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# The effect of depression, anxiety and early life trauma on the cortisol awakening response during pregnancy: Preliminary results

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## KEYWORDS

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## Summary

The purpose of this study was to examine the effects of maternal depression and anxiety on the cortisol awakening response (CAR), a marker of the hypothalamic–pituitary–adrenal (HPA) axis function, during pregnancy. Sixty-six pregnant women were studied between 25 and 33 weeks of gestation and were identified as either *Depressed* ( $n = 33$ ) or healthy, *Control* ( $n = 33$ ), based on depression scores and lifetime psychiatric history. Saliva samples were collected (passive drool) upon awakening and at +30 and +60 min thereafter. The CAR was not significantly different between women who were depressed during pregnancy compared to healthy control women. However, women taking antidepressant (AD) medication showed an attenuated CAR (time  $\times$  AD use interaction,  $p = 0.06$ ). Childhood maltreatment (as measured with the Childhood Trauma Questionnaire) was associated with a lower baseline cortisol concentration explaining 12% of the variance, controlling for wake-up time and AD use. There is a complex interplay of factors involved in the HPA axis regulation of vulnerable women during pregnancy, including depression,

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anxiety, early life stress and psychotropic medication use, which remain unclear. The CAR may provide important information about the maternal HPA axis during pregnancy and warrants further investigation in larger cohorts.

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## 1. Introduction

Although pregnancy is thought by many to be “protective” in terms of mental health and well-being, recent cohort studies have reported a similar incidence of depression and anxiety during gestation as in the postpartum period (Andersson et al., 2006; Levine et al., 2003). Anxiety, depression as well as stress during pregnancy are associated with a number of adverse outcomes, including premature delivery, fetal growth restriction, “difficult” infant temperament and impaired mental development (Austin et al., 2005; Dayan et al., 2006; Laplante et al., 2004; Wadhwa, 2005). However, not all studies agree with these observations (Andersson et al., 2004; Berle et al., 2005) and it is unclear why some infants born to women experiencing adversity remain resilient. Challenges of the existing literature include reliance on self-report measures, inconsistent definitions of maternal stress/affect, retrospective data collection and a lack of physiological measures to explain possible mechanisms.

There have been several population-based and cohort studies examining the effects of “maternal” or “prenatal stress” as mediators of infant developmental outcomes. The differences in stress measurements as well as a lack of consensus on the definition of maternal stress create challenges when investigating the factors involved. Maternal anxiety during pregnancy has often been identified as “maternal stress”, and/or maternal-rated anxiety is used in a total composite measure of stress and anxiety (e.g., Saunders et al., 2006). It is important to note that depression and anxiety disorders often coexist with high comorbidity in the general population, as well as in pregnant women (Faisal-Cury and Rossi Menezes, 2007; Kendler et al., 2007; Ross and McLean, 2006; Sutter-Dallay et al., 2004). Depression and anxiety disorders not only share symptoms, but also respond to comparable treatment strategies (Morilak and Frazer, 2004) and similar genes have been implicated in both (Kendler, 1996). These overlapping features suggest common neurophysiological substrates. Based on the interrelations between maternal stress, depression and anxiety, as well as common developmental outcomes reported for infants and children, we suggest that similar pathophysiological mechanisms may exist.

Examination of physiological correlates may explain the shared negative sequelae of depression, stress and anxiety during pregnancy. Both the sympathetic branch of the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis are activated during acute stress (Miller and O’Callaghan, 2002). Chronic and/or unpredictable activation of these stress response systems can lead to a diminished capability to respond appropriately (Shea et al., 2005). Alterations in the HPA axis associated with chronic and/or early-life stress and mood disturbance may

contribute to HPA axis dysregulation, which may have negative consequences for healthy fetal development.

