated when children were 5 years of age.

[1] Findings reported here did not change when removing one member of the sibling pair, so both siblings were included in analyses