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Short Communication

Withdrawal of plasma estradiol is associated with increased anxiety reported by women in the first 12 hours after delivery

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ABSTRACT

The aim of this study was to verify if the fall of plasma concentrations of steroid hormones in the first 12 h postpartum would be associated with changes in the same period in the emotional state of healthy women. Subjective and hormonal data were collected from 14 women (28.5 ± 7.1 years old) at zero (only hormones), 1, 2, 6 and 12 h after delivery. Subjective measures were taken using the Visual Analogue Mood Scale (VAMS), which consists of four factors (anxiety, sedation, discomfort, and cognitive impairment). Cortisol was measured by radioimmunoassay and estradiol and progesterone by chemiluminescence immunoassay. Women reported a significant increase in anxiety (relative increase: 43.8% ± 77.6) and discomfort (125.9% ± 218.5) within the 12 h postpartum. There were also significant decreases in the plasma concentration of estradiol (relative decrease: 96.5% ± 3.1), progesterone (78.1% ± 8.7) and cortisol (71.7% ± 18.0). The relative decrease in estradiol concentrations was significantly correlated with the relative increase in anxiety. No significant associations between progesterone and cortisol concentrations and subjective measures were observed. Changes of estradiol but not of progesterone and cortisol concentrations were associated with changes in the reported emotional state of healthy women in the immediate postpartum period. The role of this association as a predictor of mood disorders in the postpartum period should be explored in further studies.

1. Introduction

Transient mood changes, also known as postpartum blues, occur in 15–85% of women in the immediate puerperium (Henshaw, 2003) and are usually described as predictors of postpartum depression (DPP) (Reck et al., 2009). DPP is a severe condition affecting around 10–22% of the mothers (Gaynes et al., 2005). In recent reviews investigating predictors of postpartum depression, besides the role of postpartum blues and environmental stressors, hormonal changes were addressed as possible important biomarkers for this period (Garcia-Leal et al., 2017; Guintivano et al., 2018).

Although fluctuations in hormonal levels occur in different female reproductive stages (Burger et al., 2002), it is in the peripartum period that changes in the hormonal environment are more significant. The placental steroidogenesis is responsible for significant changes in cortisol, estradiol and progesterone concentrations, which are significantly elevated at the end of the pregnancy but exhibit an abrupt decline in the immediate postpartum period (Kammerer et al., 2006).

Mood changes commonly observed in the peripartum period may be associated with these pronounced changes in the hormonal environment (Bloch, 2000). However, the results of studies that evaluated possible associations between hormone and mood symptoms in postpartum are contradictory (Garcia-Leal et al., 2017). Particularly regarding the immediate postpartum, a negative correlation of the transient mood changes in blues with oestriol/estradiol concentrations but not with progesterone and cortisol concentrations has been described (O'Keane et al., 2011). In another study, depressed postpartum women had lower levels of estradiol and cortisol compared to euthymic postpartum women, but the severity of depressive symptoms correlated positively only with cortisol (Saleh el et al., 2013). On the other hand, negative correlations of depression scores with estradiol and progesterone but not with cortisol were also described (Zou et al., 2009).

In its turn, animal models suggest that abrupt withdrawal of hormones rather than gradual withdrawal may induce anxious or depressive behavior (Doornbos et al., 2009; Suda et al., 2008), implying that the kinetics of the drop in hormones may influence behavior. Thus, the aim of this study was to evaluate if the kinetics of the decline of estradiol, progesterone and cortisol plasma concentrations that occur in

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the 12 h immediately after delivery are associated with mood changes. We hypothesized that the sharper the decline of the hormonal concentrations, the higher will be the changes in the subjective state.