The salivary cortisol awakening response (CAR) is a non-invasive and reliable measure that can detect subtle changes in the HPA axis function (Pruessner et al., 1997). The HPA axis is often reported as hyperactive in patients with stress-related conditions such as major depression (Pariente and Miller, 2001) and depressive symptoms are reported to be associated with a greater increase in waking cortisol levels (Bhagwagar et al., 2003; Pruessner et al., 2003). However, a blunted CAR was reported in patients suffering from major depressive disorder (MDD), and almost half of those with MDD did not show a typical response (Huber et al., 2006), as defined by Wust et al. (2000) (increase of cortisol of at least 2.5 nmol/l). Other influences on the CAR include day of the week (Kunz-Ebrecht et al., 2004) and early-life stress (Meinlschmidt and Heim, 2005).

Healthy pregnancy is associated with hypercortisolism mediated by placental corticotrophin releasing hormone (CRH) (Wadhwa et al., 1997). Further changes are associated with stress and negative affect during pregnancy, particularly increased plasma cortisol and adrenocorticotropin releasing hormone (ACTH) during the 3rd trimester (Wadhwa et al., 1996) and higher urinary (free) cortisol levels in the 2nd and 3rd trimesters (Field et al., 2004; Lundy et al., 1996). However, only two studies examined the CAR in pregnant women, suggesting that the awakening response is present during pregnancy (de Weerth and Buitelaar, 2005), and that recent stressful life events are associated with a blunted CAR during early- but not late-pregnancy (Obel et al., 2005).

The aim of this study was to examine the effects of maternal depression and anxiety on HPA axis function during pregnancy using the CAR. The effects of treatment with antidepressant (AD) medication as well as, past and recent stressful life events were also examined.

## 2. Materials and methods

This study was approved by the Research Ethics Board of St. Joseph’s Healthcare and written informed consent was obtained from each participant. Subjects were participants in an ongoing clinical cohort study examining links between maternal stress and infant developmental outcomes, titled, “Maternal Adversity, Vulnerability and Neurodevelopment” (MAVAN). A sub-sample was recruited from the MAVAN study, for further examination of physiological stress correlates during pregnancy. Pregnant women presenting to the Women’s Health Concerns Clinic (WHCC) with symptoms of depression between 12 and 24 weeks of gestation (mean = 20.0 weeks) were recruited and offered a choice of treatments/interventions (*Depressed Group*). Women with a current diagnosis or history of psychotic disorder

were excluded, as well as those with serious medical conditions. Control subjects were recruited through flyers posted in the community and through the Ultrasound Department at St. Joseph's Healthcare, Hamilton (*Control Group*). Potential control subjects were excluded if they had a current or past psychiatric diagnosis, as assessed by the Mini International Neuropsychiatric Interview (Sheehan et al., 1997).

Inclusion criteria for all participants were: 18 years or older, pregnant (up to 24 weeks of gestation), and able to communicate in English. Further inclusion criteria for the *Depressed Group* were to score as "depressed", using one of the following cut-offs: the Edinburgh Postnatal Depression Scale (EPDS) score of  $\geq 13$  (Cox et al., 1987) and/or the Montgomery-Asberg Depression Rating Scale score of  $\geq 9$  (Mittmann et al., 1997; Montgomery and Asberg, 1979). These cut-offs have been suggested to identify mild- to moderate levels of depression (Matthey et al., 2006; Mittmann et al., 1997). Assuming the comorbidity between depression and anxiety, prenatal anxiety was measured using the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger, 1996). Depressed subjects with a score on the state component of the STAI of  $\geq 40$  were further identified as "depressed" and "anxious" (*Depressed/Anxious Group*). Early childhood maltreatment was measured using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) and recent stressful life events (past 6-months) were measured with the Inventory for Recent Life Stressful Events (IRLE) (Paykel, 1997). The EPDS and the STAI (state) were repeated at the same time as salivary sampling.

