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Review Article

Association between Umbilical Cord Blood Cortisol and Maternal Cortisol during Pregnancy

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Abstract

Several preclinical and clinical studies suggest that maternal psychosocial stress and anxiety during pregnancy may have persistent consequences for the long-term health of the offspring. The aim of our study was to evaluate possible associations between maternal cortisol levels, gestational age, baby's birth weight and umbilical cord blood cortisol concentration. 145 women who attended the Obstetrics' Service, Hospital de Clinicas "José de San Martín", at the time of delivery, were included in this study. The population was divided into two groups: group 1 was constituted by 89 healthy women (26.5 ± 7.0 years) while group 2 was made up of 56 women (29 ± 7.8 years) who presented different pathologies. Total population was also divided according to the type of birth (cesarean section or vaginal). Group 2 was divided considering baby's APGAR 5/10 score and birth weight. Cortisol was measured by a chemoluminiscent method (Immulite 2000 Siemens). Umbilical cord blood cortisol concentration correlated with pregnancy week (r=0.451, p=0.0001), birth weight (r=0.284, p=0.010) and maternal cortisol concentration; (r=0.424, p=0.0001). After dividing the population according to the type of birth, significant differences were found in umbilical cord blood cortisol concentration (p=0.003), pregnancy week (p=0.0001) and birth weight, (p=0.002), were found. A linear regression analysis was performed showing that maternal cortisol and pregnancy week were associated with umbilical cord blood cortisol concentrations (F=6.502, p=0.004) even after adjusting for birth weight. The correlation found between maternal cortisol and umbilical cord blood cortisol levels could be related to a probable fetal programming of the hypothalamic-pituitary-adrenal axis.

Keywords: Maternal cortisol; Umbilical cord blood cortisol; Stress; Fetal programming

Introduction

Early life stress has long-term consequences, making children more vulnerable to physical and mental health problems in adulthood [1]. The main stress response system is the Hypothalamic Pituitary Adrenal (HPA) axis [2], which is immature at birth and sensitive to early experiences [3]. Cortisol is the final product of the HPA axis. During pregnancy, women have elevated cortisol levels, mainly since estrogen and placental Corticotropin Releasing Hormone (CRH) stimulate the maternal HPA-axis increasing the production of cortisol [4]. By the third trimester, the circulating cortisol is 2-4 times higher than before pregnancy [4,5]. The secretion of cortisol is essential for fetal development but may be harmful in high concentrations [6]. Maternal HPA axis modifications during pregnancy and delivery may induce alterations in HPA axis that persist in postpartum period, returning to pre-pregnancy function 2 months after birth, approximately [7-9]. Several studies found a relation between maternal cortisol concentrations, stress and anxiety during pregnancy [10-14]. The mechanisms through which maternal HPA axis activity can influence fetal development in humans has not been fully understood yet [15]. A better knowledge of maternal HPA axis role and its relationship with perinatal development would allow predicting maternal stress impact throughout child's life (fetal programming) [13,16-18]. It has also been proposed that maternal cortisol can cross the placenta affecting fetal cortisol concentration and HPA axis development. The activity of placental enzyme 11 β-hydroxysteroid-dehydrogenase type 2 protects the fetus from maternal cortisol [19,20] by converting it into inactive cortisone. However, evidence from animal studies suggests that prenatal stress could affect placental function and expression of 11 β-hydroxysteroid-dehydrogenase enzyme [21].

A stress-activated HPA axis may have health consequences due to its association with immune and inflammatory processes. Several studies showed that infants who experienced early life stress have an abnormal HPA axis activity, which might lead to cardiovascular diseases, obesity, metabolic alterations and increased risk of developing mental illness [22,23].

Fetal gestational age and birth weight are important markers of subsequent infant development. Low birth weight has been linked to lower IQ scores [24], hyperactivity and lack of attention [25-27] found that birth weight and gestational age are associated with increased emotional problems. Gestational age and birth weight were therefore included as markers of infant's health at delivery.

The aim of this study was to evaluate the possible impact of maternal cortisol levels in gestational age, baby's birth weight and umbilical cord blood cortisol concentration in order to establish

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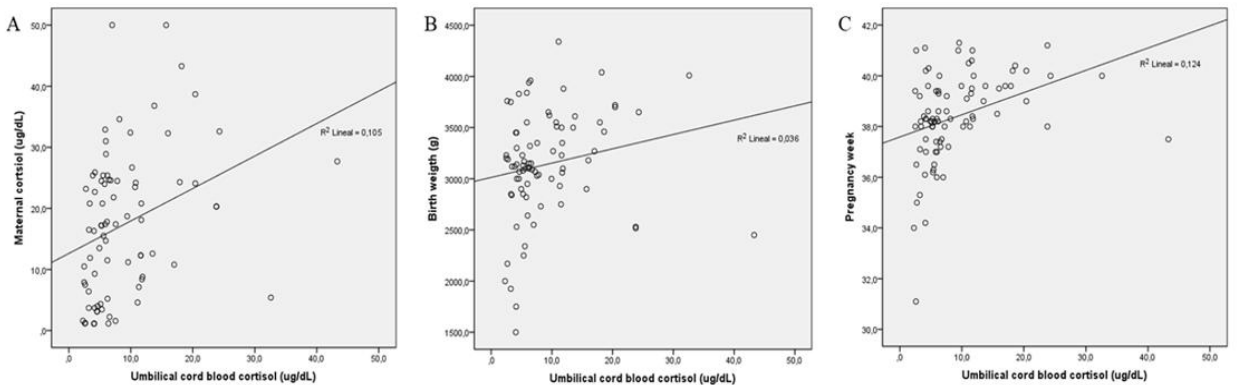

