Resumo

Introdução: A depressão pós-parto é um transtorno prevalente que afeta negativamente a qualidade de vida da mãe e da criança. Neste estudo longitudinal, nós investigamos se a memória emocional, salivary cortisol (sCORT) ou alfa-amilase durante a gravidez predizem sintomas depressivos no período pós-parto.

Métodos: Um total de 44 mulheres grávidas (14 eutímicas com diagnóstico de transtorno depressivo maior [TDM] e 30 voluntárias sadias) entre 19 e 37 anos de idade (idade média = 29.5±4.1 anos) foram avaliadas longitudinalmente no 2º trimestre da gravidez (12-22 semanas de gestação) e novamente no 14-17ª semana pós-parto. Sintomas depressivos foram avaliados utilizando a Escala de Depressão Pós-Natal de Edimburgo (Edinburgh Postnatal Depression Scale, EPDS).

Resultados: Quarenta e uma mulheres completaram o seguimento (7% de perda). sCORT coletado imediatamente antes de um teste de aquisição de memória durante a gravidez foi preditor dos escores da escala EPDS no período pós-parto (b=-0.78, t=-2.14, p=0.04). Memória emocional positiva (p=0.27) ou negativa (p=0.85) não foram preditores dos escores da escala EPDS no período pós-parto.

Conclusão: Os resultados deste estudo indicam que altos níveis de sCORT durante um teste de aquisição de memória na gravidez estão associados com baixos escores na escala EPDS no período pós-parto. Um estudo longitudinal, no entanto, é necessário para confirmar este achado.

Descritores: Gravidez, depressão pós-parto, transtorno depressivo maior, cortisol salivar, memória emocional.
**Introduction**

Pregnancy and postpartum are particular vulnerable periods where the onset or exacerbation of depressive episodes is common and affects approximately 8% of Canadian women. While the hypothalamus-pituitary-adrenal (HPA) axis has long been associated with the neurobiology of major depressive disorder (MDD), the role of the HPA axis in perinatal depression is less known. Individuals with unipolar depression exhibit flattened diurnal cortisol rhythms and have a lower peak of awakening cortisol. It has been postulated that an augmented positive feedback loop leading to higher levels of cortisol and to placental corticotropin-releasing hormone (pCRH) during pregnancy and a longer HPA refractory period in postpartum may be associated with increased risk for postpartum depression (PPD). Salivary cortisol (sCORT) awakening response in the 3rd trimester of pregnancy has been shown to negatively predict HPA stress responses in postpartum.

Alpha-amylase is an enzyme that has been shown to be a marker of sympathetic nervous system activity as levels increase in humans in response to stressors. Inducing psychosocial stress in early 2nd and 3rd trimester pregnant women resulted in attenuation of alpha-amylase in the stress response compared to non-pregnant women and prolonged cortisol recovery in early 2nd trimester pregnant women compared to early 3rd trimester pregnant and non-pregnant women. Many risk factors for PPD have been identified, including poor marital and social support, life stressors, low self-esteem, pessimism about pregnancy, and antenatal depression and anxiety. However, no biological markers have been clearly established in the genesis of this disorder.

This longitudinal study is a follow-up to a recent cross-sectional study where we found that euthymic women with a history of MDD had worse recognition memory than women without a lifetime history of MDD for negative, but not positive images, an effect that was independent of sCORT and salivary alpha-amylase (sAA) during incidental encoding. Given that previous studies have shown that elevated levels of sCORT and sAA during incidental encoding is associated with better memory for emotional content, and individuals currently depressed recall more negative compared to positive content, our results suggested that clinical remission may be associated with an opposite cognitive processing of negative emotional information.

**Objectives and hypotheses**

The main objectives of this study were to investigate: 1) whether normalized memory sensitivity (for negative and positive images) during pregnancy predicted Edinburgh Postnatal Depression Scale (EPDS) scores in postpartum; and 2) whether sCORT and sAA during pregnancy predicted EPDS scores in postpartum. We hypothesized that normalized memory sensitivity during pregnancy would be associated with higher EPDS scores in postpartum in participants with a history of MDD compared to participants without a history of MDD. We also hypothesized that salivary hormones (sCORT, sAA) during pregnancy would predict postpartum depressive symptoms (as measured by EPDS) in participants with a history of MDD.

