

Maternal depression and offspring's cortisol concentrations in a Brazilian sample

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Abstract

Postpartum depression (PPD) is believed to cause a variety of child developmental problems, including alterations of the hypothalamic-pituitary-adrenal (HPA) axis function. The association of maternal depression with children's salivary cortisol level was investigated in three different moments: at birth (N=58), at four (N=64) and 36-month (N=81) after delivery. Mothers were screened for PPD at four months and for depression at 36-months after delivery using Edinburgh Postnatal Depression Scale (EPDS). Through ANOVA analysis results revealed a marginal difference of moderate effect size on cortisol concentration with higher levels for newborns whose mothers would be later screened for PPD when compared with control group. Contrary to our hypothesis we did not find this difference at four and neither at 36-months. Assuming that infants of mothers at risk for depression are born with slightly higher cortisol baseline, this difference among groups could not be verified on subsequent analysis at four and 36-months.

Keywords: Depression; Postpartum depression; Childhood development; Cortisol; Stress.

Depressão materna e concentração de cortisol de recém-nascidos em uma amostra brasileira

Resumo

Acredita-se que a depressão pós-parto (DPP) possa prejudicar diversos aspectos do desenvolvimento infantil, incluindo alterações das funções do eixo Hipotálamo-pituitária-adrenal (HPA). A associação entre depressão materna e nível de cortisol salivar dos filhos foi investigada em três amostras brasileiras diferentes: ao nascimento (N=58), aos quatro (N=64) e 36 meses (N=81) após o parto. Mães preencheram a Escala de Depressão Pós-parto de Edinburgh aos 4 e 36 meses após o parto. Por meio da ANOVA resultados indicaram diferença marginal com tamanho de efeito moderado na concentração de cortisol com maiores concentrações em recém-nascidos cujas mães desenvolveram depressão pós-parto em comparação ao grupo controle. Contrariando nossa hipótese, esta diferença no nível de cortisol basal não foi encontrada aos quatro e aos 36 meses. Admitindo que os filhos de mães com sinais de DPP nascem com níveis basais de cortisol ligeiramente mais altos, esta diferença não foi verificada em momentos posteriores.

Palavras-chave: Depressão pós-parto; Depressão; Desenvolvimento infantil; Cortisol; Estresse.

La depresión materna y la concentración de cortisol del recién nacido en una muestra brasileña

Resumen

Se cree que la depresión post-parto (DPP) causa una variedad de problemas del desarrollo, incluyendo alteraciones funcionales en el eje hipotálamo-hipofisario-adrenal (HPA). Nuestro objetivo era el investigar la posible asociación entre niveles de cortisol salivar en hijos y depresión materna en tres momentos distintos: 2 días después del parto (N=58), cuatro meses después (N=64) y 36 meses después (N=81). Las madres completaron la Escala de Depresión Postparto de Edimburgo a las 4 y 36 meses después del parto. Un test de ANOVA mostró diferencias marginales de efecto moderado en los niveles de cortisol en hijos de madres con DPP comparados con grupo de control. Suponiendo que los hijos de madres con DPP tienen niveles de cortisol ligeramente elevados al nacer, no se observaron estas diferencias en otros momentos.

Palabras clave: Depresión; Depresión post-parto; Desarrollo infantil; Cortisol; Estrés.

Epidemiologic studies have shown that after delivery one in five women will experience a relatively disabling and persistent form of mood disturbance known as postpartum depression (PPD) (O'hara & McCabe, 2013) characterized by emotional lability, lack of interest on daily activities, anxiety, feelings of incapacity, among other symptoms, that occur few weeks after delivery although studies have shown that depressive symptoms can be detected antenatally (Nierop, Bratsikas, Zimmermann, & Ehlert, 2006; Verreault et al., 2014). PPD has been associated with disrupted mother-infant interaction and the risk of child developmental and behavioral problems (Brennan et al., 2008; Essex, Klein, Cho, & Kalin, 2002; Herrera, Reissland, & Shepherd, 2004; Pearlstein, Howard, Salisbury, & Zlotnick, 2009; Morais, Lucci, & Otta, 2013). A significant relationship between mother PPD with higher cortisol levels in infants, children and adolescents has also been shown, (Brennan et al., 2008, Luecken et al., 2013), possibly due to unpredictable and stressful maternal caregiving. Therefore, and perhaps because sample collection for cortisol measurement in young infants may appear as a challenge to many researchers, no previous study, as far as we know, has evaluated how early this impact might affect the HPA in newborns. However, early detection of the deleterious impact of PPD on infant's HPA functioning would help the implementation of preventative care measures.

