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The role of estrogen and progesterone in depression after birth

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Abstract

Previous reports suggest that massive hormonal changes that accompany the peripartum period may trigger perinatal depression. We investigated the relationship between magnitude of change and total level of estrogen and progesterone and grade of peripartum depression and depressive symptoms. One hundred and ninety two women were assessed in the 38th week of pregnancy (SDS scores), peripartum period (DSM-III-R diagnosis ($n = 105$); SDS scores) and 6 months postpartum (EPDS; $n = 89$) regarding diagnosis of depression, self-ratings of depressive symptoms and levels of estrogen and progesterone. The comparison of three diagnostic groups (lifetime major depressive disorder MDD ($N = 7$), MDD at birth ($N = 12$), healthy controls ($N = 70$)) showed that there were no differences in the magnitude of decline of estrogen and progesterone from day 1 to day 3 after birth. With respect to total levels of estrogen and progesterone, estrogen on day 3 was significantly higher [$F(2,92) = 6.6, p < 0.05$] in women with current MDD than in those with lifetime MDD or normal controls. Depression scores were significantly higher at the end of pregnancy (12.6% self-identified as depressed) than in postpartum period (5.8% day 3 $p < .0004$; 9.2% day 5 $p < .008$), whereas 13.3% of women received a DSM-III-R diagnosis for MDD 5 days postpartum.

The results were in contrast to the current hypotheses of estrogen withdrawal or hypogonadal levels as an etiological factor for peripartum depression. But a limitation of the actual study is the low number of subjects with depression; therefore the current non-significant findings should be interpreted with great caution.

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1. Introduction

While phenomenology and prevalence of postpartum depression do not differ from non-puerperal depression, the tremendous changes of gonadal hormones during the puerperium led to the hypothesis that perinatal depression may be triggered through hormonal changes accompanying pregnancy, birth and the postpartum period (Stahl, 2001). Several hormones: estrogen, progesterone, testoster-

one, cortisol and prolactin in their biologically bound and free fraction (Harris et al., 1989; O'Hara et al., 1991a) were proposed to be of importance in the etiology of postpartum depression. Current pathophysiological understanding incorporates various theories ranging from hypogonadal states (Ahokas et al., 1998) to the “withdrawal” theory (Bloch et al., 2000), interaction between the hypothalamic–pituitary–adrenal system and the hypothalamo–pituitary–gonadal system (Young et al., 2000), as well as the fluctuation of gonadal hormones (Halbreich, 2000).

To date, several studies have investigated the role of estrogen in postpartum depressive symptoms (Gard et al.,

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1986; Harris et al., 1989; Harris et al., 1994; Heidrich et al., 1994; Hohlagschwandtner et al., 2001; O'Hara et al., 1991a) with contradictory results regarding estrogen levels in the pre- and postpartum period and the association of hormone levels with postpartum mood symptoms. Indeed, estrogens have a multitude of central actions and influence neurotransmitter systems in several ways (Stahl, 1998). Studies of gonadal hormones in depressed women in the absence of reproductive events or menstrual disorders are sparse. Current research suggests that estrogen could have a 5-HT (serotonin) agonistic function (Fink and Sumner, 1996; Halbreich, 1997; Rubinow et al., 1998). As a matter of fact, in a study of women who did not have any reproductive event in the past year, Young et al. reported significantly lower estradiol plasma levels in the follicular phase in the depressed group than in the control group (Young et al., 2000).

Depression rates have been described as relatively low during pregnancy, suggesting a protective effect of gonadal hormones, which show their peak levels during the last trimester of pregnancy. After birth, all gonadal hormones drop very sharply within a few days, indicating a possible association with a sudden rise in the occurrence of non-psychotic and psychotic illnesses (Stahl, 2001). A NIH research-group simulated two hormonal conditions related to pregnancy and parturition in euthymic women with a history of postpartum depression ($n = 8$) and a healthy control group ($n = 8$). Compared with the control group there was an increase in depressive symptoms in the group with a history of postpartum depression in the phase simulating pregnancy (estrogen and progesterone was added) with a peak during the withdrawal phase (simulation of birth) of gonadal hormones. These findings suggest that not hypogonadism per se but rather the sudden postpartum withdrawal may be a trigger of depression and that women with a history of Postpartum Depression (PPD) may have a differential response to abrupt reduction of plasma levels of gonadal steroids. The study further suggests that women who develop postpartum depression might be more sensitive to changes in gonadal steroids. Most importantly these findings indicate that the onset of depression before rather than after parturition may be the rule rather than the exception in postpartum depression (Bloch et al., 2000). This study assumes that the supraphysiologic doses of estradiol and progesterone imitating pregnancy, rather than the lack of gonadal hormones may be a trigger for depressive symptoms in a subgroup of women. Additional support for this hypothesis was found by an epidemiological study of antenatal and postnatal depression with over 12,000 women in the UK, which showed that depressive symptoms are highest in late pregnancy and less prevalent after birth (13.7% vs. 9.1%) (Evans et al., 2001).