**Methods**

**Sample**

Forty-four female participants were recruited at the Women’s Health Concerns Clinic at St. Joseph’s Healthcare Hamilton and a Community Midwives clinic in Hamilton, Ontario, Canada. All participants provided written informed consent and the study was approved by the St. Joseph’s Healthcare Hamilton research ethics board. Detailed inclusion and exclusion criteria for the current sample can be found in a recent report. Of the 44 individuals initially enrolled in the study, three were unable to be contacted in postpartum. Therefore, a total of 41 pregnant participants between the ages of 19 and 37 years (mean age = 29.2±4.1years) completed the longitudinal study (13 euthymic pregnant women with a history of MDD and 28 pregnant women without a history of MDD). Participants were studied at 12-22 weeks of gestational age and 14-17 weeks of postpartum. The Structured Clinical Interview for DSM-IV (SCID-I) confirmed a past diagnosis of MDD in participants with a history of MDD. All women with a history of MDD were euthymic for at least 3 months prior to study entry.

**Measures**

Severity of depressive symptoms were assessed using the EPDS, anxiety symptoms using the State-Trait Anxiety Index (STAI), and sleep quality using the Pittsburgh Sleep Quality Index (PSQI). Incidental encoding and recognition memory tasks including positive, neutral, and negative images selected from the International Affective Picture System (IAPS) and sorbettes used to collect the salivary hormone samples are previously described. Collection time of samples was based on the participants’ schedule and occurred between 10:00 and 19:00 hrs.

**Procedure**

The Salimetrics® Cortisol and α-Amylase Kinetic enzyme assay kits procedure instructions for
quantifying sCORT and sAA, respectively, are described in detail elsewhere.\textsuperscript{17,18} sCORT and sAA samples were collected at four time points throughout the visit: 10 minutes before the incidental encoding task (time -1), immediately before the task (time 0), immediately after the task (time 1), and 10 minutes after the task (time 2). Participants returned a week later to complete the incidental recognition memory task.\textsuperscript{10} Participants were then contacted by phone at 14-17 weeks postpartum where they completed the EPDS and were re-administered the Major Depressive Episode module of the SCID-I to assess depressive symptoms and/or episodes.

**Data analysis**

Statistical analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows. Differences in age, education, gestational age, anxiety symptoms (STAI) and sleep quality (PSQI) during pregnancy (Table 1) were analyzed using a one-way analysis of variance (ANOVA). For the incidental recognition memory task, Hit and False Alarm rates were calculated for each individual participant. These rates were in turn used to calculate the sensitivity indexes (d’) (for full details see Williams et al., 2015\textsuperscript{10}). The area under the curve with respect to ground (AUC\textsubscript{G}) was used to incorporate the four time points of hormonal collection.

Multiple linear regression models were used to estimate the predictors of postpartum EPDS scores (dependent variable): 1) the relation between the cortisol AUC\textsubscript{G}, which is the plot of cortisol vs. time, and the alpha-amylase AUC\textsubscript{G}, which is the plot of alpha-amylase vs. time, during pregnancy and EPDS scores in postpartum; 2) the relation between recognition memory (i.e., normalized memory sensitivity) for positive and negative images during pregnancy and EPDS scores in postpartum; 3) the relation between sCORT samples collected 10 minutes before the incidental encoding memory task, immediately before the task, immediately after the task, and 10 minutes after the task, and postpartum EPDS scores; and 4) the relation between sAA samples collected 10 minutes before the incidental encoding memory task, immediately before the task, and 10 minutes after the task, and postpartum EPDS scores; and Group, AUC\textsubscript{G} for sCORT and sAA, normalized memory sensitivity (for positive and negative images), and sCORT and sAA samples collected 10 minutes before, immediately before, immediately after, and 10 minutes after the incidental encoding memory task were included as predictors.

**Results**

EPDS scores in postpartum were predicted by sCORT collected immediately after the incidental encoding memory task across groups during pregnancy (b=-0.78, t\textsubscript{-2.14}, p=0.04). This model explained 15% of the variance in EPDS scores in postpartum ($R^2=0.15$, $F_{5,40}=1.27$, p=0.04). These results indicate that higher levels of sCORT immediately after the incidental encoding memory task in pregnancy were associated with lower EPDS scores later in the postpartum period.

