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Cesarean Delivery and Infant Cortisol Regulation

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Abstract

Background—Cesarean delivery reduces the risk of infant and maternal morbidity and mortality when medically indicated, however, the cesarean delivery rate is estimated to be two to three times higher than medically necessary. The World Health Organization and American College of Obstetricians and Gynecologists have expressed concern over the high rates of cesarean delivery, citing evidence that cesarean delivery has negative short- and long-term consequences for the health of the infant, mother, and for future pregnancies. Infants delivered by cesarean are at an increased risk of metabolic disease and immune dysfunction throughout the lifespan. Preliminary research suggests that the hypothalamic pituitary adrenal (HPA) axis is a plausible pathway linking cesarean delivery to poor health later in life. The present study examines the relation between mode of delivery and HPA axis function in six-month-old infants. We also examine whether the cesarean delivery was elective or indicated altered to the relation between mode of delivery and infant cortisol profiles.

Methods—The sample included 136 mother/infant pairs. Thirty-nine women delivered by cesarean and 97 delivered vaginally. Maternal and infant medical records were reviewed for prenatal medical history and birth outcomes. Infant saliva was collected for cortisol analysis at a 6-month well-baby checkup. Samples were collected upon arrival to the appointment (baseline) and 20 minutes after exposure to a painful stressor, the inoculation procedure (response). A mixed

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Authorship contribution

EPD, LMG, CAS designed the study and acquired the data. DAW assisted with data acquisition. LDM and EPD performed the analyses, LDM wrote the initial draft of the manuscript. All authors participated in interpretation of analyses and review and editing of manusript drafts.

Conflict of interest

The authors report no conflict of interest.

model ANCOVA was conducted to determine whether salivary cortisol concentrations differed between the two delivery groups. To examine whether complications related to having an indicated cesarean delivery contributed to any association between mode of delivery and cortisol production, cortisol concentrations were compared between the subgroup of infants whose cesarean deliveries were elective (e.g. maternal request or previous cesarean delivery) to infants delivered vaginally.

Results—Infants delivered by cesarean had lower cortisol concentrations at baseline and after the inoculation procedure compared to those delivered vaginally. Further, the relation between mode of delivery and cortisol levels persisted even when the analyses were restricted to compare only the elective cesarean deliveries (e.g. maternal request or previous cesarean delivery) to those delivered vaginally.

Discussion—This study provides evidence for an association between cesarean delivery and infant HPA axis function in infancy. Findings are consistent with the hypothesis that the HPA axis is a plausible pathway that links cesarean delivery with long-term health outcomes.

Keywords

cesarean delivery; cortisol; HPA axis; delivery mode; stress

1.0 Introduction

Cesarean delivery is a life-saving treatment that reduces risk of maternal and infant morbidity and mortality when medically indicated (Molina et al., 2015). The World Health Organization estimates that intervention with cesarean delivery prevents these risks in 10–15% of births (World Health Organization Human Reproduction Programme, 2015). However, the cesarean delivery rate in the United States is 32% (Martin et al., 2017), and cesarean delivery rates are as high as 40.5% in some countries (Betrán et al., 2016). This high rate is in part due to cesarean procedures that are not medically necessary (i.e. elective) (Barber et al., 2011; Meikle et al., 2005; Osterman and Martin, 2014; Zhang et al., 2010). Although cesarean delivery has clear benefits when medically indicated, it also is associated with long-term adverse health consequences for the infant and mother that are particularly important considerations for elective procedures (Sandall et al., 2018). Empirical and meta-analytic evidence indicates that offspring delivered by cesarean are at increased risk for metabolic disease and immune dysfunction later in life, including obesity, diabetes, asthma, allergies, and celiac disease (Cardwell et al., 2008; Cho and Norman, 2013; Darmasseelane et al., 2014; Sevelsted et al., 2015; Thavagnanam et al., 2008). A recent study utilizing a within-family design to partially account for genetic and environmental effects concluded that individuals delivered by cesarean were 64% more likely to develop obesity compared to their siblings delivered vaginally (Yuan et al., 2016). The American College of Obstetricians and Gynecologists and the World Health Organization have expressed concern over the high rate of cesarean delivery given evidence of short and long-term health consequences for the infant, mother, and her potential future pregnancies, prompting efforts to reduce rates of non-medically indicated cesarean delivery (American College of Obstetricians and Gynecologists, 2019; Curtin et al., 2013; National Institutes of Health, 2006; U.S. Department of Health and Human Services, 2010; World Health Organization, 2018).