1.1. Aims of the study

The current study aimed to extend prior research by investigating the relationship between the magnitude of

estradiol and progesterone change from late pregnancy to postpartum and depressive symptoms after childbirth. More specifically, self-rated depressive symptoms peripartum and at 6 months postpartum in three groups of participants were assessed: women diagnosed with depression after parturition, those with a history of non-puerperal depression and women who were never depressed. The self-ratings were then related to estradiol levels and to the magnitude of sudden “withdrawal” in early postpartum. Furthermore, we compared rates of depressive symptoms in late pregnancy and early postpartum.

2. Materials and methods

We investigated the relationship between hormones (estrogen, progesterone) and mood symptoms during early postpartum comparing women with current and past major depression and healthy controls (NC).

Women were approached in the maternity hospital at the Medical University Vienna shortly before childbirth and invited to participate in the investigation. After full explanation of the nature and procedure of the study, women gave written consent and provided several blood samples for hormone assays, as well as demographics and depression self-ratings. Psychiatric interviews were obtained within 5 days of parturition, but only a subset could be interviewed due to early discharge of several women. None of the women approached for the interview refused to participate in the subsequent investigation. The study has been approved by the local ethics committee and was carried out in accordance with the Declaration of Helsinki.

Inclusion criteria were normal singleton pregnancies in women without serious mental (such as suicidality, psychoses, substance abuse, but subjects with major depression were included) or physical health problems. Women with metabolic disorders, pregnancy complications or physical illness, requiring treatment or admission to hospital, or fetal complications were not included. All subjects were medication free except for occasional sleep medication.

2.1. Participants

One hundred and ninety two women agreed to participate and provided demographic data, Zung SDS depression self-ratings (pre-and post delivery) and blood samples for analyses of hormones. Eighty-seven (45%) of the initial 192 women left the hospital before they could be invited to participate in the psychiatric assessment; the remaining subsample of 105 women underwent a structured psychiatric interview within 5 days after delivery. There was a tendency to miss women discharged either very early following delivery or during weekends or holidays. The sample comprised a Caucasian, metropolitan population, ranging from lower to upper middle-class with approximately one-third of the mothers having undertaken education beyond the age of 16. Most women were

working full-time before their pregnancy, and more than half were primiparous. Their age range was 17–44 with a mean of 28 years, 14% of women had a cesarean section and 11% ventouse delivery.

2.2. Assessments

Various mood and hormone assessments were made at the following time-points: 38 weeks of pregnancy, day 1–10 after birth and 6 months after birth:

- A. Clinical diagnosis: The SCID German-Version (Spitzer et al, 1990; Wittchen et al., 1990) is a semi-structured clinical interview based on the Diagnostic and Statistical Manual of Mental Disorder, 3rd Edition Revised criteria (APA, 1987) and was assessed by a trained psychiatrist (MM) five days after birth. A diagnosis of DSM-III-R Major Depressive Episode (MDD) current or lifetime and family history was derived from the interview.
- B. Symptoms of depression were assessed by self-rating: The SDS Zung self-rating depression scale (SDS-German-version; CIPS, 1986) was given in the 38th week of pregnancy and from day 1 to 10 after birth. The SDS is a standard measure of depression (cut-off score above 48 is considered “probable depression”) (CIPS, 1996; Zung, 1965). At 6 months postpartum the EPDS (Edinburgh Postnatal Depression Scale) was appraised via a phone-interview and rated the mother’s self-assessment of her mood symptoms (Muzik et al., 2000). The EPDS was used only for the 6 months assessment, as it had not been validated in German language at the conception of the study. The cut-off of for the Austrian sample was above a score of 10.
- C. Blood samples for plasma hormone assays were obtained at 38–40 weeks of gestation, and on the 1st and 3rd day postpartum. Blood draw was performed in the morning within 2 h (8 a.m. to 10 a.m.). Laboratory determinations of serum concentrations of hormones were carried out with commercially available kits using radioimmunoassay for estradiol and progesterone. The coefficients for intra-assay and interassay variation were 4.3% and 6.8% for estradiol and 5.1% and 8.8% for progesterone (Hohlagschwandtner et al., 2001).