Participants were asked to provide salivary samples, by method of passive drool, for cortisol analysis during mid- to late-gestation (25–33 weeks, mean = 28.4 weeks). These samples were collected to establish the CAR (immediately upon awakening, +30 and +60 min). Subjects completed a diary indicating wake time, the number of hours slept and time for each sample collected. Subjects were also instructed to refrain from brushing their teeth, eating or drinking anything except water during the sampling. Sampling was repeated over 2 days in the same week and the mean of the 2 days was used. Samples collected past 10 min from waking were not used in the analyses. The single measure intraclass correlations for pairs of samples collected at the same point ranged from 0.45 to 0.60, with Cronbach's alpha values ranging from 0.62 to 0.75, comparable to previous research (Wust et al., 2000).

Subjects stored the samples in their home freezers until they were picked up or brought into the clinic. Samples were stored at  $-20^{\circ}\text{C}$  until analyzed, when they were thawed, vortexed for 5–10 s and centrifuged at 3000 rpm for 15 min. Cortisol concentrations were determined by enzyme immunoassay (EIA) (Salimetrics; State College, PA, USA). Controls, standards and unknowns were pipetted in duplicate. The intra-assay coefficients of variation for cortisol were 8.3% for a low, and 6.9% for a high-concentration sample, respectively.

The demographics and score data were compared between groups using one-way ANOVA (age, EPDS, MADRS, STAI, CTQ, pre-pregnancy weight, weeks of gestation at testing, wake time) and the Chi-square test (partner status, parity). Values from 1 day (if only 1 day was compliant) or mean values were Ln-transformed to normalize

the distribution. The raw (untransformed) baseline sample values were used to locate outliers for each group (3 or more standard deviations from the mean). A repeated-measures ANCOVA was done with three group levels (*Depressed* versus *Depressed/Anxious* versus *Control*). Pearson correlations were used to examine effects on cortisol values (variables: weeks of gestation, wake time, number of other children and cigarettes smoked per day, current EPDS and STAI (State) scores; IRLE and CTQ scores; Ln-transformed baseline cortisol, change after awakening (delta)). Wake time had a significant effect on the cortisol variables and was used as a covariate; AD medication was used as an additional covariate. MANCOVA was used to compare the Ln-transformed baseline value, and the change (calculated by subtracting the 1st sample from the 2nd sample) using the same group levels and covariates. A paired *t*-test was done to compare the EPDS and STAI scores from intake to those collected at the time of salivary analyses. Linear regression analyses were used to examine the influences of childhood trauma/stress (order: AD use, wake time, CTQ total score), and current depression, anxiety scores and recent stressful life events (order: AD use, wake time, EPDS, STAI (State) on the baseline Ln-transformed cortisol and change (delta)). Differences were considered significant at  $p \leq 0.05$ .