During the last decade, a significant number of studies extended the body of evidence of the deleterious effects of exposure to maternal depression and anxiety during pregnancy and the months following the birth on children cortisol levels (O'Connor, Bergman, Sarkar, & Glover, 2013; Fernandes, Stein, Srinivasan, Menezes, & Ramchandani, 2014). Frequent over activation of the HPA has been associated with an increased risk for emotional and behavioral problems as well as subsequent mental illness (Baumeister, Lightman, & Pariante 2014; Brennan et al., 2008). These experiences along with poor protective relationships can lead to disruptive physiologic responses and produce "biological memories" that enhance risk for later diseases (Garner et al., 2012; Gunnar, Talge, Herrera, 2009). In contrast, responsive caregiving provided by mothers (despite their depression), fathers (de Mendonça, Bussab, Lucci, & Kärtner, 2015) or other caregivers, may mitigate the deleterious effects of maternal depression on children (Gunnar, Talge, & Herrera, 2009).

Increased concentrations of salivary cortisol were found by Brennan et al. (2008) in 6-month old infants born from depressed women independently of delivery conditions. A longitudinal study showed that

PPD has a stronger effect on toddler cortisol levels and reactivity to stress than other forms of maternal stress (Essex, Klein, Cho, & Kalin, 2002). Whereas a marked decrease in cortisol response when facing mild stressors occurs between 2 and 4-months in the infants of healthy women (Gunnar & Donzella, 2002); such a dampened response may not occur in the infants of depressed women (Azar, Paquette, Zoccolillo, Baltzer, & Tremblay, 2007).

One risk factor for PPD is heightened psychological and cortisol reactivity in response to psychosocial stress already during pregnancy (Nierop, Bratsikas, Zimmermann, & Ehlert, 2006) with, as a consequence, fetus exposure to higher cortisol concentrations. While cortisol is necessary for normal brain development and late gestational lung maturation (Peña, Monk, & Champagne, 2012; Howerton, & Bale, 2012), fetal exposure to high concentrations in utero is thought to affect the prefrontal cortex, hippocampus and amygdala. These brain areas, besides to be involved with executive functioning, emotion regulation, attention, memory and fear, also regulate the HPA axis mechanisms (Beijers, Buitelaar, & de Weerth, 2014). It seems, therefore, reasonable to think that newborn's alterations in HPA function of women who will develop PPD may possibly be detected at birth, anticipating PPD diagnosis. Our aim was to examine if the effects of maternal depression on the function of the infant HPA axis can already be detected in the newborn and confirmed 4-months and 36-months later. We hypothesized that infants whose mothers will develop PPD have higher salivary cortisol concentrations 2-3 days after birth, higher cortisol baseline and would show a stronger cortisol response to stress at 4 and 36-months of age when compared to infants of non-depressed women.

Methods

The samples were comprised of infants whose mothers participated in a larger four years longitudinal study of postpartum depression in São Paulo, Brazil. Women were recruited from Public Health Centers during the last trimester of pregnancy, and had their delivery at the Hospital of the University of Sao Paulo (N=123). Only full term healthy infants were included in the study.

Since not all dyads were present in all moments, the study was conducted with three subsamples, analyzed separately. The first was composed by dyads whose babies had their cortisol measured 2-3 days after birth and mothers were screened for PPD 4-months after delivery (N=58). The second subsample was composed

by infants and their mothers who were brought to our laboratory for pediatric clinical examination four months after delivery when cortisol was measured again (64). From this group only 17 were infants whose mothers showed signs of PPD. In order to equalize the number of participants of each group we selected randomly (through 'select cases' from SPSS menu) 17 infants from non PPD group, composing a sample of 34 infants. Three years later, mother-child dyads were invited to return to our laboratory for developmental assessment of the children, and for new cortisol measures (N=81). As only 23 mothers showed signs of depression, we randomly selected 23 infants from the non PPD group to equalize the number of participants and 46 infants composed the 36-months sample.

Informed consent was obtained from all the participating women after they received printed and oral information about the study. This study received approval for research with human participants from the Ethics Committees of the Psychology Institute and the Hospital of São Paulo University as well as of the São Paulo City Council. Table 1 summarizes health and demographic characteristics of each sample.