2.3. Statistical analyses

Statistics were computed using SPSS, version 11. Differences between women who continued in the actual study and those who dropped out prior to psychiatric assessment were examined with *t*-tests. Magnitude of change of total estrogen and progesterone from postpartum day 1 to postpartum day 3 was calculated by subtracting estrogen and progesterone level day 3 from level day 1 (i.e., delta estro-

gen = estrogen day 1–estrogen day 3). To assess associations between delta estrogen and delta progesterone, and depression self-rating scores Spearman’s correlation coefficients (ρ) were calculated. To calculate magnitudes and significance of decline in percentage of women scoring in depression range on SDS from prepartum to postpartum we used the Wilcoxon Signed Rank Test since SDS score frequencies did not follow a normal distribution. Women were assigned to three diagnostic groups: current major depression at birth ($n = 14$), lifetime history of depression ($n = 11$), and healthy controls ($n = 80$). Differences of mean estrogen and progesterone values and of 6 months EPDS depression scores by group status were calculated using analysis of variance (oneway and repeated measures) and post hoc analyses. To assess stability of depression from pre- to postpartum we calculated the number of women meeting criteria for probable depression from 38weeks gestation to days 3 and 5 postpartum using the cut-off score of 48 on the SDS depression score for classification of probable depression (CIPS, 1996). We applied a two-sided significance level of 0.05 to all analyses, and Bonferroni corrections were applied for multiple comparisons.

3. Results

3.1. Comparison of the samples of women who were lost after day 5 and those who continued the study up to 6 months

There were no significant differences between women who continued in the study ($n = 105$) and those who were lost prior to postpartum day 5 ($n = 87$) on maternal age, parity, infant birth weight, depressive symptoms before and after partuition, early postpartum hormone levels (all p ’s > 0.1), and frequency of Caesarian sections (see Table 1). At 6 months postpartum 89 (84.7%) of the 105 women with diagnostic assessment at birth could be reached for a phone follow-up (attrition 15.3%).

3.2. Description of depression status

Of the 105 women 76.2% ($n = 80$) had no history of depression, neither current nor lifetime. A total of $n = 22$ women had a lifetime MDD and of those 11 developed MDD at birth. 10.5% ($n = 11$) met lifetime criteria for MDD but were not currently depressed at birth. A total of 13.3% ($n = 14$) met criteria for MDD at time of birthgiving; 3 women with new onset postpartum (i.e., no prior lifetime history) and 11 with prior lifetime MDD. Women in the 3 groups (MDD at birth, MDD lifetime and NC) did not show significant differences on maternal age, parity, child sex and birth weight, as well as number of Cesarean deliveries.

Using the SDS cut-off score of 48 we yielded 24 women meeting criteria for depression in pregnancy. Of those 24 women only a small portion provided depression self-report data at three days postpartum (66%), at 5 days

Table 1
Numbers and values for women who continued in the study and those who were only assessed until day 5

Variable	Group	Number	Mean	SD
Age of mother	1	87	27.5	5.2
	2	105	28.7	4.9
Parity	1	84	1.4	.7
	2	102	1.6	.9
Birth weight in Gram	1	83	3519.1	413.1
	2	101	3499.3	434.9
Estrogen day 1	1	87	221.8	215.5
	2	105	255.7	240.0
Estrogen day 3	1	57	48.2	17.0
	2	93	54.2	37.5
Progesterone day 1	1	87	10.3	6.9
	2	105	10.5	8.1
Progesterone day 3	1	57	2.3	2.7
	2	93	2.7	.9
SDS 38th week pregnancy	1	83	37.4	8.3
	2	105	36.9	7.6
SDS day 1	1	82	36.2	7.2
	2	104	36.0	7.1
SDS day 3	1	56	34.5	6.5
	2	97	34.2	7.5
SDS day 5	1	34	35.6	7.3
	2	53	34.3	8.9
Caesarean delivery (in%)	1	67/84 (80%)		
	2	71/101 (70%)		

Given are numbers, mean, SD = standard deviation, and percentage occurrence (for Caesarean delivery only).

Group 1 are mothers who were not followed up after day 5, Group 2 are those who were seen for the length of the entire study.