2. Methods

2.1. Participants

The sample was composed of women admitted to the delivery room of obstetric units linked to the Ribeirão Preto Medical School, University of São Paulo, Brazil. Women, aged at least 18 years old, in labor and admitted between 8 a.m. and 12 a.m., with cervical dilatation higher than 5 cm, were invited to take part of the study. The period of inclusion was restricted between 8 a.m. to 12 a.m. considering the higher possibility of delivery during the day shift, and this would also allow the completion of a 12-hour follow-up. The exclusion criteria were the use of psychotropic drugs, occurrence of mental disorders or other medical conditions. The local research ethics committee approved the study (process n° 3169/2011). Women who spontaneously agreed to participate signed, in duplicate, a term of free and informed consent.

Seventy-one women in labor were invited to take part in the study; however, 43 refused to participate, mainly due to the intense discomfort and pain caused by the labor. Among the 28 who agreed, 13 did not have their delivery in the morning period, and one refused to complete the study. The final sample consisted of 14 women.

2.2. Subjective measures

The Visual Analogue Mood Scale (VAMS) translated to Portuguese (Zuardi and Karniol, 1981) from the original VAMS (Norris, 1971), was used. Given the transcultural influence in the interpretation of the translated scale, factorial analysis were conducted as well as adaptations in the terminology of the VAMS factors (Parente et al., 2005; Zuardi et al., 1993). VAMS is a self-report instrument, composed by 16 items. The items are distributed into four factors, named as follows: 1) anxiety, composed by the items calm/excited, relaxed/tense, and tranquil/troubled; 2) sedation, composed of alert/drowsy and attentive/dreamy; 3) cognitive impairment, composed of quick witted/mentally slow, proficient/incompetent, energetic/lethargic, clear headed/muzzy, gregarious/withdrawn, well-coordinated/clumsy, and strong/feeble; and 4) discomfort, composed of the items interested/bored, happy/sad, contented/discontented, and amicable/antagonistic. The VAMS was completed by the participants immediately before blood collection (described below), at 1 (T1), 2 (T2), 6 (T6) and 12 h (T12) after delivery.

2.3. Hormonal measurements

For the dosage of cortisol, estradiol and progesterone, 10 ml of blood were collected on five occasions: immediately after delivery (T0), and at 1 (T1), 2 (T2), 6 (T6) and 12 h (T12) after delivery. An antecubital vein was punctured by means of a flexible catheter (abbocath), and the venous access was maintained throughout the procedures with saline solution.

Shortly after blood collection, the samples were centrifuged at 3000 rpm for 10 min, and the plasma was stored at −20 °C until the time of dosing. Cortisol levels were measured using radioimmunoassay. Estradiol and progesterone were measured by chemiluminescence immunoassay, and the result was generated by autoanalyzer IMMULLITE 2000 Siemens System, with a LIS interface.

2.4. Statistical analysis

The Statistical Package for the Social Sciences (SPSS, Inc. in Chicago, USA, version 20.0) was used for the statistical analysis. Descriptive statistics included: percentages for categorical (nominal) data; and means for continuous data. For hormonal and subjective variables, we conducted the Friedman test to examine whether there were significant changes over time, considering the following time points: immediately upon delivery (T0, only for hormonal measures) and 1 (T1), 2 (T2), 6 (T6) and 12 h (T12) after delivery. For the *post hoc* analysis, we conducted Wilcoxon tests.

To assess the kinetics of changes in hormonal concentrations and mood (VAMS factors), we calculated an index of relative variation (RV %). The RV% of the hormonal levels was obtained by the formula: {[(T0 - T12)*100]/T0}. In turn, the RV% of the VAMS factors was evaluated by the formula: {[(T12 - T1)*100]/T1}. Spearman's test was used to calculate the correlations between hormonal changes and mood changes over 12 h.

A p-value < 0.05 was considered significant.

3. Results

3.1. Features of the sample

The participants mean (± SD) age was 28.5 ± 7.1 years (range from 19 to 42) and 9.5 ± 2.8 (range from 4 to 15) years of schooling. The majority of women was white (71.4%), married (85.7%) and employed (57.1%). More than three quarters of women were multiparous (78.6%) and 71.4% had cesarean delivery with epidural analgesia. The mean gestational age was 39.2 ± 1.1 weeks (range from 37.4 to 41.1). The newborns (50.0% female) weighed on average 3.47 ± 0.39 kg (range from 2.97 to 4.38), and the proportion of the Apgar test scores at 1 and 5 min equal or higher than 7.0 were, respectively, 92.9% and 100%. All the babies were in the room with their mother and were breastfeeding.