The majority of research investigating pathways leading cesarean delivery to poor health outcomes has focused on colonization of the infant microbiome during delivery (Houghteling and Walker, 2015; Neu and Rushing, 2012; Penders et al., 2014). Infants delivered vaginally are exposed to the host of microflora present in the birth canal, which then colonize the infant gut (Mueller et al., 2015). This colonization promotes development of the infant immune system, intestinal tract, and metabolism (Mueller et al., 2017). Thus disruptions to this colonization, such as cesarean delivery, may lead to long-term poor immune and metabolic health outcomes (Penders et al., 2013; Sevelsted et al., 2015). The infant microbiome is not the only system affected by cesarean delivery, however, and it is likely that additional mechanisms contribute to health outcomes in offspring.

A plausible, yet understudied, pathway by which cesarean delivery might impact later health is alterations to the hypothalamic pituitary adrenal (HPA) axis following cesarean delivery. Cortisol is a glucocorticoid and an end-product of the HPA axis, one of the primary stress regulatory systems (Chrousos, 2009; Engel and Gunnar, 2019; Maniam et al., 2014; McEwen et al., 1997). Dysregulation of cortisol production increases risk for metabolic disease and immune dysfunction throughout the lifespan (Adam et al., 2017; Bellavance and Rivest, 2014; Bose et al., 2009; Incollingo Rodriguez et al., 2015; Müller and Quinkler, 2018). Several studies that have examined cortisol concentrations in infants born by vaginal and cesarean delivery indicate that cesarean delivery disrupts cortisol production. For example, venous and mixed cord blood concentrations of cortisol are lower in cesarean deliveries compared with vaginal deliveries (Bird et al., 1996; Gitau et al., 2001; Goldkrand et al., 1976; Mears et al., 2004; Nejad, 2016; Vogl et al., 2006; Warren and Goland, 1995). These differences are observed 72 hours after birth (Schuller et al., 2012), and evidence suggests that the association persists to two months of age (Miller et al., 2005; Taylor et al., 2000). It is unknown whether these alterations persist beyond early infancy. If reduced production continues beyond the neonatal period, such hypocortisolism may confer long-term health risks (Maripuu et al., 2016; McEwen, 2008; Varghese et al., 2016). Evaluating the impact of cesarean delivery on infant cortisol production may help explain the link between cesarean delivery and poor health outcomes.

1.2 Objective

The current study examines the relation between mode of delivery and infant cortisol response to a routine inoculation at six months of age. We test the hypothesis that cesarean delivery is associated with infant cortisol levels. Further, to address the possibility that the reason for having an indicated cesarean delivery contributed to the relation between cesarean delivery and infant cortisol, we compare cortisol values in the subgroup of infants whose cesarean deliveries were elective (e.g. maternal request or previous cesarean delivery) to those delivered vaginally.

2.0 Materials and Methods

2.1 Participants

The study sample included 136 mothers and their full-term infants (72 male, 64 female). Women were recruited prenatally into a longitudinal study of maternal and child

development. Participants provided written informed consent approved by the Institutional Review Board for Protection of Human Subjects. Initial recruitment criteria included singleton pregnancy, English-speaking, and over the age of 18. Exclusion criteria were fetal chromosomal or congenital anomalies, maternal endocrine problems, prenatal corticosteroid treatment, and substance use during pregnancy (smoking, recreational drugs, alcohol). Ninety-seven women delivered vaginally and 39 by cesarean.

2.2 Measures

2.2.1 Demographic and Clinical Data—Demographic data were collected by semi-structured interview (Table 1). Household income and years of education were used a calculate a socioeconomic status composite score (Cohen et al., 2006). Maternal and infant medical records were reviewed to assess prenatal medical history and birth outcomes.

2.2.2 Elective Cesarean Delivery—A dichotomous variable was used to indicate whether cesarean deliveries were considered elective or medically necessary. Cesarean deliveries were considered elective if the only indication for cesarean was previous cesarean delivery (n=17). Five of the women in the elective condition experienced labor.

2.2.3 Indicated Cesarean Delivery—Twenty-two women had medical indications for cesarean delivery other than previous cesarean. Indications included abnormal fetal heart rate patterns(American College of Obstetricians and Gynecologists, 2009) (n=4), breech presentation (n=5), maternal medication condition (n=3), macrosomia (n=4), protracted active phase (n=1), arrest of active phase (n=7), protracted descent (n=1), severe intrauterine growth restriction (n=1), cord prolapse (n=1), failed vacuum (n=1), and polyhydramnios (n=1). Fourteen of the women in the indicated condition experienced labor.