SDS (Zung) is a self-rating measurement of depressive symptoms.

postpartum (50%), and 6-months postpartum (33%), thus limiting inferences about stability from pre-to postpartum depression. We found that 2/9 (22%) women meeting criteria of depression at day 3 postpartum (SDS > 48) had been already classified as depressed in pregnancy (SDS > 48); 4/8 (50%) women depressed at day 5 were already depressed in pregnancy, and 3/14 (21%) women depressed at 6 months postpartum (EPDS > 10) were depressed in pregnancy.

3.3. Relationship between estrogen and progesterone levels and diagnostic status after parturition

Oneway ANOVAs were used to identify group differences in hormonal levels of estrogen and progesterone on postpartum days 1 and 3 across the three diagnostic groups (current MDD, $n = 14$; lifetime MDD without active depression after birth, $n = 11$; and healthy controls [NC], $n = 80$), computed separately for each time point. Significant group differences emerged only for mean estrogen levels on day 3; posthoc comparisons indicated that women with a current diagnosis of depression had higher day 3 estrogen levels (in pg/ml) than the NC ($M = 84$, $SD = 72$ vs. $M = 47$, $SD = 23$; $F(2, 92) = 6.6$, $p < 0.05$). There were no significant group differences in progesterone levels (in pg/ml) measured on days 1 or 3 postpartum. For means and standard deviations for each of these measures across

the 3 groups see Table 2. Note that the difference between prepartum levels (week 38) and postpartum days 1 and 3 could not be analyzed because the available kit did not measure levels above 4.500 pg/ml for estrogen and above 35 pg/ml for progesterone; all prepartum levels were at or above the ceiling level of the testing kit, indicating high levels but not interpretable for analysis. We extended the analysis of these data to test for possible interactions between time of hormonal assay (i.e., progesterone or estrogen level day 1 or day 3) by depression group status at birth; we conducted a repeated measures multivariate analysis of variance separately for estrogen and progesterone. For these analyses, the within-subject factor was estrogen or progesterone on days 1 and 3, and the between-subjects factor was depression group status. Results confirmed a main effect of time, showing that levels of estrogen [Wilks' Lambda $F(2, 90) = 1.23$, $p = .30$] and progesterone [Wilks' Lambda $F(2, 90) = .39$, $p = .67$] decreased from day 1 to 3. However, the interaction between group status and time was not significant for either estrogen or progesterone. Thus, while there was some suggestion that the depressed group had higher estrogen levels at day 3, change in hormonal levels did not significantly differ across the diagnostic groups.

The next set of analyses explored associations between stability of pre-to postpartum depression and differences in the change in estrogen and progesterone levels from day 1 to day 3. Women who were stable in their depression from pregnancy to days 1 or 3 (at both time-points above SDS cut-off 48) were contrasted with women who were only depressed in pregnancy (above SDS cut-off 48 in week 38) but not depressed at either day 1 or 3 (below SDS cut-off 48 on day 1 or day 3). Results of the repeated measures analysis of variance tests (computed separately for estrogen and progesterone) yielded main effects for time but no interaction by stability of depressive symptoms.

Table 2
Means and standard deviations of estrogen and progesterone across the 3 diagnostic groups

	MDD current (A) <i>M</i> (SD)	MDD lifetime (B) <i>M</i> (SD)	NC (C) <i>M</i> (SD)	Post hoc
<i>Estrogen (pg/ml)</i>				
...week 38 preg	>4.5000	>4.5000	>4.5000	^a
Day 1	261 (170)	291 (238)	249 (252)	$A = B = C$
Day 3	84 (72)	59 (24)	47 (23)	$A > C^*$, $A = B$, $B = C$
<i>Progesterone (pg/ml)</i>				
...week 38 preg	>35	>35	>35	^a
Day 1	11 (5)	12 (12)	10 (8)	$A = B = C$
Day 3	2 (1)	2 (1)	2 (1)	$A = B = C$

M = mean, *SD* = standard deviation.

* Significant at a $p < 0.05$ level.

^a The difference between prepartum levels (week 38) and day 1 and day 3 could not be analyzed because the available kit did not measure above 4.500 pg/ml for estrogen and above 35 pg/ml for progesterone; so all prepartum levels had the same magnitude.