3.2. Subjective measures

As seen in Fig. 1, there were statistically significant changes in the four factors of the VAMS during the 12 h after delivery (Friedman test: anxiety, $p = 0.026$; sedation, $p = 0.026$; cognitive impairment, $p = 0.020$; and discomfort, $p < 0.001$). *Post hoc* tests showed a significant increase between T6 and T12 for the discomfort factor ($p = 0.002$) and a significant decrease between T2 and T6 for the sedation factor ($p = 0.008$). From T1 to T12, there was a significant increase in the anxiety ($p = 0.023$) and discomfort ($p = 0.002$) factors. The cognitive impairment decreased significantly between T1 and T2 ($p = 0.039$) and increased between T6 and T12 ($p = 0.026$).

The relative variation (RV%) from the first hour to the 12th hour after delivery showed an increase in the discomfort (125.9% ± 218.5) and anxiety (43.8% ± 77.6) factors but not in the sedation (2.3% ± 75.0) and cognitive impairment (0.9% ± 26.8) factors.

3.3. Hormonal measures

Fig. 2 shows the variation in hormonal concentrations over 12 h after delivery. There was a statistically significant decrease (Friedman test, $p < 0.001$) of the concentrations of the three hormones in all measured periods. There was also a significant relative decrease in the plasma concentration of estradiol (96.5% ± 3.1), progesterone (78.1% ± 8.7) and cortisol (71.7% ± 18.0).

3.4. Correlational analysis

We found a significant correlation between estradiol RV% and anxiety RV% (rho = 0.593, $p = 0.033$), i.e., the greater the relative variation (decrease) of the plasma estradiol, the greater was the relative variation (increase) of the subjective anxiety. No significant correlations were found between other mood changes (discomfort, cognitive impairment, and sedation) and hormones (progesterone and cortisol). Fig. 2 shows the spearman correlation between anxiety scores (RV%)

