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Diurnal rhythm of cortisol during late pregnancy: Associations with maternal psychological well-being and fetal growth

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Summary Maternal psychological functioning during pregnancy affects both maternal and fetal well-being. The hypothalamic—pituitary—adrenal (HPA) axis provides one mechanism through which maternal psychosocial factors may be transduced to the fetus. However, few studies have examined maternal psychological factors or birth outcomes in relation to the diurnal pattern of cortisol across the day. The current study examined maternal psychological well-being, parity status, and birth weight in relation to the maternal cortisol diurnal rhythm in a group of 98 low-risk pregnant women (51 primiparae). At 36 weeks gestation, participants completed both pregnancy-specific and general self-report measures of psychological functioning and provided saliva samples at 8:00, 12:00, and 16:00 h on 2 consecutive working days for the assay of cortisol. The expected diurnal decline in salivary cortisol was observed. Higher trait anxiety was associated with a flatter afternoon decline for all mothers. For primiparae, steeper morning cortisol declines were associated with lower infant birth weight. The findings suggest that regulation of the HPA axis may differ by parity status with downstream implications for fetal growth and development.

There is much interest in the role of maternal psychological functioning during pregnancy with respect to maternal and fetal well-being. The hypothalamic—pituitary—adrenal (HPA) axis may be a key mechanism whereby maternal psychosocial factors mediate their effects on the fetus. In general, the release of corticotrophin-releasing hormone (CRH) and arginine-vasopressin (AVP) from the hypothalamus stimulates the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary and the subsequent release of cortisol from

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the adrenal cortex. During pregnancy, peripheral CRH of placental origin rises dramatically over non-pregnant levels. This increase in CRH is paralleled by elevations in both ACTH and total cortisol levels (for reviews, see Levine et al., 2007; Mastorakos and Ilias, 2003). Free (bioavailable) cortisol remains at non-pregnant levels until around the 25th week of gestation and rises thereafter (Allolio et al., 1990; Demey-Ponsart et al., 1982). The elevated free cortisol levels of late pregnancy may be due to a resetting of the sensitivity of the HPA axis (Scott et al., 1990). Despite these functional alterations during pregnancy, the diurnal rhythm of cortisol is largely maintained with peak levels at approximately 30-min post-waking and a gradual decrease across the day to an early evening nadir (Allolio et al., 1990; de Weerth and Buitelaar, 2005).

While cortisol is often suggested as a mediator of maternal psychological well-being on fetal development (Wadhwa, 2005; Weinstock, 2005), evidence that maternal experience of stress is associated with cortisol levels during pregnancy is inconsistent. In general, self-reported measures of maternal stress, including reports of life events, daily hassles, and perceived stress, are often unrelated to maternal cortisol during pregnancy (Petraglia et al., 2001; Urizar et al., 2004; Wadhwa et al., 1996), but small positive associations with cortisol levels have been reported (Buitelaar et al., 2003; Diego et al., 2006). In contrast, one study incorporating measures of both waking and late evening cortisol during the third trimester observed 27% higher evening cortisol levels among women who experienced a stressful life event or were concerned about pregnancy complications during the second trimester. Morning cortisol levels were unaffected suggesting a shallower decline in cortisol across the day in stressed women (Obel et al., 2005). Therefore, the pattern of the daily diurnal decline may be an important indicator of the influence of maternal psychology on the function of the HPA axis.

A focus on general, rather than pregnancy-specific measures of stress may also contribute to the sparse associations observed between maternal psychological stress and cortisol during pregnancy. Pregnant women are confronted with changes in their physical condition (e.g., weight gain, sleep quality), anxiety about fetal well-being, impending labor, and new challenges related to balancing work and family (Affonso et al., 1994; Arizmendi and Affonso, 1987; DiPietro et al., 2003; Norbeck and Anderson, 1989; Yali and Lobel, 1999). Previous experience with pregnancy (i.e., parity) may heighten or attenuate the intensity of pregnancy, possibly influencing both psychological and physiological responses to this context (Condon and Esuvaranathan, 1990; DiPietro et al., 2005). In support of this, there is evidence that HPA axis activity differs by parity status. Higher midday total cortisol levels have been observed in primiparae as opposed to multiparous women throughout pregnancy (Rasheed, 1993; Vleugels et al., 1986). In contrast, lower waking cortisol levels have been observed among primiparae as compared to multiparous women (Jones et al., 2006). During the postpartum period, primiparae display greater total cortisol output across the day, while the diurnal rhythm of multiparae is influenced by feeding choice (bottle vs. breastfeeding; Tu et al., 2006). Among mothers of 2-year-olds, having multiple children has been associated with lower morning cortisol levels and a flatter decline in cortisol across the day (Adam and Gunnar, 2001). Therefore, parity might exert an influence on the cortisol diurnal rhythm that extends beyond pregnancy.

Alterations in the function of the HPA axis due to parity or pregnancy-specific experiences could result in differential fetal exposure to maternal glucocorticoids with implications for fetal development. The fetus is largely protected from elevated maternal cortisol levels through the catabolic activity of placental 11β-hydroxysteroid-dehydrogenase (11β-HSD; Benediktsson et al., 1997). However, the work of Gitau and co-workers has demonstrated that maternal cortisol may still account for 33–40% of the variance in fetal cortisol concentrations (Gitau et al., 1998, 2001). Consequently, maternal free cortisol has the capacity to directly influence fetal growth and development (for review, see Seckl and Meaney, 2004). While there appears to be sensitive period in the early second trimester for maternal cortisol to influence the timing of labor (Sandman et al., 2006), late pregnancy, a period of accelerated fetal somatic growth, is a critical period for the determination of size at birth. The peak velocity of adipose tissue deposition occurs after 28 weeks gestation (Tanner, 1989) and environmental influences during this period have the capacity to affect birth weight (Paige and Villar, 1982; Ulijaszek et al., 1998). Placental 11β-HSD deficiency, resulting in fetal overexposure to maternal glucocorticoids, has been linked to lower birth weight (McTernan et al., 2001; Murphy et al., 2002; Shams et al., 1998; Stewart et al., 1995). In contrast, low maternal, amniotic, and umbilical cord cortisol levels have been observed in cases of intrauterine growth retardation (IUGR; Nieto-Diaz et al., 1996; Strinic et al., 2007). Taken together, these findings suggest that levels of bioavailable cortisol levels in late pregnancy may be associated with somatic size at birth. However, little is known about the role of cortisol in regulating fetal growth in normative populations.

In summary, interest in the role of maternal psychological functioning on fetal development during pregnancy has prompted a great deal of research, but many questions remain. Basal cortisol levels have been examined as a mediator of these effects, but few studies have examined the cortisol diurnal rhythm as a potential indicator of maternal regulation of the HPA axis during pregnancy. In particular, parity may be an important determinant of maternal perception of the "ups and downs" of pregnancy and this may be translated to the fetus via changes in physiological regulation with implications for both maternal and fetal well-being. The purpose of the current study is (1) to determine if maternal psychological functioning and neonatal birth outcomes are associated with the diurnal rhythm of late pregnancy in a group of low-risk pregnant women; (2) to determine if the maternal cortisol diurnal rhythm differs by parity status; (3) to determine if maternal parity status moderates associations between salivary cortisol, psychological functioning, and birth outcomes.

1. Methods

1.1. Participants

Eligibility was restricted to normotensive, non-smoking adult women (18 years or older) with uncomplicated preg-