Cortisol was measured in saliva samples collected from the newborns (one single sample from each infant) 2-3 days after birth at the hospital. Also, two samples were collected at each interview at 4 and 36-months postpartum at our laboratory at the Psychology Institute of the University of São Paulo, prior and after a 30 minutes clinical examination that aimed to assess head circumference, weight, height as well as language and motor skills expected for that age. None of them suffered from any condition known to influence cortisol levels. Although circadian variation in cortisol production has not been clearly established in young infants previously (Peña, Monk, & Champagne, 2012), all samples were collected during the same period of the day (10h am to 13h pm). Mothers were instructed to not feed their infants 1 hour before sampling. Sterile cotton swabs were used (cotton devices are approved by the manufacturer of the assay for saliva collection aiming cortisol measurement) and the saliva retrieved by centrifugation was immediately stored at -20°C. Cortisol concentrations were measured with a commercial enzyme immunoassay (Salimetrics® State College, PA) following the manufacturer's protocol.

TABLE 1
Demographic and health characteristics of mothers and children from each of the samples:
birth, 4-months and 36-months.

<i>Socio-demographic characteristics</i>	<i>Birth</i>	<i>4-months</i>	<i>36-months</i>
	<i>% (N)</i>	<i>% (N)</i>	<i>% (N)</i>
Infants			
Girls	59.3% (35)	47.1% (16)	64.4% (29)
Boys	40.7% (24)	52.9% (18)	35.6% (16)
Mothers			
Primiparous	42.4% (25)	38.2% (13)	43.5% (20)
Normal delivery	52.5% (31)	52.9% (18)	53.3% (24)
Instrumental delivery	20.3% (12)	20.6% (07)	26.7% (12)
Caesarean section	27.1% (16)	26.5% (09)	20% (09)
Desired pregnancy	75.9% (44)	67.6% (23)	73.9% (34)
Lives with partner	84.7% (50)	79.4% (27)	69.6% (32)
Maternal Depression	–	26.6% (17)	25.3% (23)
Previous Episodes of Depression	30.5% (18)	38.2% (13)	31.8% (14)
	<i>Mean (±SD)</i>	<i>Mean (±SD)</i>	<i>Mean (±SD)</i>
Infants			
Apgar at 10th min after birth	9.86 (±0.3)	9.8 (±0.4)	9.8 (±0.3)
Birth Weight (g)	3324 (±455)	3287.5 (±418)	3168.8 (±406)
Birth Length (cm)	49.2 (±2.4)	49.5 (±2.5)	48.6 (±2.1)
Head Circumference (cm)	34.87 (±1.1)	34.65 (±1.2)	34.4 (±1.2)
Mothers			
Age at delivery (years)	24.73 (±6.1)	24.6 (±5)	24.4 (±5.7)
Mother's education (years)	8.89 (±2.6)	8.9 (2.8)	8.4 (±2.9)

This assay sensitivity is 0.19 nmol/L. Intra- and inter-assay coefficients of variation were all lower than 12%. Samples were assayed in duplicate. Concentrations of cortisol were obtained as $\mu\text{g/dL}$ and converted to nmol/L of saliva.

Four months after delivery Edinburgh Postnatal Depression Scale (EPDS) (Cox, Holden, & Sagovsky, 1987) was used to assess postpartum depressive mood. A validation of the EPDS in a sample of Brazilian women showed that the most appropriate cut-off score in our country context [11/12] provided 72% sensitivity and 89% specificity (Santos, Martins & Pasquali, 1999). Therefore, scores of 12 or more were considered suggestive of depression.

At 36-months mother-child dyads were invited to return to our laboratory for maternal mood assessment by means of Edinburgh Depression Scale (EDS) (Cox, Chapman, Murray, & Jones, 1996) and children's developmental screening.

Statistical analysis

a) Preliminary analysis

Statistical analysis was conducted in several steps. Cortisol concentrations were log-transformed to improve the normality of the distribution. Groups of mothers with depressive and non-depressive profile were compared to identify potential confounding variables by means of singular ANOVAs with Brown Forsythe correction (mother's age, infant weight, height and head circumference at delivery) and by means of χ^2 test (type of delivery and infant's sex).

