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Behavioral and cortisol responses to stress in newborn infants: Effects of mode of delivery

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ABSTRACT

Suboptimal birth characteristics have been associated with altered reactivity to stress in infants. However, previous studies have not controlled for mode of delivery, which may influence the neonatal onset of stress responses. The present study assessed stress-related behavior and salivary cortisol before and after an inoculation at two hours after birth, and compared infants born through VD (N = 70) and elective CS (N = 72). The results indicated that overall stress behavior and body movements were increased immediately after inoculation in infants born through CS compared to VD. Infants born through CS did not show significant cortisol increases following inoculation and their overall cortisol reactivity (i.e., AUC_G) was lower compared to infants born through VD. However, unexpectedly, cortisol levels in infants born through VD were highest before inoculation and subsequently decreased. Cortisol was significantly related to behavior in both groups, but in opposite directions. These results support the view that mode of delivery influences neonatal stress reactivity, although future studies should try to disentangle the effects of mode of delivery and related variables.

1. Introduction

Studies of cortisol reactivity in infants have contributed to our understanding of the development of the hypothalamic-pituitary-adrenal (HPA) axis and its relation to behavior (for review see Gunnar, 1992). Contrary to the previous belief that the HPA system is unresponsive to stress at birth (e.g., Cathro et al., 1969), evidence has indicated that cortisol typically increases during crying and other stress-related behaviors elicited by mildly painful procedures in newborn infants (for review see Gunnar, 1989; Jansen et al., 2010). Furthermore, neonatal cortisol reactivity has been related to subsequent temperament (Gunnar et al., 1995; Wilson et al., 2003) and may thus represent an early developmental marker of stress sensitivity.

Various obstetrical and physical characteristics have been associated with neonatal stress reactivity. For instance, Gunnar et al. (1987) found diverging relations between cortisol and behavior in newborn infants categorized as optimal or non-optimal according to gestational age, fetal distress and Apgar scores. Higher cortisol during a medical examination was associated with more efficient behavioral regulation in infants with optimal characteristics, but increased behavioral distress in infants with non-optimal characteristics (Gunnar et al., 1987). Selective cortisol reactivity to noxious stimulation was found in newborn infants with higher birth weights and Apgar scores, in contrast to cortisol increases that generalized to non-noxious stimulation (Gunnar et al., 1988) and failed to habituate after repeated exposure (Gunnar et al., 1991) in infants with less optimal characteristics. Several studies also reported reduced cortisol reactivity in infants with suboptimal biomedical characteristics. Blunted cortisol reactivity was found in preterm newborns who had been exposed to cocaine (Magnano et al., 1992), as well as in two-month old infants with smaller compared to larger head circumference, and lower compared to higher Apgar scores (Ramsay and Lewis, 1995). These differences reversed before six months of age, through an age-related decline in cortisol reactivity that was apparent only in infants with optimal characteristics (Ramsay and Lewis, 1995). Overall, these results have shown that various biomedical characteristics, ranging from gestational age, fetal distress and Apgar scores to birth weight and head circumference, modulate the relation between cortisol and behavior in newborn infants, and may influence the developmental trajectory of the HPA axis.

Recent evidence suggests that mode of delivery is also associated with differences in behavioral and biological responses to stress in infants. By comparing infants born through vaginal delivery (VD) and elective Caesarean section (CS), Bergqvist et al. (2009) found dampened facial and vocal responses to pain and cold stimuli in the former group.

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They also observed that heart rate responses to pain amplified throughout the first few hours after birth, but only in infants born through VD (Bergqvist et al., 2009). While these differences may be explained through transient neonatal analgesia, another study (Taylor et al., 2000) suggested that the effects of mode of delivery on stress reactivity persist beyond the first postnatal days. Eight-week old infants born through CS showed blunted cortisol responses to an inoculation, compared to those born through VD (Taylor et al., 2000). These results raise the question of whether the effects of mode of delivery on cortisol reactivity can be observed in newborn infants. In addition, considering that mode of delivery has not been controlled in previous research on optimality of birth characteristics and cortisol responses, it is possible that some of the findings may be explained, at least partially, by this variable. Finally, and from a broader perspective, the study of the effects of mode of delivery on stress responses in newborn infants may uncover precursors of subsequent emotional and cognitive differences that have been found between infants (e.g., Al Khalaf et al., 2015) and children (e.g., Kelmanson, 2013) born through VD and CS.

The aim of the present study was to investigate the effects of mode of delivery on cortisol reactivity and stress-related behaviors following an inoculation done at two hours after birth. To our knowledge, cortisol reactivity to stress has not been assessed at such a short interval after birth. One potential benefit of such an early cortisol assessment is that it allows the description of HPA activity at a time when birth-related influences (e.g., neonatal analgesia) may still be active, and may shed light on the postnatal onset of this neuroendocrine response. Alternatively, the effects of the recent stress of delivery may obscure individual differences in stress sensitivity. In order to isolate the effect of mode of delivery, we controlled for a host of potential confounds such as gestational age, birth weight and Apgar scores. Based on the previous literature, we expected lower cortisol reactivity in infants born through CS compared to VD (see Taylor et al., 2000), and differences in the relations between cortisol reactivity and stress-related behaviors between these groups (see Gunnar et al., 1987).