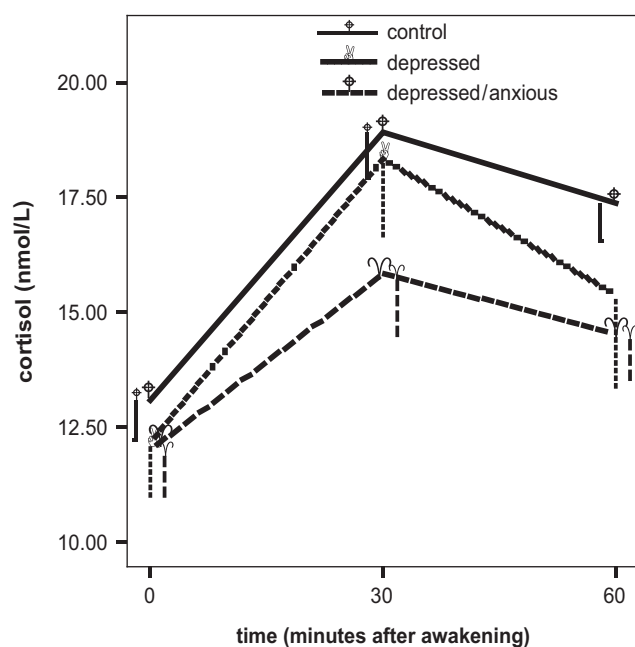
### 3. Results

Seventy pregnant women completed the saliva samples. Of these subjects, 66 (14 *Depressed*; 19 *Depressed/Anxious*; 33 *Control*) were included for the current analyses (exclusions: 3 outliers, 1 subject who had taken AD for 1 day only). In the *Depressed group*, 10 were treated with psychotherapy alone and four were treated with psychotherapy and AD medication; in the *Depressed/Anxious group*, 10 were treated with psychotherapy alone and nine were treated with psychotherapy and AD. A variety of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors were used, the specific kind selected on a case-by-case basis by the attending psychiatrist. Table 1 describes demographics; baseline and test time depression and anxiety scores, as well as test time characteristics.

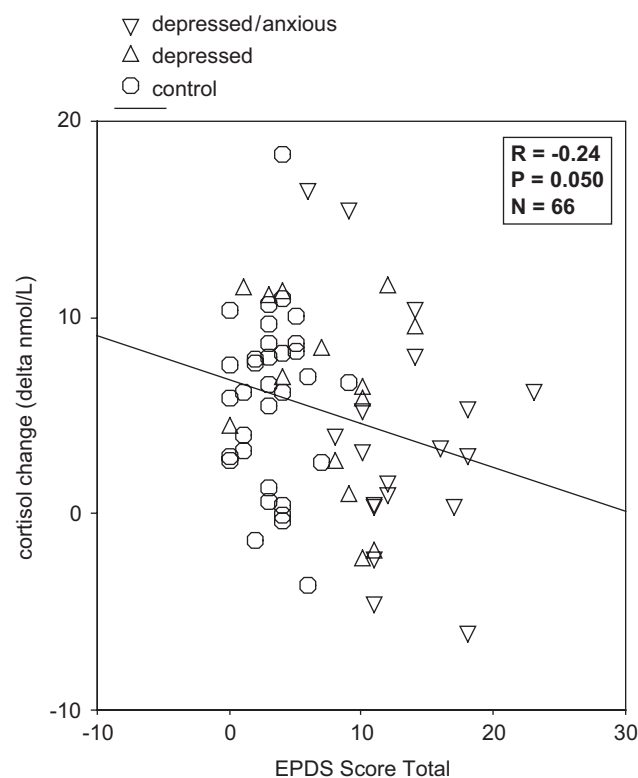
Overall, the pregnant women showed a cortisol response to awakening (Wilks' lambda = 0.88;  $F_{(2,60)} = 4.23$ ;  $p = 0.02$ ). The mean (unadjusted) cortisol increase 30 min after awakening was 5.3 (5.0) nmol/l, which is lower than the 9 nmol/l reported in healthy (non-pregnant) subjects (Clow et al., 2004). A typical CAR has been defined by at least a 2.5 nmol/l increase in cortisol during the first 30 min after awakening; 73% of participants met this criterion. The majority of the "non-typical" CAR profiles were in the *Depressed/Anxious* group (42% of this group), while only 21% of the *Control* and 21% of the *Depressed* subjects had a cortisol increase less than 2.5 nmol/l. Of the participants who took AD at time of assessment, 42% did not show a typical CAR. However, there was neither a group  $\times$  time effect nor a difference between the groups in cortisol change (calculated by subtracting the 1st sample from the 2nd sample: delta; Table 1; Figure 1). Subjects taking AD medication had an attenuated (trend) CAR (time  $\times$  drug effect:  $F_{(2,122)} = 2.82$ ;  $p = 0.06$ ); within-subject tests indicated that AD medication was associated with a linear time  $\times$  drug effect ( $F_{(1,61)} = 4.46$ ;  $p = 0.04$ ).

