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# Psychological distress and salivary cortisol covary within persons during pregnancy

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Diurnal

**Summary** The mechanisms whereby maternal stress during pregnancy exerts organizational effects on fetal development require elaboration. The aim of this study was to assess the plausibility of cortisol as a biological link between maternal psychological distress during pregnancy and fetal development. Previous research has resulted in equivocal findings for between-persons differences in stress and cortisol. Ecological momentary assessment was used to simultaneously assess mood and cortisol 5 times daily for 3 days in 83 women (gestational ages 6–37 weeks). Results from multilevel analysis indicated a robust within-person association between negative mood and cortisol. For each 1.0% increase in negative mood there was a corresponding 1.9% increase in cortisol. This association was unaffected by advancing gestational age. The results suggest that cortisol is a plausible biological mechanism for transducing the effects of maternal psychological distress during pregnancy to fetal development.

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## 1. Introduction

The observation that children born to mothers with elevated levels of psychological distress are at increased risk for poor birth and developmental outcomes (for reviews see Alder et al., 2007; Schlotz and Phillips, 2009) have given rise to the proposal that maternal experiences of stress and distress

may ‘program’ fetal development. According to the fetal programming hypothesis, the morphological and functional organization of a variety of systems are sensitive to environmental input during critical windows of exposure and the nature of this exposure programs set points within those physiological systems (Barker et al., 1997).

### 1.1. Cortisol as a mediator of fetal programming effects

Results from both rodent and primate models of fetal programming indicate that exposing pregnant females to stressful

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environments (e.g., restraint) leads to increased basal glucocorticoid levels and prolonged glucocorticoid response to stress in offspring (Clarke et al., 1994) as well as enhanced vigilance and fearfulness (e.g., less time spent in open field; Vallee et al., 1997) and changes in brain structure and function (e.g., decreases in glucocorticoid and mineralocorticoid receptors; Matthews, 2002). These findings suggest that the effects of maternal psychological distress on fetal development may be indirect – that is, mediated, at least in part, by the maternal hypothalamic pituitary adrenal (HPA) axis.

A substantial body of empirical evidence in pregnant and non-pregnant humans points to the HPA axis as a central feature of the stress response (see for example, McEwen, 1998; de Weerth and Buitelaar, 2005; Wadhwa, 2005). When individuals are confronted with internal or external demands that exceed their self-perceived resources, the HPA axis initiates a complex set of neurophysiological changes, including the synthesis and/or release of 3 key hormones – corticotrophin-releasing hormone, adrenocorticotropin hormone, and cortisol – that facilitate adaptation (e.g., heightened vigilance, and defense-related learning and memory) and restoration of homeostasis through negative feedback to the pituitary (Miller and O'Callaghan, 2002). However, the typical functioning of this stress response may be fundamentally different during pregnancy because gestation is associated with profound alterations in HPA axis function.

Maternal cortisol increases 2–4-fold over the course of pregnancy (Mastorakos and Ilias, 2003; Sandman et al., 2006). Despite this dramatic functional alteration, the circadian rhythm (with a peak shortly after waking and gradual decline over the day) remains intact (de Weerth and Buitelaar, 2005). Nevertheless, these changes appear to attenuate the HPA axis response to physical, pharmacological and psychosocial stresses during pregnancy (de Weerth and Buitelaar, 2005; de Weerth et al., 2007; Entringer et al., 2010; Fink et al., 2010; Nierop et al., 2006). Given such powerful pregnancy-related alterations, it is not clear to what extent the maternal HPA axis remains responsive to psychological stress. Furthermore, such changes call into question the plausibility of cortisol as a biological link between maternal psychological distress and fetal development.

## 1.2. Associations between psychological distress and cortisol in pregnancy

The majority of what is known about the association between psychological stress and cortisol during human pregnancy comes from laboratory-based studies using acute stressors. Few clinical studies have examined naturally occurring stressors and the majority of these have reported non-significant or low associations. This is especially true of studies using single measures of cortisol from amniotic fluid (Bergman et al., 2010), serum (Petraglia et al., 2001; Bergman et al., 2010; Davis et al., 2010; Goedhart et al., 2010), or saliva (Davis et al., 2007; Davis and Sandman, 2010). Studies assessing diurnal variation in cortisol have provided stronger evidence of an association between psychological distress and cortisol during pregnancy, although the findings across studies are not consistent. Two studies reported flatter afternoon declines in cortisol for women with high levels of psychological distress in late gestation (Obel et al., 2005; Kivlighan et al., 2008) and another reported higher mid afternoon cortisol levels among

women experiencing intimate partner violence (Valladares et al., 2009). In contrast, the most intensive assessment to date of stress and cortisol in pregnant women found no association between experiencing a recent stressor and daily levels of total cortisol (Harville et al., 2009).

Methodological differences between these studies can account for some of the differences in findings, including, for example, use of single versus multiple samples and single versus multiple days to estimate average cortisol as well as inconsistent inclusion of control variables that affect cortisol during pregnancy (e.g., previous pregnancy experience, maternal age, and gestational age; Kivlighan et al., 2008). The major limitation of these studies, however, is that they focus on individual differences between average levels of psychological distress and cortisol. Such approaches are concerned with determining whether individuals who experience more psychological distress also exhibit higher levels of cortisol. While this research has the potential to inform our understanding of the relative ranking of individuals with regard to psychological distress and cortisol (or how predictable one is from the other), it is uninformative of the biobehavioural coordination of these processes *within* individuals. It is precisely such intra-individual approaches that are needed to evaluate the claim that maternal cortisol, consequent to psychological distress, is a plausible biological mechanism with the potential to affect fetal development.

Ecological momentary assessment (EMA) is a method that facilitates tracking of concurrent processes within individuals in the context in which they naturally occur. By assessing psychological distress and cortisol at various measurement moments over the course of several days, it is possible to accumulate a reliable record of variation in these processes and determine the extent to which they covary within persons (Hruschka et al., 2005). EMA approaches also eliminate recall bias and mental aggregation of moods over a prolonged period of time specified by retrospective methods (e.g., the usual paper-and-pencil self-report measures). This approach will help to clarify the nature and strength of the association between psychological and HPA axis changes during pregnancy because it directly assesses whether these process 'track together' within individuals.

## 1.3. Current study

The current study was designed to clarify the intra-individual association between psychological distress and cortisol during pregnancy. Specifically, our goal was to determine whether: (1) moment-to-moment changes in psychological distress are associated with momentary changes in cortisol; (2) day-to-day changes in stress are related to daily changes in cortisol; and (3) any observed associations are moderated by individual differences in gestational age (GA), maternal age, previous pregnancy experience, symptoms of anxiety or depression, and a history of stress exposure.

## 2. Materials and methods

### 2.1. Participants

A subsample of pregnant women between 6 and 37 week GA who were enrolled in an ongoing longitudinal study of nutrition

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