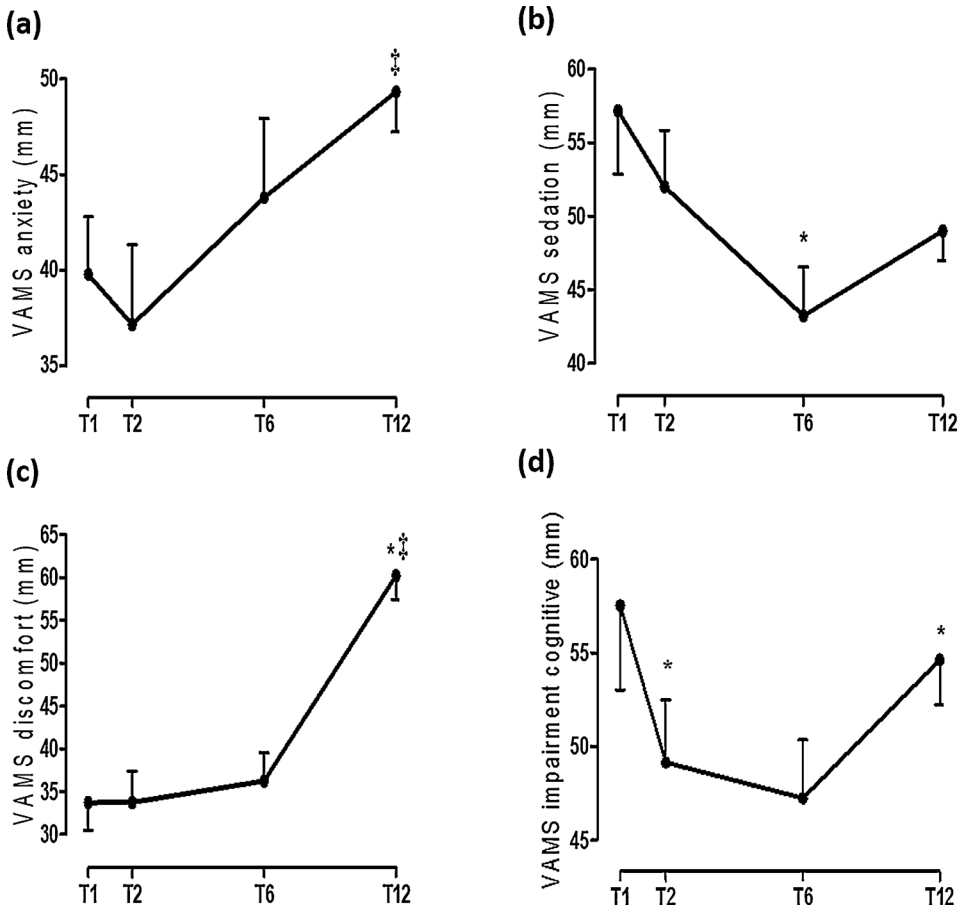

Fig. 1. Mean and standard error of the scores of anxiety (a), sedation (b), discomfort (c) and cognitive impairment (d) of the VAMS factors, over time. (T1) 1 h, (T2) 2 h, (T6) 6 h and (T12) 12 h after delivery; *p < 0.05 for time compared with the previous time; ‡p < 0.05 for T12 compared with T1.

and estradiol, cortisol, and progesterone levels (RV%).

4. Discussion

We aimed to evaluate the occurrence of associations between changes in hormonal concentrations and changes in the subjective state of women immediately after delivery. Our findings showed that in the 12 h postpartum, there was a significant decrease in the plasma concentrations of estradiol, progesterone and cortisol as well as a significant increase in subjective complaints of anxiety and discomfort. Mainly, we observed that changes in anxiety scores correlated significantly with changes in plasma estradiol.

We found that the higher the relative reduction in estradiol at 12 h postpartum, the higher was the relative increase in anxiety. These results are consistent with animal studies showing that abrupt withdrawal of gonadal hormones is associated with anxious or depressive behavior (Doornbos et al., 2009; Suda et al., 2008). The positive correlation between a higher drop in estradiol levels and increased anxiety observed in our participants may suggest an individual susceptibility to abrupt changes in the hormonal environment, which can represent a risk for mood disorders in the postpartum period (Bloch, 2000; Doornbos et al., 2009). Gonadal hormones, especially estradiol, modulate serotonergic receptors, which are widely implicated in the neurobiology of depression and anxiety (Graeff et al., 1996) and appear to respond more rapidly to changes in the gonadal hormones (Doornbos et al., 2009). In ovariectomized rats, a fall in estrogen concentrations induced changes in the expression of 5-HT2 receptors in the anterior frontal cortex, cingulate gyrus and nucleus accumbens (Cyr et al., 1998), brain regions associated with mood, behavior and cognition.

In the present study, no associations were found between subjective changes and progesterone concentrations, which is in agreement with previous data showing significant associations between estradiol and mood symptoms but not with progesterone (O'Hara et al., 1991). However, other studies have shown alterations of both estrogen and progesterone (Feksi et al., 1984; Zou et al., 2009) or progesterone alone (Abou-Saleh et al., 1998) in postpartum women with mood disorders. It is noteworthy that no previous study evaluated hormone levels in the first hours immediately after delivery.

Subjective changes also had no correlation with plasma cortisol. Cortisol is the end product of hypothalamic-pituitary-adrenal (HPA) axis activity; its functioning, after delivery, presents a deregulated pattern that would be associated with adaptation challenges to the environment (Magiakou et al., 1996). However, in animal models, while levels of gonadal hormones in two groups of rats were withdrawn either gradually or abruptly, corticosterone levels did not differ between the groups (Doornbos et al., 2009).