Finally, we explored the contribution of potential confounders such as maternal age and parity on the association between depression status and postpartum hormone levels. While there were no significant differences regarding maternal age between the 3 groups (MDD at birth, MDD lifetime and NC), at the bivariate level maternal age was correlated with postpartum SDS depression scores at day 5 ($r = -.26, p < .05$) and EPDS depression scores at 6 months ($r = -.22, p < .05$), in that older women were less likely to be depressed. We therefore repeated all analyses testing effects of depression status on differences in day 1 and day 3 hormone levels controlling for maternal age.

All analyses were also repeated using only data for primiparous women ($n = 142/192, 68.3\%$), and results regarding depression status and day 1 to day 3 hormonal levels did not differ as compared to the whole sample. [Wilks' Lambda $F(2,47) = .52, p = .60$ for estrogen day 1 to day 3, and Wilks' Lambda $F(2,47) = .97, p = .45$ for progesterone day 1 to day 3].

3.4. Relationship in magnitude of estrogen and progesterone drop after childbirth to depression scores at 6-months postpartum

Results of non-parametric correlational analyses (Spearman's rho) revealed no significant relationship between magnitude of estrogen drop from day 1 to day 3 and 6-months postpartum depression scores on the EPDS (Spearman's rho = $-.04, p = .74, ns$). Similarly, drop in progesterone from day 1 to day 3 after childbirth did not predict depression scores at 6 months (Spearman's rho = $-.12, p = .28, ns$).

3.5. Rates of depression in prepartum, peripartum and postpartum

Rates of depression measured by the SDS using a cut-off of 48 (raw score; a score of 48 excludes very light forms of depressive symptomatology CIPS, 1996) for the whole sample were compared across the 3 different time-points. In late pregnancy the percentage of women who had self-identified as moderately depressed was 12.6% ($n = 24/192$); this percentage dropped to 5.8% ($9/155$) on day 3, and 9.2% ($n = 8/87$) on day 5 postpartum. The SCID diagnosed 14 women (13.3%) as depressed on day 5. The decline of the SDS scores was significant in the signed rank

test from prepartum to day 3 ($N = 154, p < .0004; sig.$) and from prepartum to day 5 ($N = 86, p < .008; sig.$). Women with MDD at birth showed higher EPDS scores at 6 months compared to lifetime MDD and normal control subjects, this difference reached significance $F(2,88) = 3.3; p < 0.05$. See Table 3.

4. Discussion

4.1. Hormonal changes and peripartum and postpartum depression

This study could not detect a relationship between depressive symptoms at the end of pregnancy and in the first five days after birth and both estrogen and progesterone total levels and magnitude of change of estrogen and progesterone. Interestingly, we were not able to find hypogonadal levels of estrogen in women with peripartum depression, but instead a tendency of higher levels of estrogen in women who suffered from depression early after birth (day 3) compared to non-depressed. This is in accordance with two studies which had assessed hormone levels in relationship to blues symptoms (postpartum dysphoria) showing higher levels of estradiol and estriol in affected women (Heidrich et al., 1994; O'Hara et al., 1991b). If postpartum dysphoria represents the mild end of affective disorder, both studies evaluating the blues and hormonal factors, especially estrogen, find elevated rather than decreased levels in those women who suffer from affective symptoms. However, our results also show that any potential hormonal contributions to mood symptoms in early postpartum are very complex. While there was suggestion in our data that the depressed group had higher estrogen levels at day 3, repeated measure analyses of variance showed that the change in hormonal levels from day 1 to day 3 did not significantly differ across the diagnostic groups.

The withdrawal hypothesis was investigated in a study including 182 women with an analysis of potential biological and psychosocial causative factors for postpartum blues (O'Hara et al., 1991b). This study indicated that women with blues symptoms had higher levels of free estriol and total estriol in late pregnancy and at day 2 and 3 postpartum; there was a weak support for the hypothesis of the association of estrogen withdrawal and blues. With respect to postpartum depression there are two reports about higher ante partum estrogen levels; one study with a small sample ($n = 23$) found higher pre-delivery estrogen levels in the more irritable women (Nott et al., 1976). Also, Gard et al. (Gard et al., 1986) suggested higher levels of prenatal estradiol and estriol to be associated with postpartum symptoms and diagnosis of depression.