We used GLM to test potential effects of sex, type of delivery as well as infant weight, length and head circumference at birth, four months and 3-years old on cortisol concentrations.

b) Main Analysis

As the subsamples had different numbers of participants, we conducted separate analyses instead of a unique longitudinal one. To test if newborns ($N=58$) salivary cortisol concentration would be different depending on mother's PPD measured 4 to 16 weeks later, we used ANOVA with Brown Forsythe correction. The effect size was determined using Cohen's d . We performed ANOVA with repeated measures on each one of 4 and at 36-months subsample in order to verify if: (a) cortisol concentration would differ between groups of mothers, (b) cortisol concentration would vary before and after a clinical assessment. For each ANOVA with repeated measures we considered depression assessed at the same time cortisol was measured (4 and 36-months).

Analyses were conducted using the software SPSS 21 for windows. For all tests, significance was defined as $p<0.05$.

Results

Preliminary Analysis

Regarding PPD, no significant association was found with mother's age ($F=0.800$, $p=0.373$), type of delivery ($X^2=0.652$; $p=0.722$) neither with newborn outcomes: sex ($\chi^2=2.673$; $p=0.102$), weight ($F=0.292$; $p=0.590$); length ($F=0.464$; $p=0.497$) and head circumference ($F=2.09$; $p=0.648$).

Regarding newborn's cortisol levels 2-3 days after birth, there were no effects of mother's age ($F_{1,55}=0.915$; $p=0.343$), type of delivery ($F=0.652$; $p=0.722$) and newborn outcomes as weight ($X^2=0.307$; $p=0.579$), length ($X^2=0.867$; $p=0.352$), head circumference ($X^2=1.487$; $p=0.223$) and sex ($F=2.673$; $p=0.78$).

Statistical analysis did not show effect of infants' and children's outcomes (sex, weight and height) on baseline cortisol concentrations measured at 4 and 36-months. As these variables were not significant for the model, repeated measures ANOVAs were conducted using only time (before and after clinical assessment) and mother's depression.

Main Analysis

ANOVA with Brown Forsythe correction yielded a marginal effect of PPD on newborns cortisol concentration ($F_{1,39}=3.724$; $p=0.061$) of medium effect-size ($d=0.6$) measured between the second and third day after delivery. Newborns whose mothers had signs of PPD showed higher mean cortisol concentration (2.30 ± 1.0) in comparison with newborns (1.84 ± 0.7) whose mothers did not show signs of PPD measured four months later (Figure 1). We then tested infant cortisol concentration at 4 and 36-months.

Repeated measures ANOVA conducted at four months showed that cortisol concentration increased in response to a clinical examination ($F_{1,29}=1.9479$; $p=0.005$) (Figure 2). There was no significant effect of PPD on cortisol concentration ($F_{1,29}=0.559$; $p=0.461$) nor interaction between PPD and time (before and after clinical assessment) on infant cortisol levels at four months ($F_{1,29}=0.848$; $p=0.365$) as we had hypothesized.

Repeated measures ANOVA at 36-month did not reveal any significant effect on cortisol concentration of PPD ($F=0.335$; $p=0.566$), time (before and after clinical assessment) ($F=0.20$; $p=0.889$), nor the interaction of these factors ($F=0.684$; $p=0.413$). It is notable that 36-month old infants' cortisol levels did not increase in response to the clinical examination (Figure 3).

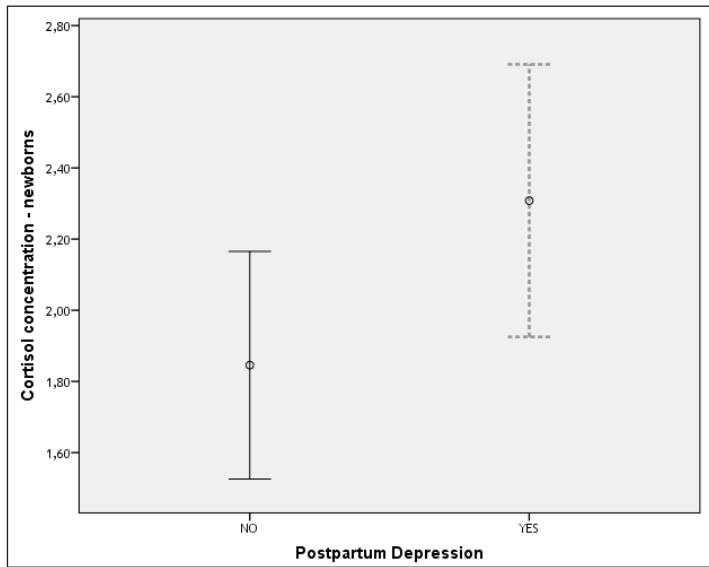


Figure 1. Newborn's cortisol concentration by group of mothers with and without symptoms of postpartum depression.