**Table 1** Subject demographics and score data at study intake and during time of assessment (time of CAR).

| Group                            | Control (N = 33) | Depressed (N = 14) | Depressed/<br>anxious (N = 19) | p                 |
|----------------------------------|------------------|--------------------|--------------------------------|-------------------|
| Age (years)                      | 31.9 (4.3)       | 29.8 (4.8)         | 28.6 (6.1)                     | NS                |
| % Married/common-law             | 100              | 93                 | 100                            | NS                |
| % Nulliparous                    | 49               | 50                 | 63                             | NS                |
| BMI (kg/m)                       | 23.6 (4.1)       | 25.9 (6.3)         | 27.1 (6.7)                     | NS                |
| EPDS score (intake)              | 3.3 (2.2)        | 10.9 (4.7)*        | 15.5 (4.1)*                    | <0.001*           |
| MADRS score (intake)             | 2.7 (1.4)        | 14.1 (5.5)*        | 15.5 (4.1)*                    | <0.001*, <0.025** |
| STAI (state) score (intake)      | 26.7 (6.5)       | 34.4 (11.5)**      | 55.7 (9.3)*                    | <0.001*           |
| Weeks gestation (time of CAR)    | 28.8 (2.0)       | 28.2 (1.4)         | 27.7 (1.6)                     | NS                |
| Wake-up time (h:min)             | 7:23 (1:19)      | 7:39 (1:36)        | 8:30 (2:02)                    | NS                |
| EPDS score (time of CAR)         | 3.2 (2.2)        | 7.4 (4.3)*         | 13.1 (4.3)*                    | <0.001*           |
| STAI (state) score (time of CAR) | 26.0 (4.3)       | 34.5 (12.6)**      | 48.3 (10.7)*                   | <0.001*, <0.025** |
| CTQ                              | 31.4 (8.2)       | 41.4 (20.7)        | 40.5 (16.1)                    | NS                |
| Baseline cortisol (nmol/l)       | 13.1 (5.1)       | 12.2 (4.7)         | 12.0 (5.0)                     | NS                |
| Cortisol change (delta) (nmol/l) | 5.8 (4.4)        | 6.1 (4.8)          | 3.8 (5.9)                      | NS                |

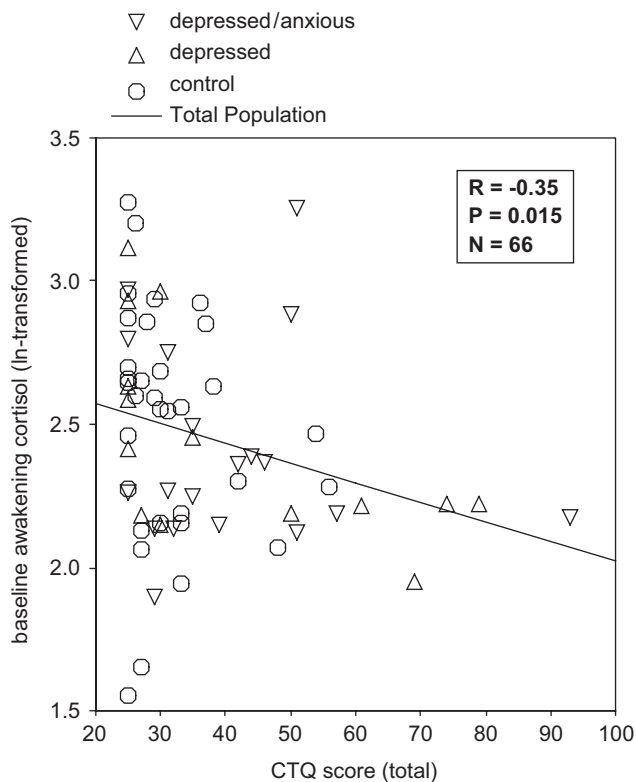
\* $p < 0.001$  versus Control group.\*\* $p < 0.025$  versus Control group.**Figure 1** The CAR in pregnant women.