2.2.4 Infant Salivary Cortisol Response to Stress—Infant saliva was collected at a 6-month well-baby checkup and assayed for cortisol. Salivary cortisol reflects the unbound or active fraction of cortisol and is highly correlated with plasma cortisol in infants and adults (Calixto et al., 2002; Kirschbaum and Hellhammer, 1989). Saliva was collected upon arrival at the appointment and a second sample was collected 20 minutes after inoculation to capture peak response to the painful stressor (Gunnar et al., 1991). Saliva was obtained by placing a swab in the infant's mouth for up to one minute. Samples were spun and stored at −20 degrees Celsius until assayed. At the time of assay, samples were thawed then centrifuged at 3,000 rpm for 15 minutes.

Cortisol levels were determined by a competitive luminescence immunoassay (LIA; IBL-America, Minneapolis, MN) with a detection limit of .005 μg/dL. The intra- and inter-assay coefficients of variance were 5.5% and 7.6% respectively. Both samples each infant were included in the same assay batch to eliminate subject inter-assay variance. Samples were assayed in duplicate and averaged.

Four infants (three born vaginally and one by cesarean) had cortisol concentrations that were four standard deviations above the mean, thus were considered outliers and excluded final analyses. However, the inclusion of outliers in analyses did not alter the significant of study

findings. Infant salivary cortisol values at baseline and response were not normally distributed and were therefore log-transformed.

2.3 Analyses

Preliminary analyses were conducted using Pearson correlations and t-tests to identify maternal and infant characteristics that were associated with mode of delivery (Table 1). Only maternal age and five-minute Apgar scores differed between the two delivery groups at the p<.10 level and thus were included as covariates in all analyses. Time of cortisol assessment did not significantly differ between the two groups (vaginal delivery, M = 11:56, SD = 2:33; cesarean delivery M = 12:15, SD = 2:29; t(−.672), p = .50).

First, we examined whether infant cortisol concentrations increased in response to the inoculation stressor. Next, we examined whether mode of delivery was associated with cortisol profiles using a mixed model ANCOVA with mode of delivery (vaginal vs. cesarean) as the between groups factor and cortisol response to the stressor (cortisol at baseline and response) as the within-groups factor.

To examine whether indicated cesarean deliveries contributed to the association between mode of delivery and cortisol levels, we repeated the mixed model ANCOVA including only the subgroup of infants whose cesarean deliveries were elective (e.g. maternal request and previous cesarean delivery) in the cesarean group. To test whether the experience of labor contributed to findings, we compared cortisol between infants in the cesarean group that experienced labor (n=19) and did not experience labor (n=20) prior to cesarean delivery using a mixed model ANCOVA to determine whether the presence or absence of labor contributed to differences in cortisol levels.

3.0 Results

The manipulation, the inoculation stressor, elicited an increase in infant salivary cortisol 0.35 μg/dL (SD=0.84) to 0.6 μg/dL (SD=0.84) [F(1, 132) = 72.71, p<.001] in the full sample. There was a main effect of group such that salivary cortisol concentration was significantly lower in infants delivered by cesarean as compared to those delivered vaginally [F(1, 130) = 6.07, p=0.02] (Figure 1a). The interaction between cortisol response to the stressor and delivery mode showed that infants delivered vaginally tended to exhibit a greater increase in cortisol baseline to response compared to those born by cesarean (mean=.18 μg/dL, SD=.23), but this did not reach standard statistical significance [F (1, 130) = 2.94, p=0.09] (Figure 1a).

When the cesarean group was restricted to only those infants who had been delivered by elective cesarean, salivary cortisol levels were lower in the cesarean group as compared to the vaginal group [F(1, 110) = 3.72, p=.06] (Figure 1b). Finally, cortisol levels did not differ between infants that experienced labor and did not experience labor in the cesarean delivery group [F (1, 36) = .001, p=.98].

4.0 Discussion

Our prospective research reveals that six-month-old infants delivered by cesarean at term exhibited lower levels of cortisol at baseline and after an inoculation procedure compared to those delivered vaginally. Notably, neither whether the caesarean delivery was elective versus medically indicated nor the experience of labor accounted for this association. These results are consistent with prior studies showing that cesarean delivery is associated with lower cortisol birth to eight weeks of age (Miller et al., 2005; Taylor et al., 2000). Our study expands this literature by showing that suppressed cortisol production persists through at least six months of age. These findings provide support to the hypotheses that delivery mode impacts development of the HPA axis, and that altered infant HPA axis functioning following cesarean delivery may be a pathway by which cesarean delivery impacts subsequent health.