It is important to note that these results were positive in the whole sample. sCORT means for the high- and low-risk groups immediately after the task were 3.63 and 2.97 nmol/L, respectively. However, there were no statistically significant differences in the prediction of postpartum EPDS scores between the high- and low-risk groups. Postpartum EPDS scores were not predicted by the cortisol AUC\textsubscript{G} (b=0.07, t\textsubscript{0.45}, p=0.66) or the alpha-amylase AUC\textsubscript{G} (b=-0.10, t\textsubscript{-0.58}, p=0.57). Similarly, postpartum EPDS scores were not predicted by emotional memory for positive (b=0.28,

**Table 1 - Demographic and clinical characteristics of participant groups during pregnancy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant &amp; MDD history</th>
<th>Pregnant &amp; no MDD history</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.6 (4.4)</td>
<td>29.0 (4.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Education (years)</td>
<td>17.3 (3.5)</td>
<td>16.8 (3.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>STAI, state score</td>
<td>27.79 (5.46)</td>
<td>25.11 (3.21)</td>
<td>0.05</td>
</tr>
<tr>
<td>STAI, trait score</td>
<td>35.29 (6.33)</td>
<td>30.53 (3.36)</td>
<td>0.002*</td>
</tr>
<tr>
<td>PSQI</td>
<td>4.43 (2.77)</td>
<td>4.62 (2.16)</td>
<td>0.81</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>18.5 (2.9)</td>
<td>17.6 (2.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Number of MDEs</td>
<td>2.9 (5.0)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data presented as mean (standard deviation).
MDD = major depressive disorder; MDE = major depressive episode; N/A = not applicable; PSQI = Pittsburgh Sleep Quality Index; STAI = State-Trait Anxiety Inventory.
* Significant at p ≤ 0.01.
t_{127} \ p=0.27) or negative (b=-0.05, t_{207} p=0.85) images. Three (7.3%) women met diagnostic criteria for MDD in postpartum, two of whom had a previous history of MDD, a result that is consistent with the 8% prevalence of PPD previously reported in the Canadian population.1

Discussion

We found that higher levels of sCORT immediately after an incidental encoding memory task during pregnancy were associated with lower EPDS scores in postpartum across participant groups. A recent study found a positive association between EPDS scores (≥10) and sCORT levels at 6 weeks postpartum, but no significant correlation between sCORT levels at 36 weeks of gestation and EPDS scores in late pregnancy and postpartum.19 In addition, another study found that higher levels of pCRH during mid-pregnancy were associated with depressive symptoms at 3-months postpartum.20 Together, these studies support the hypothesis that changes in certain HPA markers (sCORT and pCRH) may be associated with increased depressive symptoms in the postpartum period. However, contrary to our hypothesis, we did not find an association between emotional memory during pregnancy and postpartum depressive symptoms.

A healthy pregnancy is characterized by increased levels of hormones, including sCORT, from early to late pregnancy, which typically normalize within 2 weeks postpartum.21 sCORT levels that do not normalize within this time may be linked to an increased risk for PPD.21 Postpartum EPDS scores were not predicted by the cortisol or the alpha-amylase AUC_{G}. Differences in sCORT levels exist between depressed postpartum women and currently euthymic postpartum women within 30 minutes of awakening, but not at 3 and 12 hours after awakening.22 The fact that the samples were collected between 10:00 and 19:00 hrs during pregnancy (i.e., after 30 minutes of awakening) may be one of the reasons why cortisol AUC_{G} did not predict changes in EPDS scores postpartum.

The exact etiology of PPD remains unclear. PPD is currently classified in the DSM-5 under the MDD umbrella with a specifier “with peripartum onset.”23 However, this classification continues to be questioned as there is evidence to suggest differential amygdala activation in postpartum compared to non-postpartum (unipolar) depression. Two independent studies found an association between blunted amygdala activation and PPD in response to emotional stimuli,24,25 which suggests that depression in the postpartum period may be qualitatively different than depression outside the postpartum period. Future longitudinal studies are needed to identify reliable markers of risk for the development of PPD as they serve as a preventative tool to screen and allow for early identification and treatment.

Limitations

Some methodological limitations that must be considered include a relatively small sample size, which may have limited our statistical power. Second, sCORT and sAA were collected at only one time point (2nd trimester of pregnancy) and not again in postpartum. This did not allow us to examine the possible association between changes in salivary hormones and postpartum depressive symptoms. Third, sample collection occurred according to the participants’ availability, and not at standardized times for all participants. Strengths included the longitudinal design and the fact that most of the participants in the study (84% of the sample) were recruited from a Community Midwives clinic, which is less biased than results from samples originated from women treated in tertiary care centers.

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Disclosure

No conflicts of interest declared concerning the publication of this article.

References


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