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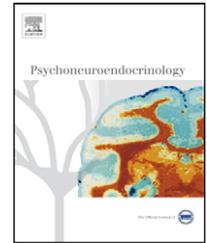
Diurnal pattern of cortisol output in postnatal depression

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Summary This study investigated the diurnal output of saliva cortisol in women with symptoms of depression postnatally. Twenty-one depressed and 30 non-depressed women at 7.5 weeks postpartum, and 21 non-perinatal controls, collected saliva at waking, 30 min, and 3 and 12 h postwaking. Women who were not depressed postnatally showed a pattern of cortisol secretion over the day similar to non-perinatal controls. There was a significant difference in diurnal pattern between postnatally depressed and postnatally non-depressed women, due to a difference in the first two time points (waking and +30 min): compared to the other two groups who each had a significant increase in cortisol levels from waking to +30 min, the depressed women had significantly higher cortisol levels at waking and no increase at +30 min. The lack of a morning rise in the depressed women is similar to that reported for posttraumatic stress disorder and chronic fatigue syndrome and may reflect a response, in vulnerable women, to the marked cortisol withdrawal that occurs after delivery.
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1. Introduction

The hypothalamic—pituitary—adrenal axis (HPA) controls a distinctive diurnal pattern of cortisol output. In most subjects there is a substantial increase in secretion between the moment of awakening and 30 min later (Pruessner et al., 1997; Clow et al., 2004), the cortisol awakening response (CAR), which seems to be under a separate central control (Fries et al., 2009). This is followed by a decrease in output throughout the day. Different patterns of output have been observed to be associated with different psychopathologies. For example, melancholic depression is associated with raised cortisol and atypical depression with reduced cortisol

output (Gold and Chrousos, 2002). Those suffering from posttraumatic stress disorder (PTSD) and other conditions including chronic fatigue syndrome, have been reported to show a blunted CAR (Wessa et al., 2006; Fries et al., 2009). The activity of the HPA axis changes markedly during pregnancy, childbirth and postpartum. During pregnancy the overall output of cortisol increases, stimulated by corticotrophin releasing hormone (CRH) produced by the placenta (Mastorakos and Ilias, 2003). The stress of childbirth is associated with a very large increase in maternal cortisol, followed by a rapid return to non-perinatal levels, although the function of the HPA axis can take a few weeks to normalize (Kammerer et al., 2006). We have previously suggested that mood disorders that can occur over the perinatal period may be partly associated with these major changes in the function of the HPA axis (Kammerer et al., 2006). For example, postnatal depressive symptoms may be triggered by cortisol withdrawal.

After delivery approximately 10% of women experience mild hypomania (the highs), followed by later depression (Glover et al., 1994; Heron et al., 2004). Other women can experience PTSD (Cohen et al., 2004). Both mild bipolar depression and PTSD are associated with symptoms of atypical depression. Magiakou et al. (1996) have shown that the ACTH response to a bolus of CRH is blunted at 3 and 6 weeks postpartum but normal at 12 weeks. This blunting was significantly more severe or long lasting in those with postpartum blues, the transient mood disturbance that is common after childbirth and a risk factor for later depression. This blunted ACTH response to CRH has also been observed in atypical rather than melancholic depression. The current study was designed to investigate whether women who are depressed following childbirth have a different pattern of cortisol output, with either a reduced output throughout the day, or a reduced awakening response, compared with non-depressed postnatal women and non-perinatal controls.

2. Methods

The protocol was approved by the ethics committee of the Canton of Zurich, Switzerland, and written informed consent was obtained from all participants. Women attending the postnatal clinic of the Stadtspital Triemli in Zurich were asked to complete the Edinburgh postnatal depression scale (EPDS), at 4 weeks postpartum (German version). All those who scored EPDS $\geq$ 13 the established cut-off for probable major depression, were invited to take part in the study, together with an age and ethnically matched sample of women who scored EPDS $\leq$ 12. Between 6 and 8 weeks postnatally participants were interviewed by telephone and asked to collect diurnal saliva samples and to fill in another EPDS sheet. Exclusion criteria for all subjects were medical or psychiatric disorder apart from major or minor depression, including a history of PTSD or current PTSD symptoms or symptoms of an acute stress syndrome (using the structured clinical interview for DSMIV diagnoses (Spitzer et al., 1992)), known abnormality of the child, fertility treatment, and inadequate German. Non-perinatal healthy controls were recruited from a student population. All women were also asked about smoking, drinking alcoholic beverages, using illicit drugs, prescribed medication, and whether they were still breastfeeding.

All the women were asked to provide salivary samples, with the non-pregnant control group collecting saliva samples on or as close as possible to day 10 of their menstrual cycle, on two consecutive weekdays. Samples were collected immediately upon awaking, 30 min later, 3 and 12 h after awakening. The participants filled out a protocol reporting the exact time they collected saliva, and recorded the time of sampling on each tube. The participants agreed to take the saliva for the first time point when they woke up, but while still in bed. They agreed not to brush their teeth, nor eat nor drink anything apart from water in the time between the first saliva (still in bed) and the second saliva, 30 min afterwards, after having got up. All postnatal women agreed not to use an alarm. The women were asked to refrain from eating or drinking, for at least 30 min before the later samples.