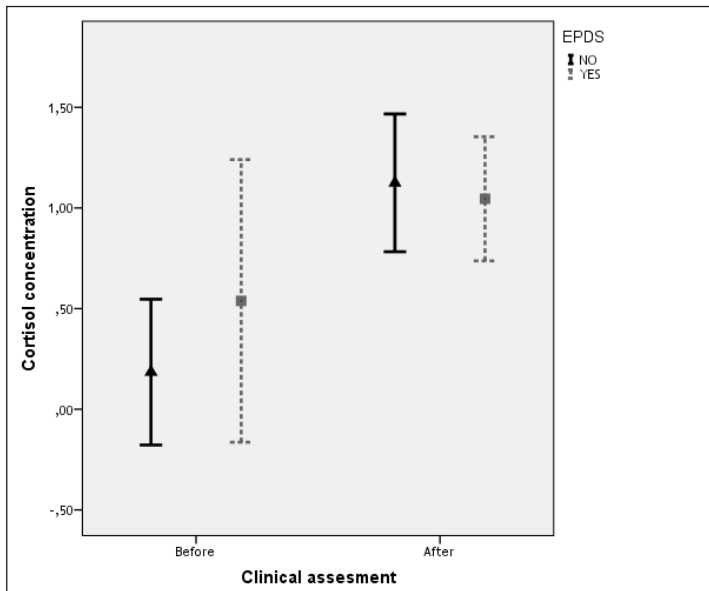


Figure 2. Confidence interval of four-month infant's cortisol concentration before and after clinical assessment by group of mothers with and without signs of postpartum depression (EPDS).

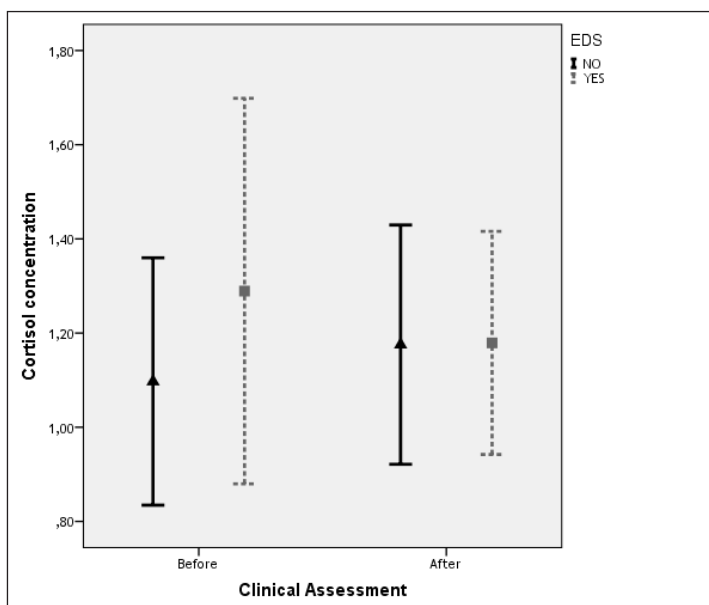


Figure 3. Confidence interval of 3 years old children's cortisol concentration before and after clinical assessment by group of mother with or without depression (EPDS)

Discussion

In our study, 26.6% of the mothers were screened for PPD four months after delivery, and 25.3% showed signs of depression at 36-months. World Estimates of PPD prevalence worldwide vary between 13 and 19% (O'hara & McCabe, 2013), whereas Brazilian studies showed higher percentages (12% to 37.1%) (Santos, Martins, & Pasquali, 1999). Approximately 30% of women reported previous episodes of depression unrelated to pregnancy. Previous episodes of depression are considered an important risk factor for postpartum depression (Aliane, Mamede, & Furtado, 2011).

Infant salivary cortisol concentrations in our study were in the normal range described in the literature. In their review, Maguire and Cowell (2007) described concentrations in the range from 0 to 28 nmol/L. As expected, newborn were significantly higher than 4-month and toddlers levels (Gunnar & Donzella, 2002).

