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Diurnal cortisol patterns and psychiatric symptoms in pregnancy: Short-term longitudinal study

Thomas G. O'Connor*, Wan Tang, Michelle A. Gilchrist, Jan A. Moynihan, Eva K. Pressman, Emma Robertson Blackmore

University of Rochester Medical Center, United States

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ABSTRACT

Alteration in the HPA axis is a robust biomarker of anxiety and depression in adults, but questions remain about this association in pregnancy. We examined the longitudinal links between diurnal cortisol and mood symptoms from self-report questionnaire and diagnostic interview in an ethnically diverse, psychosocially at-risk sample of 101 women at mid-pregnancy and early third trimester. There were modest but significant associations between depression and elevated cortisol, indexed by a decreased morning level and diminished diurnal decline; the effects were strongest for diagnostic data from clinical interview. These effects were independent of socio-demographic factors and sleep disturbance. Associations with anxiety and trauma were generally non-significant. These findings extend prior work by showing that significant mood symptoms in pregnancy are associated with altered diurnal cortisol in pregnancy, which may have implications for maternal and child health.

1. Introduction

Research findings suggest that elevated cortisol is a robust biomarker of affective symptoms, stress reactivity and vulnerability (Hellhammer, Wust, & Kudielka, 2009). Whether or not mood symptoms are associated with elevated or otherwise altered cortisol production in pregnancy has attracted considerable recent research attention for several reasons. One is that pregnancy is a period of substantial neuroendocrine change that may offer a "natural experiment" to illuminate mechanistic links between neuroendocrine changes and psychiatric symptoms. Second, elevated cortisol in pregnancy may explain the widely-reported connection between affective symptoms and poor obstetric outcome (Federenko & Wadhwa, 2004; Goedhart et al., 2010; Grote et al., 2010; Kramer et al., 2009). Third, given that there is transmission of cortisol from mother to fetus in pregnancy (Sarkar, Bergman, Fisk, O'Connor, & Glover, 2007), elevated mood symptoms in pregnancy may signal increased *in utero* exposure to cortisol in the fetus, a plausible mechanism underlying developmental programming of health outcomes (Connors et al., 2008; Glover, O'Connor, & O'Donnell, 2010; Wadhwa, Buss, Entringer, & Swanson, 2009). The current study contributes to this line of research by assessing the longitudinal connections between mood and diurnal cortisol from the 2nd to 3rd trimester in pregnancy in a consecutive series of women recruited from a clinic serving a disproportionately high-risk population.

An association between mood symptoms and altered HPA axis function in non-pregnant individuals is well-established; there is, however, considerable variation across studies in effect sizes reported and methodologies used. Knorr et al.'s (Knorr, Vinberg, Kessing, & Wetterslev, 2010) recent meta-analysis indicated small but significantly higher morning and evening cortisol values in depressed compared to non-depressed adults. Studies linking cortisol with anxiety and stress are similarly numerous and generally positive, e.g., (Michaud, Matheson, Kelly, & Anisman, 2008).

Research findings suggesting that mood symptoms may be associated with elevated diurnal cortisol in non-pregnant adults may not extend to pregnant women, however. That is, the association between mood symptoms and cortisol may be different in pregnancy because of the wide-ranging and substantial pregnancy-related changes in the HPA axis itself, and/or because pregnancy induces other changes that may alter the HPA axis and cortisol in particular, such as changes in the immune system and in levels of progesterone, e.g., (Robinson & Klein, 2012). Several studies have examined the hypothesis that mood symptoms and/or stress (a variety of constructs have been measured in studies reported so far) are associated with altered diurnal cortisol in pregnant women (see below), but substantial methodological variation among studies means that it is not yet possible to draw firm conclusions.

* Corresponding author at: Wynne Center for Family Research, Department of Psychiatry, University of Rochester Medical Center, Rochester, NY 14642, United States. Tel.: +1 585 273 12212; fax: +1 585 273 1384.
E-mail address: tom_oconnor@urmc.rochester.edu (T.G. O'Connor).

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The current study builds on and extends the existing literature in several specific ways. First, in contrast to most studies that are based on a single assessment, we employ a short-term longitudinal design. That allows us to test the hypothesis that the association between mood symptoms and diurnal cortisol changes from the 2nd to the 3rd trimester of pregnancy. That possibility was raised by several cross-sectional studies showing a blunted cortisol reactivity to an acute stress in late but not mid- or early-pregnancy (DiPietro, Mendelson, Williams, & Costigan, 2012; Glynn, Wadhwa, Dunkel-Schetter, Chicz-Demet, & Sandman, 2001; Kammerer, Adams, Castelberg Bv, & Glover, 2002); see also Schulte, Weisner, and Allolio (1990). The mechanisms are not established, but are presumed to reflect the complex of pregnancy-related biological changes that directly or indirectly alter cortisol regulation. In the current study, we test an extension of this hypothesis for diurnal cortisol assessment: the association between diurnal cortisol and mood symptoms becomes weaker as pregnancy proceeds.

A second notable feature of the study is the sampling frame. Whereas most studies assessing cortisol and mood or stress in pregnancy are based on low-psychosocial risk samples, the current sample is ethnically diverse and includes women at elevated psychosocial (but not medical) risk. This is an important extension of prior work because individuals at high psychosocial risk and of minority race/ethnicity status may exhibit a different pattern of diurnal cortisol than low-risk individuals, as has been shown in many studies of non-pregnant, e.g., (Cohen et al., 2006) and in a small number of pregnant (Bennett, Merritt, & Wolin, 2004; Glynn, Schetter, Chicz-DeMet, Hobel, & Sandman, 2007; Suglia et al., 2010) samples. The inclusion of a large proportion of pregnant women at elevated psychosocial risk also means that the findings obtained here may generalize to those for whom this research is most clinically relevant, i.e., those women who are at particularly high risk for mood disorder.