There are three important contributions of our study. First, we examined cortisol measured directly the infant, whereas most previous research has examined cord blood (Bird et al., 1996; Gitau et al., 2001; Goldkrand et al., 1976; Mears et al., 2004; Nejad, 2016; Vogl et al., 2006; Warren and Goland, 1995). Second, our findings indicate that the hypocortisolemic pattern observed in neonates delivered by cesarean persists through six months of age. Finally, our consideration of elective cesarean deliveries suggest that medically indicated deliveries do not account for the cortisol differences observed between infants delivered vaginally or by cesarean delivery.

Vaginal labor and delivery are normative experiences that serve a critical function for offspring development including stimulation of the respiratory and metabolic systems (Houghteling and Walker, 2015; Nejad, 2016). During labor and delivery, infants endure the physical stress of contractions, periods with reduced oxygen, and significant increases in maternal glucocorticoids, often for several hours (Lagercrantz and Slotkin, 1986). By comparison, cesarean delivery is a relatively calm experience for the infant. The physical stress of vaginal birth and exposure to maternal glucocorticoids during labor and delivery are important for infant development of vital organs and may facilitate programming of the HPA axis (Lagercrantz, 1996; Taylor et al., 2000). Infants delivered by cesarean are deprived of this normative experience, which may lead to reduced cortisol levels and alterations to the development of the HPA axis in infancy. This study is not powered to test differences in amount of labor experienced in the cesarean group, we did not find that the experience of labor accounted for links with cortisol in the cesarean group. Future research should compare infant HPA axis function by labor experiences and delivery mode.

The pattern of hypocortisolism observed in infants delivered by cesarean may have implications for long-term health. Cortisol is necessary for development of vital organs including the brain, lungs, liver, and pancreas, that are implicated in health and disease (Bellavance and Rivest, 2014; Davis et al., 2017, 2004; Turner-Cobb et al., 2011; Xiong and Zhang, 2013). Glucocorticoids modulate gastrointestinal and metabolic functions, and have anti-inflammatory properties that help regulate the immune system (Chrousos, 2009; Coutinho and Chapman, 2011). Hypocortisolism is associated with immune dysfunction, including allergies and atopic dermatitis, in childhood through adulthood (Adam et al., 2017;

Buske-Kirschbaum, 2009; Priftis et al., 2009; Ruttle et al., 2014; Varghese et al., 2016). Further, hypocortisolism is linked to obesity, higher BMI, dysregulated cholesterol, and metabolic syndrome (Adam et al., 2017; Daniel et al., 2006; Maripuu et al., 2016; Ruttle et al., 2013). Thus, it is plausible that the hypocortisolism observed during infancy may be associated with long term health consequences.

Future research that examines the relations among delivery mode, cortisol, and health outcomes is warranted to better understand the mechanisms by which cesarean delivery is associated with subsequent poor health. The primary focus of research on the pathway linking cesarean delivery to subsequent health has been on the gut microbiome (Mueller et al., 2017; Neu and Rushing, 2012). The present study illustrates that cesarean delivery is associated with alterations to HPA axis regulation as well. Future studies should examine the joint and independent contributions of these two systems as potential mechanisms by which cesarean delivery may be associated with subsequent health.

4.1 Strenghts and Limitations

Strengths of the present investigation include the prospective and longitudinal design with direct biological assessments of the infants. This study, however, was observational in nature and thus, causality cannot be determined. Further, due to sample size, this study cannot test the impact of specific obstetric complications that may have contributed to links between cesarean delivery and infant cortisol outcomes. We instead performed secondary analyses examining only the subgroup of infants whose cesarean deliveries were elective. That cortisol levels were lower even in the elective group partially addresses concerns related to the confounding impact of obstetric complications.

4.2 Conclusions

The benefits of cesarean delivery are clear when medically indicated. The present finding suggests that cesarean delivery has associations with the development of infant HPA axis regulation. Thus, the potential short- and long-term consequences of cesarean delivery support the call of WHO and ACOG to reduce the number of non-medically indicated cesarean deliveries (American College of Obstetricians and Gynecologists, 2019; National Institutes of Health, 2010; World Health Organization Human Reproduction Programme, 2015).

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Highlights

- Cesarean delivery is linked to subsequent metabolic disease and immune dysfunction.
- Hypothalamic pituitary adrenocortical axis dysregulation is one potential mechanism.
- Cesarean delivery predicts hypocortisolism through 6 months of age.
- Cortisol dysregulation may contribute to health consequences of cesarean delivery.

