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Prenatal maternal mood is associated with altered diurnal cortisol in adolescence

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Summary
Background: Experimental animal work shows that prenatal stress has a persisting effect on the hypothalamic-pituitary-adrenal (HPA) axis of offspring. The implications of these findings for human health and development are not yet clear.
Methods: The data are based on the ALSPAC cohort, a prospective longitudinal study of a community sample that has followed mothers and children from pregnancy. When the children were aged 15 years, diurnal cortisol samples were collected at wake-up, 30 min post-awakening and at afternoon and evening times on up to three consecutive days on $n = 889$ adolescents. Diurnal cortisol was predicted from prenatal anxiety and depression, obstetric, life-style, socio-demographic, and postnatal covariates.
Results: Multilevel model analysis indicated that maternal prenatal anxiety was associated with a modest alteration of diurnal cortisol, indexed by a reduced cortisol awakening response and flatter diurnal slope. The effects were independent of psychosocial and obstetric covariates and measures of maternal postnatal anxiety; effects were similar for prenatal maternal depression. There was no association between adolescent cortisol and paternal prenatal anxiety.
Conclusions: There are small but persisting associations between maternal prenatal mood and diurnal cortisol in the child that persist into adolescence and may constitute a programming effect.

Research findings from experimental animal studies suggest that in utero exposures may have a lasting effect on the health and development of the offspring. One prominent model emerging from this work, which is now being translated in humans, is developmental programming, or the

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hypothesis that exposures early in development instigate an adaptive response of the organism that is carried forward with persisting effects on behavior and biology (Barker, 1999; Gluckman and Hanson, 2004). A leading paradigm in this research is prenatal maternal stress or anxiety. Numerous animal experiments show that, consistent with the programming hypothesis, experimentally induced prenatal stress has sizable and lasting effects on offspring fear, reproductive behavior, immunity, neurogenesis, and stress physiology (Coe et al., 2003; Maccari et al., 2003). Several research groups are now investigating the implications for human health. The current study, based on a large, community prospective longitudinal design, extends this work by examining the link between prenatal maternal mood (anxiety and depression) and adolescent diurnal cortisol pattern, a proposed mechanism in the developmental programming model with relevance to mental disorder and somatic health outcomes.

Prenatal maternal anxiety is linked with a wide range of outcomes in the child, including temperament emotionality (Glynn et al., 2007; Bergman et al., 2007), reduced cognitive ability (Davis and Sandman, 2010), adverse neuropsychological outcomes (Glover et al., 2004), altered sleep (O'Connor et al., 2007), and behavioral problems (O'Connor et al., 2002; Van den Bergh and Marcoen, 2004), including schizophrenia (Khashan et al., 2008). The findings appear robust, but questions remain about persistence past childhood and the mechanisms of effect. The current study addressed both of these limitations by examining the long-term connection between prenatal mood and a leading candidate mechanism for its effect on the child, via the HPA axis.

A leading biological model driving the work is that elevated levels of cortisol from the (anxious) mother may cross the placenta, perhaps by altering the barrier enzyme 11β-HSD2(O'Donnell et al., 2012), to affect obstetric outcomes as well as fetal and child development via the influence on the developing HPA axis (Swanson et al., 2009). Direct evidence for this model has been reported in animal studies (Schneider et al., 1999), but human evidence is limited. Our earlier study, based on a subsample of 10 year-olds (n = 74), showed that prenatal maternal anxiety predicted raised diurnal cortisol (O'Connor et al., 2005). Other studies link prenatal maternal anxiety or an index of fetal exposure to glucocorticoids (e.g., from amniotic fluid) with altered cortisol response (Saridjan et al., 2010; Davis et al., 2011; Gutteling et al., 2004; O'Connor et al., 2013).

The current study indexes adolescent HPA axis function from diurnal cortisol output, which provides an index of the total output of the system; this index has attracted considerable research attention (Essex et al., 2011; Adam et al., 2010; Cicchetti et al., 2010; Gunnar and Quevedo, 2008). We assessed cortisol on four occasions within a day on three typical days in the adolescent's life. Within this measurement model, variation in cortisol can be assessed according to initial wake-up, cortisol awakening response, and diurnal decline. What is not yet clear is which of these indicators is reliably altered by early exposure; each has been linked to stress exposure (Adam et al., 2010; Halligan et al., 2004), and these may not index independent effects. In addition to assessing which aspect of the diurnal rhythm is affected by prenatal maternal mood, the current study also extends prior work by examining the nature of the effect. To date, studies linking (early) stress exposure to alterations in HPA axis function report disparate effects, namely, both low basal cortisol and hypo-reactivity (Heim et al., 2000a; Goldman-Mellor et al., 2012) and hyper-reactivity (Halligan et al., 2004; Rao et al., 2008; Heim et al., 2000b). These discrepant findings may be explained by several factors, including age of assessment, age of onset and chronicity of exposure, severity of stress, and current behavior. Prenatal anxiety exposure, as a potential predictor of a programming effect, may be a special case of stress exposure; however, that does not lead to a clear prediction about the nature of the effect. Experimental animal work suggests that prenatal stress leads to hyper-activation of the HPA axis (Henry et al., 1994), but limited human studies of prenatal maternal anxiety or other stresses do not yet offer a consistent pattern (Davis et al., 2011; Entringer et al., 2009). The current study, which includes a large sample size, prospective longitudinal design from pregnancy to age 15 years, and detailed diurnal cortisol assessment allows us to test the hypothesis there is a persisting and particular effect of maternal prenatal anxiety or depression on diurnal cortisol rhythm in adolescence, and to clarify the nature of that effect.

1. Methods

Data for this study were obtained as part of the Avon Longitudinal Study of Parents and Children (ALSPAC), an ongoing population-based study designed to investigate the effects of a wide range of influences on the health and development of children (Golding, 2004); see http://www.bris.ac.uk/alspac. Pregnant women residing in the Avon area of south-west England who had an estimated date of delivery between April 1, 1991, and December 31, 1992, were invited to participate in the study. It was estimated that 85—90% of the eligible population participated. The study cohort consisted of 14,541 pregnancies and 13,988 children who were still alive at 12 months of age. Ethical approval for all measures was obtained from the ALSPAC Ethics and Law Committee and from Local Research Ethics Committees.

For the current study, we proposed to assess a random subsample of 1000 of the adolescents who participated in the clinic visit scheduled when the adolescents were aged 15 years. Fig. 1 shows the rate of participation from the entire cohort to the subset of children invited to participate in the cortisol sub-study. We then applied the following inclusion criteria: (1) product of a singleton pregnancy, (2) gestation at birth >32 weeks, (3) birth weight >1500 g, (4) no current exposure to steroid medication. In addition, from the cortisol data collected at age 15 years we applied the following exclusion criteria for particular samples (i.e., not individuals): (1) undetectable/contaminated; (2) values >4 SD above the sample mean for that time point; (3) for the cortisol awakening response sample, a sample that was provided >1 h after waking. Following these exclusions a total of n = 899 participants (403 males, 496 females; average age 15 years 4 months) remained for analyses.

1.1. Procedure

Mothers completed measures of anxiety on two occasions in pregnancy (18 and 32 weeks gestation) and on multiple occasions in the postnatal period; we include in these