All participants received oral and written information about treatment possibilities for postnatal depression in the area, and this information was given for a second time to those participants who had been identified as depressed.

Saliva samples were collected in salivettes and stored at $-20\,°C$. Cortisol concentrations were assayed using a standard enzyme immunoassay for use with saliva samples, manufactured by Salimetrics LLC. The lower limit of sensitivity for this saliva assay is 0.2 nmol/l. Intra-assay coefficient variance (CV) was 6.9% and inter-assay CV was 7.1%.

3. Results

Table 1 shows the characteristics of the sample. There were no differences, except in their EPDS scores, between the postnatally depressed and non-depressed women. The non-perinatal controls were significantly younger, woke significantly earlier than the postnatal groups, and more of them were smokers. One of the depressed women was taking an antidepressant; none of the other subjects were taking any medication apart from oral contraceptives that were taken by 20 of 21 non-perinatal controls.

One (non-depressed) participant was excluded from analysis as she had not completely filled out the protocol.

The diurnal pattern of saliva cortisol output is shown in Fig. 1. Two way analysis of variance with time as a within subject factor (four levels: waking, +30 min, +3 h and +12 h), and perinatal status as a between subject factor (three groups: postpartum depressed, postpartum non-depressed and non-pregnant control women) showed a significant main effect of time of day: $F(3, 207) = 270.06$, $p < 0.001$ and a significant interaction between time and perinatal status, $F(6, 207) = 4.683$, $p < 0.001$. Fig. 1 suggests that there was a significantly reduced morning rise in cortisol concentration for those women who were depressed. Further sub-analysis (two-way ANOVA) of the cortisol data from the first two data points confirmed that the difference in diurnal pattern of cortisol between the study groups was due to a difference in the first two time points (waking and +30 min), $F(2, 69) = 11.213$, $p < 0.001$. For the third and fourth time points (+3 and +12 h) there was no interaction between time and perinatal status, $F < 1$. Post hoc analyses (least significant difference), showed that at waking the mean cortisol concentration from women in the depressed group was significantly higher compared with non-pregnant controls $p = 0.015$. The same trend was found for the depressed group

Table 1 Characteristics of the sample.

	Postpartum non-depressed, N = 30	Postpartum depressed, N = 21	Non-pregnant controls, N = 21
Age: mean (SD)	32.6 (4.2)	32.5 (3.3)	24.7 (4.6)[*]
Marital status			
1. Single (%)	11.1	10.5	100[*]
2. Married (%)	88.9	89.5	0
3. Divorced (%)	0	0	0
Ethnicity			
1. Caucasian (%)	96.7	95.2	100
2. Asian (%)	3.3	4.8	0
3. Black (%)	0	0	0
4. Other (%)	0	0	0
Baby: % male	51.1	48.4	N/A
Parity: % primiparous	59.3	42.9	N/A
Gestational age at birth: mean (SD)	40.3 (1.4)	40.2 (1.9)	N/A
Mode of delivery			
1. Vaginal (%)	56.0	71.4	N/A
2. Assisted (%)	4.0	7.2	
3. Caesarean (%)	40.0	21.4	
Breastfeeding: %	93.3	85.7	N/A
Smoker: yes	1	1	6[*]
Postpartum week tested: mean (SD)	7.5 (1.4)	7.6 (2.2)	N/A
Day of menstrual cycle for non-pregnant controls: mean (SD)	N/A	N/A	10.1 (0.7)
EPDS at testing: mean (SD)	6.1 (3.7)	17.3 (2.7)	5.4 (3.0)
Time of waking: mean hour mins (SD in mins)	7.53 (44)	8.01 (49)	6.59 (35)[*]

N = numbers of observations.

[*] $p < 0.05$ between non-perinatal controls and perinatal women.

compared with non-depressed postnatal women but this did not reach statistical significance. At +30 min both non-depressed postnatal and non-postnatal groups had significantly higher mean cortisol concentrations than the depressed group (p = 0.009 and p = 0.042, respectively). Separate analyses of the first two time points for each perinatal group (related groups t-tests) confirmed that
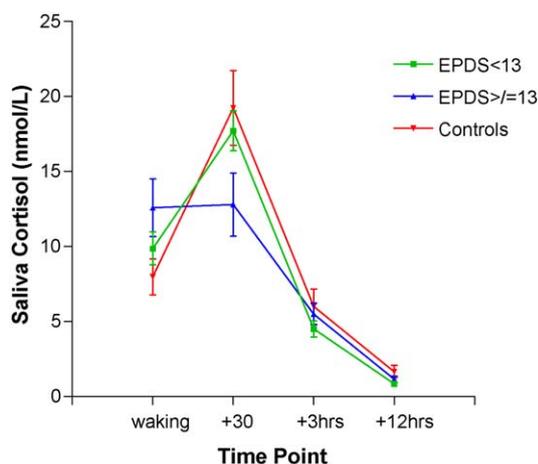

Figure 1 Diurnal variation of saliva cortisol (nmol/l) in depressed and non-depressed postnatal women and in non-perinatal controls. The error bars represent standard deviation.

women in the non-depressed group and control non-pregnant women had a significant waking rise in cortisol concentration (t(29) = 5.985, $p < 0.001$, t(20) = 5.718, $p < 0.001$, respectively), while those in the depressed group did not (t(20) = 0.238). When the single depressed subject who took antidepressants was omitted from the analyses it did not alter the significance of the findings.