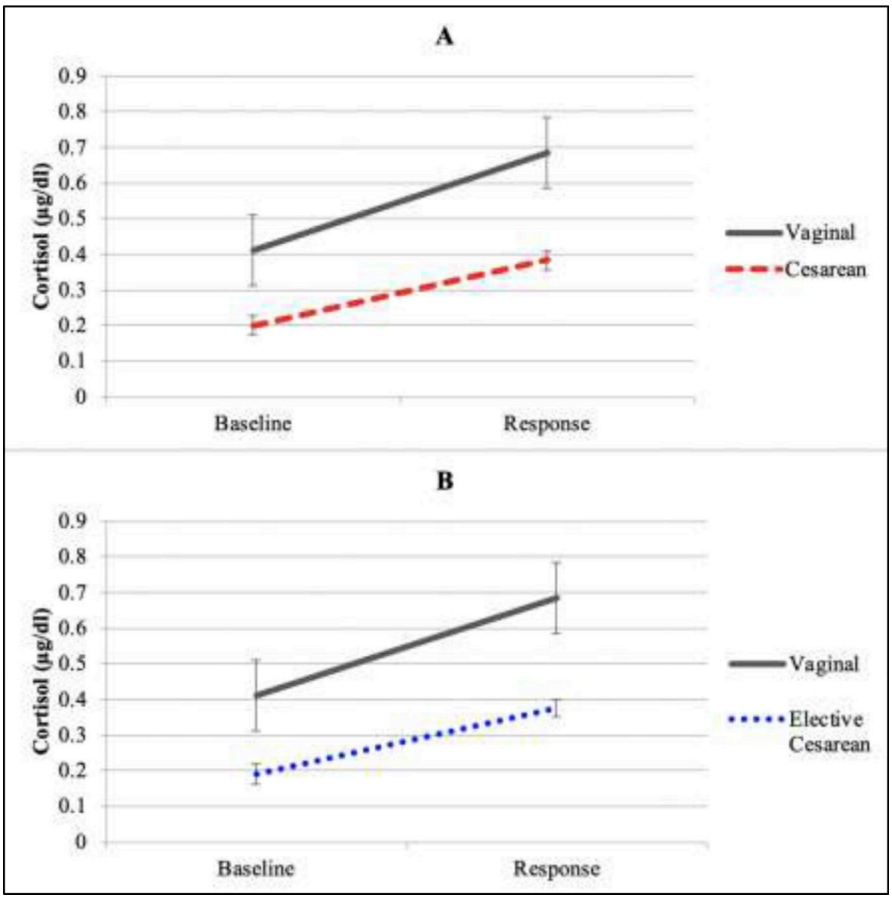

Figure 1.

Infant cortisol concentrations at baseline and 20 minutes after the inoculation procedure by (A) delivery mode, and (B) among infants whose cesarean deliveries were elective compared to those delivered vaginally.

Table 1

Descriptive information for infants and mothers.

Infant Characteristics	Vaginal (n=97)	Delivery Cesarean Delivery (n=39)	*p*
Gestational age at birth (weeks)[b]	39.5 (1.1)	39.3 (1.1)	0.427
Birth weight (grams)[b]	3384.3 (414.7)	3349.9 (518.5)	0.440
Race/Ethnicity [a]			0.139
Non-Hispanic White	49 (50.5)	23 (59)	
Hispanic	18 (18.6)	10 (25.6)	
Other	30 (30.9)	6 (15.4)	
Sex (% Male)[a]	48 (49.5)	24 (61.5)	0.203
Apgar score at 5-min[b]	9 (0.3)	9.1 (0.4)	**0.061**
Age at assessment (weeks)[b]	27 (2.1)	26.7 (1.8)	0.433
Maternal Demographics			
Maternal age at delivery (years)[b]	29.9 (5)	31.9(5)	**0.031**
Married [a]	72 (73.2)	33 (84.6)	0.192
Cohabitating with baby's father [a]	88 (90.7)	36 (92.3)	0.768
Body Mass Index[b1]	24.9 (6.6)	26.7 (7.2)	0.427
Highest level of education [a2]			0.821
High school or less	12 (12.3)	3 (7.7)	
Some college or certificate	38 (39.2)	19 (48.8)	
Bachelor degree or higher	47 (48.4)	17 (43.6)	
Annual household income [a2]			0.469
$0–50,000	36 (37.1)	12 (30.8)	
$50,001–100,000	38 (39.2)	17 (43.6)	
Over $100,000	21 (21.6)	10 (25.6)	

[a] Chi-square; N(%)

[b] t-test; Mean (SD)

[1] Maternal body mass index (BMI) was calculated using height and weight [weight (kg)/height^2 (m^2)] at 15 weeks gestation.

[2] Household income and level of education were used to calculate a socioeconomic status composite score.