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SHORT COMMUNICATION

Cortisol awakening response in late pregnancy in women with previous or ongoing depression☆

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Summary Pregnancy is associated with increased basal cortisol levels, and decreased hypothalamic-pituitary-adrenal (HPA) axis reactivity. The cortisol awakening response (CAR) is a measure of HPA-axis reactivity which has been reported to be increased in patients with ongoing depressive disorder and in individuals with remitted depression.

In this study, we investigated HPA-axis reactivity in pregnant women with ongoing or previous depression. The CAR was assessed by measurement of salivary cortisol at awakening and 15, 30, and 45 min post-awakening. Based on structured psychiatric interviews and repeated measurements of depressive symptoms during pregnancy, 134 women were included in one of the three groups: never depressed ($n = 57$), depressed prior to the current pregnancy ($n = 39$), and depressed during the current pregnancy ($n = 38$). Given the prior findings of increased CAR in non-pregnant depressed subjects, we hypothesized that an ongoing or previous depression would result in a higher CAR.

Contrary to our hypothesis, a mixed models analysis failed to yield significant group differences. Thus, our results suggest that never depressed pregnant women and women with depression during pregnancy have similar cortisol awakening responses. Furthermore, our findings suggest that the cortisol awakening response does not differ between currently healthy women with and without experience of a depressive episode during late pregnancy.

1. Introduction

Numerous studies have suggested increased hypothalamic-pituitary-adrenal (HPA) axis activity in depressed patients, although the results are ambiguous (Knorr et al., 2010). Consequently, the readjustment of the HPA-axis during, and after, pregnancy has received attention as a possible

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vulnerability factor for developing mood disorders (O'Keane et al., 2011).

The physiological secretion of cortisol is relatively high during morning hours, decreases during the day, and begins to slowly rise again a couple of hours after midnight. A marked increase in salivary cortisol (typically 50—160%) is seen between the time of awakening and 30—60 min thereafter. The size of this increase, referred to as the cortisol awakening response (CAR), has been associated with depressive symptoms and perceived stress in non-pregnant populations (Clow et al., 2004).

In a large study, Vreeburg et al. (2009) found that both remitted and ongoing major depression are associated with a significantly higher CAR, suggesting that a hyperactive HPA-axis is a vulnerability factor, rather than an acute symptom of depression. Indeed, it has been found that a high CAR is predictive of remission, but also new onset of major depression in young adults (Vrshek-Schallhorn et al., 2013).

During late pregnancy, maternal plasma cortisol levels are tripled (Jung et al., 2011). Although the absolute saliva cortisol concentration is also increased, a distinct CAR is still present in gestational week 32 (de Weerth and Buitelaar, 2005). However, in line with the generally reduced physiological stress reactivity in late pregnancy, Buss and colleagues have reported a decrease in CAR between the 17th and 31st week of pregnancy (Buss et al., 2009). A few studies have explored the CAR in pregnant women with depressive symptoms, but findings have thus far been negative (Giesbrecht et al., 2012; Shea et al., 2007). However, these studies relied on self-reported depression scores and did not take history of depression into account. Also, since the cortisol production peaks during late pregnancy, while the responsivity is dampened (Buss et al., 2009), it is possible that a vulnerability to depression originating from suboptimal HPA-axis regulation could be more evident at this time-point.

The aim of this study was to compare the CAR in third trimester pregnant women with current depressive disorder, pregnant women with prior depressive disorder (i.e. prior to the current pregnancy), and healthy, never depressed, pregnant women. Based on prior findings, we hypothesized that the CAR would be higher in women with depression during the current pregnancy and in women with a history of depression prior to the current pregnancy, due to an inability to adequately adapt their HPA-axes to the hypercortisolism of pregnancy.

2. Materials and methods

2.1. Participants and procedure

Participants were recruited within the pregnancy cohort 'Biology, Affect, Stress, Imaging, and Cognition in pregnancy and the puerperium' (BASIC), a longitudinal study investigating biological correlates of mood and anxiety disorders during pregnancy and in the postpartum period. All pregnant women in Uppsala County are invited to participate at the time of their routine ultrasound in gestational weeks 16—18. Following informed consent, women are sent web-based questionnaires, including the Swedish version of the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987; Wickberg and Hwang, 1996) at gestational weeks 17 and 32.

For this sub-study, women with EPDS score $\geq$13 in gestational week 32, and a random sample of women with EPDS scores $<$13 at gestational week 32 were invited with the intention of oversampling women with antenatal depressive symptoms (Rubertsson et al., 2011). The women visited the research laboratory at the Department of Women's and Children's Health, Uppsala University in gestational weeks 35—39. After providing written informed consent, women were interviewed about depressive and anxiety disorders with the Swedish version of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Participating women were also interviewed about medical and obstetric history, and use of alcohol. All participants filled out the EPDS during the visit. In addition, EPDS scores from gestational weeks 17 and 32, medication, educational level, and smoking during pregnancy, were available from web-questionnaires.