2. Material and methods

2.1. Participants

Women admitted to the "Gynia" Private Obstetrics and Gynecology Hospital in Cluj-Napoca were asked to allow their newborn infant to be included in this study. The procedure was explained and if mothers agreed to participate, they signed an informed consent. Pre-term (i.e., gestational age < 37 weeks), fetal distress and dexamethasone treatment during pregnancy were exclusion criteria. An a priori sample size estimation indicated that minimum 28 participants were necessary in order to have adequate power (i.e., > 0.8) to detect a medium-size effect. The present sample included N = 142 full-term newborn infants delivered through spontaneous VD (N = 70) or planned elective CS (N = 72). Study procedures were in accordance with institutional and national ethical standards for research involving human participants and with the 1964 Declaration of Helsinki and its later amendments.

2.2. Methods

2.2.1. Stress-related behaviors

Stress-related behaviors before and after inoculation were assessed using the Modified Behavioral Pain Scale (MBPS) (Taddio et al., 1995). This observation scale focuses on three types of stress-related behaviors in infants: (1) facial expressions, assessed on a scale from 0 (e.g., smiling) to 3 (e.g., furrowed brow and eyes tightly closed); (2) crying, assessed on a scale from 0 (e.g., giggling) to 4 (e.g., full lunged cry); and (3) body movements, assessed on a scale from 0 (e.g., resting and relaxed) to 4 (e.g., agitation and rigidity). Higher scores indicate increased levels of stress-related behaviors. A recent study showed that MBPS scores predicted temperament assessed at 12–18 months (Horton et al., 2015).

2.2.2. Salivary cortisol

Saliva samples were collected using SalivaBio Infant's Swabs (Salimetrics LCC, Philadelphia, PA, USA) and stored at −20 °C. They were first thawed, vortexed and centrifuged at 1500 × *g* for 15 min, and then cortisol was assayed using the Salimetrics Cortisol Enzyme Immunoassay Kit (Salimetrics LCC, Philadelphia, USA), following the manufacturer's protocol. Optical densities were read on PR 4100 Absorbance Microplate Reader (Bio-Rad Inc., Hercules, CA, USA) at 450 nm, with a secondary filter correction at 492 nm. The final concentrations of salivary cortisol were calculated based on 4-parameter curve fit and were expressed in μg/dL.

2.3. Procedure

Behavioral assessments and saliva collection were done during a routine Hepatitis B inoculation in the first two hours after birth. Behavioral stress assessments were made by trained nurses, at three time points: two minutes before, immediately after and fifty minutes after inoculation. Saliva collection coincided with the behavioral assessments, with the exception of the second sample that was collected twenty minutes after inoculation in order to capture the peak of salivary cortisol.

2.4. Statistical analysis

Changes in stress-related behaviors (MBPS scores) and salivary cortisol were investigated using repeated measures ANOVA, with time of assessment (two minutes before vs. immediately after/twenty minutes after vs. fifty minutes after the inoculation) as within-subject factor, and type of delivery (VD vs. CS) and infant sex (girls vs. boys) as between-subject factors. The skewed distribution of cortisol levels was corrected using a base 10 logarithm transformation. Within-subject main effects were followed up using Bonferroni-corrected pairwise comparisons, and interactions with between-subject factors were followed up using repeated measures ANOVA in each separate group. Between-subject main effects were followed up using Student *t*-tests for independent samples. Effect sizes are reported as η_P^2 (ANOVA) and Cohen's *d* (Student *t*-test). When the homogeneity assumption was not supported, Greenhouse-Geisser corrected degrees of freedom were used. In light of the law of initial values, additional analyses aimed to corroborate the effects of mode of delivery on reactivity estimates that controlled for baseline differences. Specifically, Student *t*-tests for independent samples compared standardized residual scores indexing the change in behavior from pre- to post-inoculation. As measures of reactivity, standardized residual scores are more stringent than simple difference scores (see Burt and Obradović, 2013), and reflect the extent to which an individual's response deviates from the expected level derived from baseline (i.e., pre-inoculation) values. As global measures of cortisol reactivity, area under the curve relative to ground (AUC_G) and area under the curve relative to increase (AUC_I) (Pruessner et al., 2003) were compared between infants born through VD and CS, using Student *t*-tests for independent samples.

While the study was not designed to investigate the potential influence of medication during delivery, additional analyses were run to examine the effects of local anesthesia and oxytocin administration during delivery. Non-parametric Kruskal–Wallis and Mann–Whitney tests were used to compare between groups.

3. Results

3.1. Sample description

Table 1 shows the characteristics of the two groups. The distributions of sex and time of delivery were not significantly different