In particular, the subjective measures of sedation and cognitive impairment may have been influenced by obstetric and diurnal variables. Thus, during the 1st postpartum hour, most of the mothers were under the effect of labor fatigue and/or analgesia effects, which probably implied a cognitive decline. After this period, there was a cognitive improvement, followed by another decline between 10:00 p.m. and 12:00 p.m. when most of the mothers showed somnolence. These conditions probably reflected in a cognitive deterioration. In consonance, we found that alterations in sedation followed a pattern similar to that of the cognitive changes curve.

With respect to the discomfort factor, there are no reports in the literature addressing associations between discomfort and/or anxiety in the care of the newborn specifically during 12 h period after childbirth. We also did not find studies analyzing changes in oxytocin or prolactin

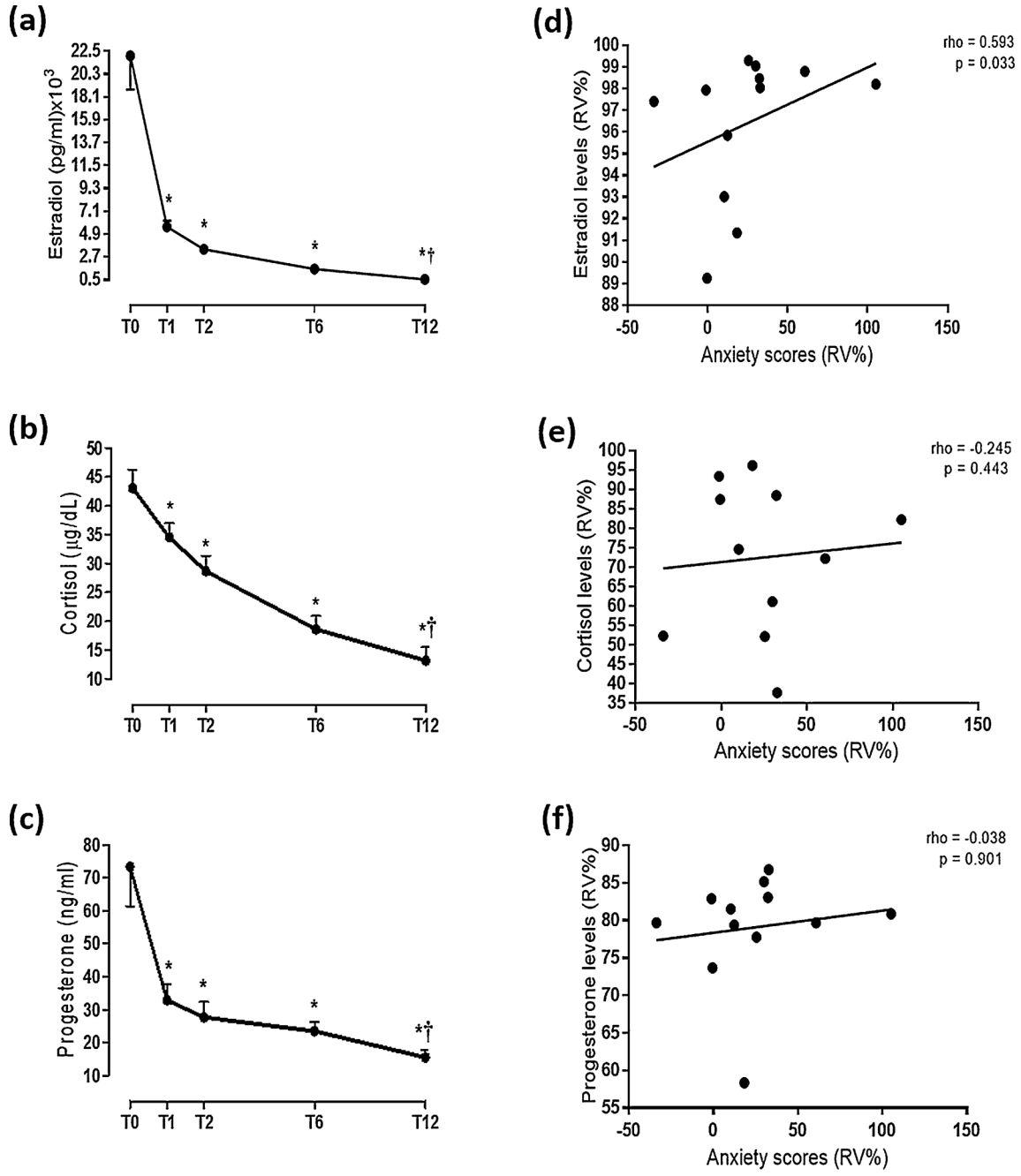

Fig. 2. Mean and standard error of estradiol (a), cortisol (b) and progesterone (c) levels, over time; and spearman correlation between anxiety scores (RV%) and estradiol levels (RV%) (d), cortisol levels (RV%) (e), and progesterone levels (RV%) (f). (T0) Immediately upon delivery and (T1) 1 h, (T2) 2 h, (T6) 6 h and (T12) 12 h after delivery; (RV%) relative variation; *p < 0.05 for time compared with the previous time; †p < 0.05 for T12 compared with T0.
Note: For a better graphic illustration of the correlational figures, one participant was omitted. This exclusion did not alter the statistical significances.

levels during this period. Despite that, one study showed that on the second postpartum day plasma concentrations of oxytocin and prolactin were mediated by other obstetric variables, such as epidural analgesia (Jonas et al., 2009). It is important to highlight, however, that during breastfeeding high levels of prolactin and oxytocin may affect the bonding process between the mother and the newborn (Olza-Fernández et al., 2014). In our study, all mothers were next to their child and breastfeeding.

The greatest limitation of this study is the small sample size, which can be understood when considering the inherent difficulty for a woman in labor to adhere to a research protocol. Another limitation is the fact that most deliveries were of the cesarean type, which is much higher than the rate of caesarean sections in the obstetric center under study. We speculate that