The data was further analysed using stricter selection criteria for depressed and non-depressed postpartum groups as defined by the EPDS. The non-depressed group was defined as EPDS ≤ 10 (n = 17) and the depressed group as EPDS ≥ 15 (n = 13). The non-pregnant control group remained the same (n = 21). The diurnal pattern of mean cortisol concentration for each of these groups was similar to the previous ones. The three groups were again compared by two-way analysis of variance with time as a within subject factor (four levels: waking, 30 min after waking, 3 h and 12 h after waking), and perinatal status as a between subject factor (three groups: postpartum depressed, postpartum non-depressed and non-pregnant control women). Again there was a significant main effect of time of day: F(3, 46) = 205.340, $p < 0.001$ and a significant interaction between time and perinatal status, F(6, 94) = 4.584, $p < 0.001$.

There were no significant correlations between mean cortisol levels (AUC) nor cortisol at time of waking and age, parity, time of waking and whether they breastfed or not (all ns). When the few non-breastfeeding postnatal women were excluded from the analyses the results

remained similar and the difference in diurnal pattern between the depressed and non-depressed remained significant ($p < 0.001$).

4. Discussion

This study has shown that the pattern of the diurnal output of cortisol in postnatal women with symptoms of depression differed from that of women who were not depressed. Notably, the morning rise in cortisol was significantly reduced. Women who were not depressed showed a circadian pattern of cortisol very similar to that of the non-pregnant controls. The pattern of cortisol secretion by the women with depression observed here is similar to that reported in subjects suffering from PTSD (Wessa et al., 2006), although subjects with symptoms of PTSD were specifically excluded from this study.

There is a discussion in the literature as to whether depression that occurs in the postnatal period is similar to that at other times (Kammerer et al., 2006). It is possible that the large withdrawal in hormone levels, oestrogen, progesterone and cortisol that occur after parturition may contribute to the development of psychological symptoms in some subjects. The results presented here suggest that in women with postnatal depressive symptoms the function of the HPA axis is not that found in melancholic depression, in which cortisol output is raised. It may be more related to the hypocortisolaemic disorders which include PTSD, atypical depression, bipolar disorders, and chronic fatigue syndrome (Gold and Chrousos, 2002). Unfortunately, the psychometric measure used for this analysis does not allow the differential diagnosis of melancholic and atypical subtypes of depression. It may be more related to the other disorders which have been shown to lack a CAR which include PTSD (Wessa et al., 2006) and chronic fatigue syndrome (Roberts et al., 2004; Nater et al., 2008). It is of interest that a recent study has shown that symptoms associated with depression differ antenatally from postnatally, and that fatigue is particularly associated with postnatal depression (Kammerer et al., 2009). Lactation is a potential variable affecting the pattern of cortisol output. Suckling provides a neural stimulus that dampens the HPA axis circadian rhythm and reduces stress responses. Reduced noradrenergic input activity and central prolactin seem to be involved in reduced stress responses in lactation (Heinrichs et al., 2002; Tu et al., 2006; Slattery and Neumann, 2008; Russell et al., 2008). However, almost all of our postnatal subjects were breastfeeding, and excluding those who were not did not affect the results.

Another potentially relevant variable is sleep pattern. It is possible that the postnatally depressed women had a more disturbed sleep. However, they did not report a different time of waking (Table 1). And Dettenborn et al. (2007) have shown that sleep interruptions did not influence the CAR in healthy women. Wust et al. (2000) have reported that neither age, nor the use of oral contraceptives, habitual smoking, time of awakening, sleep duration or using/not using an alarm clock had a significant impact on cortisol levels after awakening. However, it would be of interest to obtain objective sleep data together with CAR data with comparable samples in future research.

There is some evidence from twin studies that the cortisol awakening response may be under substantial genetic, control (Bartels et al., 2003). It is of interest whether the lack of awakening response, observed here in women with symptoms of depression in the postnatal period, is a state or trait phenomenon. Thorn et al. (2009) found in their sample that CAR is susceptible to short-term changes in state variables (notably perceived arousal). It may be that women with a specific genetic vulnerability, indicated by the lack of awakening response, are particularly vulnerable to the effects of the hormonal changes of parturition. It may also be that the type of depression experienced in the postnatal period causes a reduced CAR. Future research is needed to confirm the findings reported here and to determine whether the women continue to show a lack of awakening response when not depressed.

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Conflict of interest

Acknowledgements

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