All women received verbal and written instructions as how to perform the saliva sampling and were provided four labeled Salivette tubes (Sarstedt, Sweden). The first saliva sample was to be taken immediately after awakening, and the remaining three samples at 15, 30, and 45 min post-awakening. No food, drink, toothbrushing, or smoking was allowed within one hour before sampling. The women were instructed to fill in time of awakening and the four sampling time-points on a report-sheet, and to return the samples by post.

The study procedures were in accordance with ethical standards for human experimentation and the study was approved by the Regional Ethical Review Board in Uppsala.

2.2. Salivary cortisol measurements

The cortisol analyses were performed on a Cobas8000 e602 instrument with the Cobas Elecsys cortisol reagent kit (Roche Diagnostics, Bromma, Sweden) at the Department of Clinical Chemistry, Uppsala University hospital.

2.3. Statistical analyses

Three groups were created; control subjects (never depressed), women with prior major or minor depressive disorder, and women with current major or minor depressive disorder. Control subjects were defined as having no current or prior depressive or anxiety disorder as assessed by the MINI-interview. Women with a prior depressive episode had a history of at least one previous major or minor depressive episode according to the MINI-interview, but not during the present pregnancy as indicated by EPDS scores $<$13 at all time-points (gestational weeks 17, 32, and at the visit). Women with a current depressive episode had a current depressive disorder according to interview, or had a previous depressive episode and an EPDS score of $\geq$13 at any time-point during pregnancy, indicating that the prior (or last) episode had been ongoing during the present pregnancy.

A pilot analysis gave a cortisol concentration standard deviation of 5.5 nmol/l. We hypothesized that pregnancy would amplify the difference in cortisol concentration, compared to the 2 nmol/l difference found by Vreeburg et al. (2009), and used a difference of 3.0 nmol/l in the sample size calculation. The statistical power to detect this difference

between 65 never depressed and 45 previously depressed women was calculated to be 0.8 (Lenth, 2006).

Logarithm-transformed salivary cortisol levels at each time-point were compared between groups by one-way ANOVAs. The area under the curve with respect to the ground (AUCg) and increase (AUCi), nmol/(l min), was calculated for subjects with valid cortisol levels at all four time-points ($n = 108$). The cortisol awakening response was analyzed using linear mixed models (LMM), enabling the use of all subjects with at least one valid cortisol value ($n = 134$). All statistical analyses were performed with IBM SPSS Statistics 20.

3. Results

3.1. Descriptive statistics

Two hundred and sixteen women were included, among which 163 (75%) returned the saliva samples. There were no significant differences in age, parity, or depression status between responders and non-responders. Twenty-five women were excluded due to: delay of first sample more than 5 min after awakening ($n = 19$), postpartum sampling ($n = 3$), insufficient amount of saliva at all four time-points ($n = 2$), or outlier cortisol values (>2 SD from the mean) at all four time-points ($n = 1$), leaving 138 women. In addition, four women with an ongoing anxiety disorder were excluded from the control group of never depressed participants. In all, CAR-data from 134 women, with at least one valid cortisol measurement were included in the analyses. Five cortisol concentrations from three of the 134 participants were considered outliers (>2 SD from the mean) and were excluded from the analysis. Thirty-five additional values were missing due to insufficient amount of saliva or problems at analysis, thus the analyses were based on 496 cortisol measurements from 134 subjects (57 never depressed, 39 previously depressed, and 38 women with depression during pregnancy).

All women had singleton pregnancies and term deliveries. Descriptive group data is found in Supplementary Table 1.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2013.08.007.

3.2. Cortisol awakening response

Contrary to our hypothesis, no significant differences in cortisol concentrations, or cortisol AUCg or AUCi, were found between groups (Fig. 1 and Table 1). An expected main effect of time-point was evident in the LMM analysis ($F(3,346) = 11.94$; $p < 0.001$), suggesting a clear cortisol response to awakening in late pregnant women. However, no significant main effect of group was found ($F(2,136) = 0.67$; $p = 0.515$), indicating that the size of the CAR during pregnancy was not influenced by ongoing or previous depressive disorder. Similarly, the group by time-point interaction term had no significant effect ($F(6,346) = 0.46$; $p = 0.835$), i.e. the shape of the CAR did not differ between groups. These results remained essentially unchanged when age, educational level, and SSRI treatment were added as covariates (data not shown).