women admitted to a caesarean section compared to women in normal labor could be in less discomfort and pain and, consequently, more prone to taking part in a study. The influence of the type of delivery on the hormonal changes will need to be considered in future studies. Finally, due to the sample size, it not was possible to perform multifactorial analysis to assess the influence of sociodemographic or obstetrics variables on anxiety and mood during the analyzed period. We were also not possible to create additional subgroups for comparation.

Additionally, we cannot rule out whether the collection of subjective measures was influenced by intervening variables, such as the presence of relatives and health staff, the behavior of the baby and the number of patients in the room and their companions, during the

assessments. On the other hand, the strengths of the present study include the use of the VAMS, a well-validated scale for the measurement of changes of subjective feelings over short periods, and a design that includes subjective and hormonal measurements taken simultaneously at 12 h postpartum, which allowed a direct comparison of these measures in the very early postpartum period.

Finally, a recent review investigated the role of reproductive steroids in the regulation of mood and behavior, suggesting an etiopathogenic relevance of hormonal changes in the alteration of mood of women in the peripartum period (Schiller et al., 2016). In this sense, the present study corroborates with these findings.

In conclusion, the kinetics of abrupt withdrawal of estradiol plasma concentrations but not withdrawal of progesterone or cortisol were associated with increased levels of anxiety in the first 12 h postpartum. These data corroborate the role of hormones in emotional processes and provide evidence for further studies aiming to explore the role of the kinetics of changes in hormonal concentrations in the very first few hours postpartum as a risk factor for depression or other postpartum disorders. The identification of women with greater individual vulnerability to the emergence of emotional disorders associated with abrupt changes in hormonal concentrations may help in the development of preventive strategies. Also, we emphasize the importance of a specific evaluation and intervention during immediate postpartum in case of relevant anxiety increase.

Conflict of interest

None.

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