The current EPDS scores at time of salivary testing were significantly lower than the scores at intake, indicating improvement in mood (paired  $t$ -test:  $t = 2.75$ ; d.f. = 65;  $p = 0.01$ ), while there was no change for the STAI (State) scores. Pearson correlation analyses indicated that the delta cortisol change was significantly negatively related to current EPDS scores ( $R = -0.24$ ;  $p = 0.05$ ; Figure 2), but this was not significant when wake-up time and AD medication were controlled for in the linear regression analyses ( $R = 0.28$ ; beta =  $-0.18$ ;  $t = 1.29$ ;  $p = 0.20$ ). Pearson correlation analyses also indicated that the baseline cortisol level was negatively related to the CTQ score

**Figure 2** The relationship between current depression (EPDS) scores and the change in cortisol levels over the first 30 min following awakening in pregnant women. This association was not significant after controlling for wake-up time and AD medication.

( $R = -0.27$ ;  $p = 0.03$ ). The linear regression analysis indicated that higher CTQ scores were associated with lower baseline awakening cortisol levels ( $R = 0.35$ ; beta =  $-0.30$ ;  $t = 2.50$ ;  $p = 0.02$ ), explaining 12% of the variance, controlling





**Figure 3** The relationship between early life trauma (CTQ) and the baseline awakening cortisol level in pregnant women. Linear regression analyses indicated that the CTQ was negatively related to the baseline morning cortisol level, controlling for wake-up time and AD medication.

for AD use and wake time (Figure 3). There were no significant associations between baseline awakening or delta (change) cortisol levels and current STAI scores or the IRL.

#### 4. Discussion

To our knowledge, this is the first attempt to measure the CAR in pregnant women experiencing depression/anxiety as well as HPA axis changes associated with AD medication during pregnancy. We report that maternal depression scores during pregnancy were associated with a decreased CAR, and that a history of childhood trauma had a significant influence on cortisol regulation. When the wake-up time and the AD medication were entered as covariates, however, the association with the EPDS scores was no longer significant, suggesting that the covariates exerted more influence than the current symptoms of depression. These preliminary results should be interpreted with caution since the sample size in each group was small and some of the effects showed only marginal significance. Further studies in larger cohorts of pregnant women experiencing depression and anxiety are required.

Pregnancy is associated with increased circulating levels of CRH and cortisol. CRH, mostly of placental and fetal origin, increases from the eighth to tenth week of pregnancy onwards (Karteris et al., 1998; Riley and Challis, 1991). The placental CRH system and the maternal HPA axis are interrelated; placental CRH stimulates maternal pituitary

ACTH secretion, influencing maternal glucocorticoid secretion (Wadhwa et al., 1997). Maternal unbound cortisol (as in saliva) rises during pregnancy, particularly after the 21–25th week reaching levels that are more than two-fold those of non-pregnant women (Allolio et al., 1990; Demey-Ponsart et al., 1982). Glucocorticoids actually promote placental CRH secretion, rather than providing negative feedback, by up regulation of placental mRNA (Jones et al., 1989; Robinson et al., 1988). If maternal baseline cortisol levels are lower, as shown in our depressed subjects, especially those with a history of early childhood trauma, there may not be sufficient positive feedback on placental CRH, which may be detrimental for healthy fetal development. CRH also influences vasodilation of uterine arteries (Clifton et al., 1994; Linton et al., 1993); lower than normal CRH levels may affect healthy uterine circulation.

Fetal concentrations of cortisol were found to be linearly related to maternal cortisol concentrations and it was suggested that maternal cortisol may account for 40% of the variance in fetal cortisol (Gitau et al., 1998). Since glucocorticoids are required for development of particular organ systems (e.g. lungs) (Garbrecht et al., 2006), we speculate that lower levels of maternal cortisol, as associated with increased depression and child maltreatment scores in the current study, may not provide adequate stimulation for healthy *in utero* development.