A third key feature of the study is that we assessed multiple overlapping phenotypes; depression and anxiety were measured using both self-report symptom measures and interview-based diagnostic assessments; trauma exposure was also ascertained. We adopted an assessment strategy of several putative risk phenotypes because, as noted, research on diurnal cortisol in pregnancy has included a wide range of constructs, and this may have led to inconsistencies among reports. For example, Shea et al. (2007) found decreased levels of awakening cortisol with retrospectively reported childhood trauma but no link between cortisol and anxiety or stress; Kivlighan, DiPietro, Costigan, and Laudenslager (2008) found that trait anxiety but not stress was associated with a flatter diurnal decline in cortisol at 36 weeks gestation; Giesbrecht, Campbell, Letourneau, Kooistra, and Kaplan (2012) reported momentary mood was associated with cortisol; and Obel et al. (2005) found that stressful life events were associated with elevated evening but not morning cortisol and in late but not early pregnancy. Furthermore, in their analyses of about 60 pregnant women in the third trimester, Pluess et al. (2012) reported that morning cortisol was significantly related to positive life events ($b = -.26$) but less so to negative life events ($b = -.22$); in a separate paper they (Pluess, Bolten, Pirke, & Hellhammer, 2010) reported that awakening cortisol was negatively related to trait anxiety, with stronger effects in the first compared with the third trimester. Finally, in a sample of 25 women, Entringer, Buss, Andersen, Chicz-Demet, and Wadhwa (2011) reported that an ecological momentary assessment of negative mood was associated with higher cortisol at awakening. Although the overall impression is that there may be a significant association between diurnal cortisol and mood symptoms or stress, no clear patterns have yet emerged. In the current study we focused on the dimensions of depression and anxiety because they have attracted considerable research attention in pregnant women, but made no *a priori* predictions about which dimension would be more strongly associated with altered diurnal cortisol. Particularly novel is the inclusion of diagnostic assessments, which complement self-report measures that have been exclusively used in previous studies. Diagnostic data offer a more direct index of the clinical significance of the variation in diurnal cortisol patterns in pregnancy and have methodological advantages over self-report questionnaires.

In summary, we enrolled a racially/ethnically diverse sample of women at high psychosocial risk and examined them in the 2nd and 3rd trimesters of pregnancy with self-report and diagnostic measures of depression and anxiety to test the hypothesis that mood symptoms would predict alteration in diurnal cortisol; we also examined the hypothesis that the association between mood symptoms and diurnal cortisol would diminish over time. Exploratory analyses considered the strength of the prediction from depression and anxiety, and if the association with diurnal cortisol was stronger for more severe disturbance (i.e., clinical diagnosis). Detailed assessments of socio-demographic risk and sleep were included given their proposed influence on cortisol and possibly confounding effect on the association between mood symptoms and diurnal cortisol patterns.

2. Methods

2.1. Sample and procedures

Women were consecutively recruited from a university hospital-based obstetrics practice in a mid-sized city serving a generally low-income population. Exclusion criteria were (a) under 20 years of age or over 34 years, (b) history of psychotic illness, (c) medical high-risk pregnancy as determined from OB clinic assessment (including medical complications in the mother and prenatal drug use) based on detailed obstetric evaluation, (d) non-singleton pregnancy, (e) non-English-speaking. Because of the specific focus on cortisol in pregnancy, analyses for the current study are limited to the $n = 101$ women from the overall sample of $n = 149$ on whom cortisol data were available. Written consent was obtained from the mothers; the project was approved by the university institutional review board.

Women meeting criteria were asked by a nurse practitioner at the conclusion of the initial prenatal assessment if they were interested in participating in a research project on moods and feelings in pregnancy; this initial intake visit was typically conducted within 10–14 weeks gestation. Women agreeing to participate were then approached by a study team member who obtained written consent (it was not possible to determine precisely the percentage of women agreeing to participate). Participants were administered questionnaire measures and a clinical interview at approximately 20 weeks gestation and again at approximately 32 weeks gestation; each visit corresponded to a regularly scheduled obstetric visit. All questionnaires were read aloud to women to pre-empt comprehension problems. All interviewers were female with an advanced degree in a mental health field or considerable clinical research experience and formal training in clinical interviewing. At each assessment women were instructed in the procedures for collecting saliva (see below).

3. Measures

Affective symptoms from questionnaires and clinical interview. Two questionnaire measures of symptoms are the focus of this report. Depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (Cox, Holden, & Sagovsky, 1987), a 10-item self-report measure that is widely used in perinatal research with established reliability and validity (Murray & Carothers, 1990). The Penn State Worry Questionnaire (Meyer, Miller, Metzger, & Borkovec, 1990) is a widely-used index of worry that has been used in perinatal research (Swanson, Pickett, Flynn, & Armitage, 2011); it includes 16 items focusing on worry.[1] In addition, women were interviewed using the depression and anxiety segments of the structured clinical interview for DSM-IV (First, Spitzer, Gibbon,

[1] In addition, the 20-item state subscale of the State-Trait Anxiety Inventory was also administered (Spielberger, Gorusch, & Lushene, 1983); it is a widely-used index of anxiety in pregnancy (Sarkar, Bergman, O'Connor, & Glover, 2008). Findings from this measure parallel those of the PSWQ, with which it was highly correlated, and so are not discussed in detail.