4. Discussion

Based on previous findings in depressed, and previously depressed, non-pregnant subjects (Vreeburg et al., 2009), we hypothesized that third trimester pregnant women with ongoing or past depression would display an increased CAR in comparison with healthy, never depressed pregnant women. However, in line with Shea et al. (2007) we found no significant difference between the never depressed controls and women with an ongoing depression during the current pregnancy, even though sample collection took place in late pregnancy when baseline cortisol levels are high and the HPA-response is dampened (Buss et al., 2009). Furthermore, our results gave no support for the hypothesis that biological

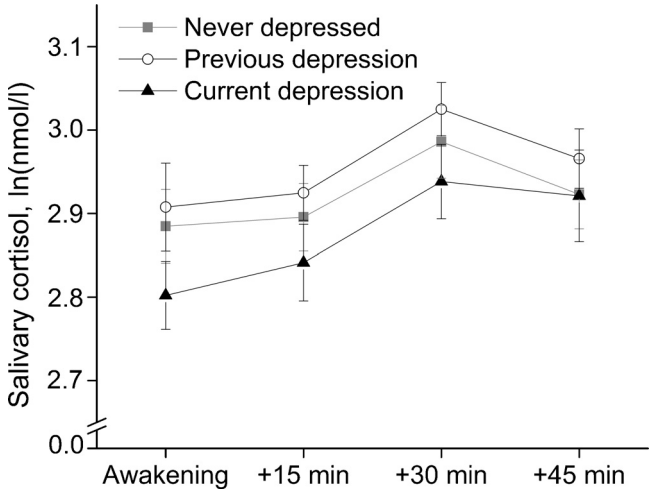

Figure 1 Cortisol awakening response in women with no depression, previous depression, and antenatal depression according to interview. Data is presented as natural logarithm of mean and SEM. No significant group differences in cortisol levels, or interaction with time-point.

Table 1 Cortisol awakening response, salivary cortisol concentrations, mean (SD).

Cortisol values, nmol/l (SD)	Never depressed (n = 57)	Depressed prior to current pregnancy (n = 39)	Depressed during current pregnancy (n = 38)	p-Value[a]
Awakening	18.8 (6.0)	19.2 (6.4)	16.9 (3.9)	0.296
Awakening + 15 min	18.9 (5.5)	19.0 (3.8)	17.9 (5.8)	0.394
Awakening + 30 min	20.8 (6.4)	20.9 (3.9)	19.5 (5.0)	0.411
Awakening + 45 min	19.4 (5.8)	19.8 (4.2)	19.6 (7.3)	0.747
AUCg[b]	896.0 (239.7)	882.2 (153.8)	819.7 (199.8)	0.271
AUCi[b]	36.0 (160.9)	29.1 (227.9)	73.9 (154.1)	0.646

[a] According to one-way ANOVA comparisons of natural logarithm transformed values.
[b] AUC values were calculated for women with valid cortisol values at all time-points (n = 108).

vulnerability to, or a scar after, a depressive episode is visible as a higher CAR in pregnant women with a history of depression.

Cortisol secretion displays a large inter-individual variation, why a relative reactivity measure such as the CAR could theoretically be more useful to distinguish depressed individuals from healthy subjects. The largest study on CAR in non-pregnant individuals (Vreeburg et al., 2009) found 2–2.5 nmol/l higher absolute cortisol concentration at 45 min after awakening in subjects with previous, or ongoing, depression. This was also reflected in a higher AUCi in depressed patients (Vreeburg et al., 2009). In contrast, we observed around 2 nmol/l *lower* absolute cortisol levels at awakening in women with ongoing depression in comparison with never depressed women. While this finding was at odds with our hypothesis, an inverse group difference compared to the non-pregnant population cannot be ruled out, given the risk of type II error. However, a post hoc power calculation suggests that 110 subjects per group would be required to detect a significant effect size of this modest magnitude (Cohen's d = 0.38). Furthermore, to detect a difference similar to that of Vreeburg et al., with a statistical power of 0.8, would require approximately 275 women per group.

It thus appears as though the physiological change of pregnancy, which involves higher absolute cortisol levels and lower reactivity (Buss et al., 2009), may erase the higher CAR during depression seen in non-pregnant populations. Furthermore, women with previous depression had virtually identical cortisol levels and AUC values as the never depressed women, suggesting that the hypercortisolism of pregnancy erases the vulnerability-related, or scar-like, alterations of HPA-reactivity associated with depression. However, higher evening salivary cortisol has been found in depressed pregnant women in gestational week 32 (O'Keane et al., 2011), which underlines the link between HPA-axis function and depression during pregnancy.

The strengths of this study include a careful group designation based on a structured psychiatric interview concerning current, as well as previous, depressive episodes, and repeated self-reports of depressive symptoms during pregnancy. The participating women were also in a narrow gestational age-range, which should have minimized variation caused by the dampening of cortisol reactivity with gestational age. We also excluded subjects who collected the wake-up sample more than 5 min after the reported wake-up time. However, the lack of control over participants' coherence to the sampling protocol must be considered a limitation.

We conclude that a CAR is still present in gestational weeks 36–40; however, we found no significant difference between women with ongoing depression and healthy controls. Furthermore, we did not find a higher CAR in women with a history of depression prior to the current pregnancy, suggesting that the altered HPA-reactivity associated with depression in non-pregnant populations is concealed by the hypercortisolism of pregnancy.

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Conflict of interest statement

None declared.

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