On the other hand, no association was observed between estradiol levels and postpartum symptoms in two studies by Kuevi et al. (1983) and Harris et al. (1989). The latter did not find any association of depression 6–8 weeks

Table 3
Depressive symptoms (EPDS score) at 6 months in relation to depressive status at birth

	MDD at birth <i>A</i>	MDD lifetime <i>B</i>	NC <i>C</i>	POSTHOC
<i>N</i>	12	7	70	
<i>M</i>	8.7	3.0	4.9	<i>A > B, C</i>
<i>SD</i>	7.8	2.4	5.0	

N = Number of women, *M* = mean value, *SD* = standard deviation. Analysis of Variance, $F(2,88) = 3.3; p < 0.05$.

postpartum with estrogen, only progesterone was significantly correlated to mood symptoms with an additional influence of feeding methods. This is in contrast with our findings which do not indicate an association of mood with progesterone levels. Nevertheless, feeding method was not assessed in the current study.

O'Hara et al. found lower levels of estrogen when assessing 168 childless and 165 childbearing women regarding current depression, gonadal hormones and psychosocial risk (O'Hara et al., 1991a). These results are in contrast to the findings of the current investigation which found higher levels of estradiol on day 3 in depressed childbearing women. The findings regarding progesterone are consistent with our study; there was no association with depressive status. However, the assessment of depression in O'Hara's study was performed at 6 weeks postpartum, whereas the current investigation assessed peripartum depression on day 5 after birth and postpartum depression at 6 months postpartum. This might have played a role in the different findings of the two studies.

O'Hara et al. state that besides measurement issues the inclusion of patients who have reached some criterion level of severity would probably help to identify hormonal abnormalities.

Regarding blues and concentrations of cortisol and progesterone pre- and postpartum, a study by Harris et al. (Harris et al., 1994) showed that women with maternity blues had significantly higher antenatal and lower postnatal progesterone concentrations than women without blues. This group argues for a possible substitution of progesterone as prophylactic but only for women who breastfeed. In the Cardiff Puerperal Mood and Hormone Study III postnatal depression at 5–6 weeks was related to hormonal correlates and no association with progesterone levels were seen. Consequently progesterone augmentation following delivery as a prophylactic against postpartum depression is discouraged in this study (Harris et al., 1996). Furthermore in a recent review of all data regarding the use of progesterone in the management of postpartum mood disorders and its use as treatment or prophylaxis is discouraged because of a total lack of controlled randomized trials (Granger and Underwood, 2001). This is supported by the results of the current study where no association of levels of progesterone with postpartum mood could be found.

4.2. Rates of depression from pre- to postnatal time

In our study, higher rates of depressive symptoms at the end of pregnancy than in the peripartum period, with an increase at 6 month postpartum, were detected. Interestingly, depressive symptoms decreased significantly from week 38 to the days after delivery. The SDS depression rates found in our sample are consistent with findings in other studies using self-rating scales (e.g., EPDS) evaluating late pregnancy and early postpartum (Evans et al., 2001; Heron et al., 2004; Matthey et al., 2000). The SCID

shows a prevalence of 13.3% on day 5, while the SDS shows a rate of 9.2% 5 days after birth. The SDS might be underestimating depressive symptoms in a peripartum sample, the SCID being a much more reliable diagnostic measure. Our study supports findings from other studies that previous depressive episodes are the most powerful predictor for postpartum depression, nearly 80% of those who had an episode prior to the birth developed postpartum depression and those who had a previous episode had a 50% risk to develop depression at birth (Marks et al., 1992; Beck, 2001).

This study explored potential contributions of estrogen and progesterone to the presence of peripartum depression. Our results highlight the complexity of these potential associations; while depression may be in part related to higher levels of estrogen on postpartum day 3, the drop of hormone levels (particularly estrogen) from day 3 to day 5 does not differentiate between diagnostic groups. In addition, we explored that these results are robust for primipara and independent of maternal age. However, the results were in contrast to the current hypotheses of estrogen withdrawal or hypogonadal levels for peripartum depression. Several limitations may have impacted our findings. Hormone levels were only taken at three time-points and only until postpartum day 3. This allowed for the evaluation of level variations but did not permit to evaluate the development of hypogonadal states, which would only show at a later time point. Furthermore, as it was the case in previous studies (O'Hara et al., 1991a; O'Hara et al., 1991b) only the total fraction of gonadal hormones was evaluated but not bound and free fractions separately. The mode of infant feeding, which may have altered hormone levels – as bottle-feeding rather than breastfeeding can alter hormonal levels in the peripartum period (Harris et al., 1994; Hendrick et al., 1998) – could not be assessed. A further limitation of the actual study is the low number of subjects with depression; therefore the current non-significant findings should be interpreted with great caution. Further studies are needed to address these limitations.

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