We expected different cortisol levels in 4-month old infants whose mothers experienced PPD. We wondered if this difference would also be found as soon as 2 days after birth and later when the children were 36-months old. Our results support part of our hypothesis: cortisol baseline of newborns whose mothers would meet criteria for PPD diagnosis 12 weeks later differed marginally from cortisol levels of healthy women's newborns. The newborns of the PPD group showed higher mean cortisol concentration when compared with those of non PPD group, although this difference was only marginally significant. Research on PPD has shown that the infant is at risk not only for behavioral problems and delayed cognitive or psychosocial development (Grace, Evindar, & Stewart, 2003), but also for health problems including poor physical growth and an increased risk of gastrointestinal illness (Wachs, Black, & Engle, 2009). Dysregulation of the HPA axis was also reported both in women with PPD (Jolley, Elmore, Barnard, & Carr, 2007) and in their children (Fernandes, Stein, Srinivasan, Menezes, & Ramchandani, 2014; Brennan et al., 2008; Essex, Klein, Cho, & Kalin, 2002; Azar, Paquette, Zoccolillo, Baltzer, & Tremblay, 2007). An upregulated cortisol response to stress during pregnancy has been linked to higher risk of depressive mood in the postpartum period (Nierop, Bratsikas, Zimmermann, & Ehlert, 2006). The impact of prenatal stress and fetal exposure to high concentrations of glucocorticoids on offspring HPA axis functioning has been widely established in rodents and other animal species, including primates (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006).

Contrary to our hypothesis, in our study cortisol levels of 4-month old infants were very similar

in both groups. These data contradict the results of other studies (Brennan et al., 2008) but are consistent with Azar, Paquette, Zoccolillo, Baltzer and Tremblay (2007) who also found no correlation between postpartum depression and four months infant cortisol baseline. However, whereas Azar and colleagues (2007) observed increased cortisol reactivity in babies of mothers suffering lifetime Major Depression, in our study cortisol response to stress did not differ between infants of depressed and non-depressed mothers. Interestingly, however, in our study inter-individual variation of the cortisol response was significantly higher among infants of depressed mothers suggesting a more heterogeneous reactivity to stress.

Again, contrary to our initial hypothesis, cortisol baseline at 36-months was similar in both groups. This result is in line with Azak, Murison, Wentzel-Larsen, Smith and Gunnar (2013) who did not find higher levels of diurnal cortisol on infants of depressed mothers measured at 6, 12 and 18 months, although the authors found a significantly difference when mothers were comorbid for depression and anxiety. Our result is also in accordance to Ashman, Dawson, Panagiotides, Yamada and Wilkinson (2002) that did not find a simple main effect of maternal depression on 7 and 8 years old children's cortisol level. At 36-months we didn't find difference on cortisol variation before and after clinical assessment. One possibility is that clinical assessment was interpreted by the 3 years old children in a pleasant way, where researchers were giving attention and interacting positively.

This result suggests that four months and 3-years old children of depressed women could have adjusted their physiological response according to their reality and may have developed a stress hypo-responsivity that could buffer or protect their development and hence, become stress resilient children (Gunnar & Quevedo, 2007).

Framing our data in the context of the larger longitudinal study is not only important as leads to very interesting considerations: actually, regarding children's development, our results do not support the hypothesis of highly deleterious effects of PPD. It was found, for example, that while some developmental delay in infants of mothers with Postpartum Depression was detected at four, eight and twelve months of age, these children showed better results in fine motricity and language at 12 months (Morais, Lucci, & Otta, 2013). We found also that depressive symptoms do not impair mother-infant interaction (Fonseca, Silva, & Otta, 2010) and that fathers reported being more involved with their three-year-old child when mothers had PPD (Mendonça, Bussab, Lucci, & Kärtner, 2015). These findings confirm that the relationship between postpartum depression

and child development is far from simple or linear and that a range of compensatory factors may balance the damaging effects of maternal mood.

The homogeneity of our sample regarding demographic, social and health conditions of the participants is one of the strength of our study. Its counterpart is the relatively modest size of our sample and not considering comorbidities (such as anxiety) and the quality of mother-child interaction. Future research should consider a longitudinal assay with the same participants over the time, beginning with prenatal depression and cortisol assessment, maternal stress reactivity and measures of dyadic interaction quality.

By means of our results, our conclusion is that, although clear symptoms of postpartum depression only can be assessed several months after birth, PPD can possibly affect basal cortisol concentration of the newborn infant but this difference among groups could not be verified on subsequent analysis at four and 36-months.

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