Dysregulation of the HPA axis has been associated with changes in maternal affect. Two studies have reported that depressed pregnant women had elevated urinary cortisol during the 2nd and 3rd trimesters of pregnancy (Field et al., 2004; Lundy et al., 1996), which is inconsistent with our results. However, several factors in these studies were not specified (i.e., time of day, maternal weight, pregnancy age, smoking status, early life trauma experience) making results difficult to compare. A more recent study found that women with postpartum depression had lower cortisol stress responses than controls (Jolley et al., 2007), which may be similar to our observation that negative affect in the perinatal period may be associated with decreased HPA axis function. The lower cortisol levels associated with early life stress of child maltreatment in our subjects may be etiologically important for the negative affect reported by our depressed subjects. It is unclear whether a dysregulated HPA axis is a cause or consequence of current mood state. The early life stress of child maltreatment has been shown to be associated with increased risk for adult psychopathology, particularly depression and anxiety (MacMillan et al., 2001). Alterations of HPA axis function are found in women with a history of child maltreatment, particularly decreased baseline and stimulated plasma cortisol levels (Heim et al., 2001), which is comparable to our results. Decreased CAR has been reported in war refugees with of PTSD and in subjects with early loss experience (parental death or divorce) (Rohleder et al., 2004; Meinlschmidt and Heim, 2005; Wessa et al., 2006). In our study, the severity of child maltreatment explained a significant proportion of the variance, which highlights the contribution of early-life events to HPA axis function during pregnancy.

As mentioned earlier, inpatients with MDD showed a blunted CAR compared to non-depressed inpatients, but 68% of the depressed were taking ADs (Huber et al., 2006). A non-typical response was reported for almost half of the

MDD patients in this study, similar to the proportion (42%) of our own depressed subjects taking ADs. Animal studies have demonstrated that long-term administration of ADs increases glucocorticoid receptor mRNA and protein levels, which leads to enhanced susceptibility of the HPA axis to negative feedback by glucocorticoids (Pariante and Miller, 2001). In humans, an attenuated cortisol response to pharmacological stimulation was seen in depressed patients after 2 weeks of treatment with citalopram (Nikisch et al., 2005). The repeated-measures ANOVA indicated that the AD medication in the current study had a trend effect on the CAR, which may be due to changes in glucocorticoid receptor density. However, with only 13 subjects taking AD medication, our conclusions must remain conservative. Given the importance of the HPA axis during fetal development, further examination of the AD effects during pregnancy is warranted.

In summary, our study found that women experiencing depression and anxiety during pregnancy did not significantly differ from healthy, control subjects on the CAR, but that AD medication was associated with an attenuated HPA axis response to awakening. Also, higher childhood trauma scores were associated with a lower baseline cortisol level. Further studies of depressed and anxious pregnant women are necessary to understand whether lower cortisol levels are a cause or consequence of mood disturbance. Long-term follow-up of this population will help to determine whether these changes have transgenerational effects.

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Funding for this study was provided by the Canadian Institutes of Health (CIHR); the CIHR had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

## Conflict of interest

Dr. Steiner is a consultant for Eli Lilly, Pfizer, GlaxoSmithKline, Lundbeck, Novartis, Wyeth Pharmaceuticals, Barr Laboratories, Procter & Gamble, Ortho-McNeil, Warner Chilcott, Astra-Zeneca and Azevan Pharmaceuticals; is on the Speakers Bureau for Astra Zeneca, Eli Lilly, Pfizer, GSK, Lundbeck and Wyeth Pharmaceuticals; is on the advisory board for Eli Lilly, Pfizer, GSK, Barr Laboratories, Lundbeck, Procter and Gamble, Ortho-McNeil Pharmaceutical, Warner Chilcott, Wyeth Pharmaceuticals, Sherring, Ferring and Azevan and currently receives grant support from Wyeth and Pfizer. There are no conflicts of interest for the other authors.

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