Figure 1: Spearman correlation between umbilical cord blood cortisol and marternal cortisol, birth weight and pregnancy week. A) Spearman correlation between umbilical cord blood cortisol and maternal cortisol (r=0.42; p=0.001); B) Spearman correlation between umbilical cord blood cortisol and birth weight (r=0.28; p=0.01); C) Spearman correlation between umbilical cord blood cortisol and pregnancy week (r=0.45; p=0.001).

possible associations with the infant's state at birth (APGAR score).

Materials and Methods

Subjects and sampling

The studied population included 145 women who attended the Obstetrics' Service, Hospital de Clínicas "José de San Martín", at the time of delivery. Population was divided according to the type of birth (cesarean section, n=68 or vaginal, n=77). In addition, total population was also divided into two groups: group 1 was made up of 89 healthy women (26.5 ± 7.0 years) while group 2 was constituted by 56 women (29 ± 7.8 years) who presented different pathologies such us hypo and hyperthyroidism, diabetes and preeclampsia. Subsequently, this last group was divided considering baby's APGAR 5/10 score and birth weight.

The participants of this study did not receive any kind of compensation for participating and all of them gave written prior informed consent. The study was approved in advance by the Hospital Ethic Committee and was performed following the Helsinki Declaration for medical studies in humans.

Psychosocial and obstetric covariates

At the time of delivery, information was obtained about the mother's age and health status, type of birth and pregnancy week. On the other side, baby birth weight and general state at birth (APGAR 5/10 score) were collected.

Methods

Maternal cortisol levels in blood samples obtained during delivery and umbilical cord blood concentration were measured by a chemoluminiscent method (Immulite autoanalyzer 2000, Siemens). The intra-assay (CVi) and inter-assay (CVe) variation coefficients for cortisol were <5% and <9.7% respectively.

Statistical methods

Results were expressed as mean ± standard deviation (SD) or median (range), according to the data distribution. Mean or median differences were performed by *t*-test or Mann–Whitney test, respectively. Spearman correlation was used for nonparametric variables. A linear regression analysis was carried out introducing umbilical cord blood cortisol concentration as dependent variable and mother's cortisol concentration and pregnancy week as independent variable. A p-value of less than 0.05 was considered as statistically significant. The Statistical Package for Social Sciences (SPSS: version 23.0) was used for data analysis.

Results

The characteristics of the studied population (n=145) and cortisol levels are shown in Table 1. We found a correlation between umbilical cord blood cortisol concentration and pregnancy week, birth weight and maternal cortisol concentration (r=0.451, p=0.0001; r=0.284, p=0.010; r=0.424, p=0.0001, respectively, Figure 1A-1C). In addition, we observed that pregnancy week positively correlated with birth weight (r=0.626, p =0.0001).

Regarding the type of delivery, we found that umbilical cord blood cortisol concentration, pregnancy week and birth weight were lower in cesarean delivery compared to vaginal birth (p=0.003, p=0.0001, p=0.002); no significant differences were found in maternal cortisol. A linear regression analysis was performed showing that maternal cortisol and pregnancy week were associated with umbilical cord blood cortisol concentrations (F=6.502, p=0.004) even after

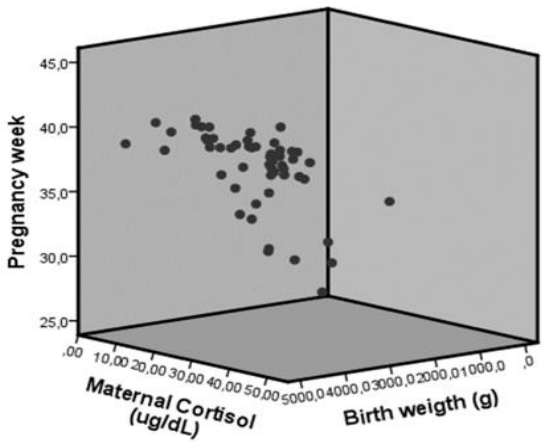

Figure 2: Linear regression between maternal cortisol, pregnancy week and birth weight. Linear regression performed by dividing the Group 2 according to the risk of the baby at the time of delivery. The following criteria were used: APGAR <7 and PN <2500g.

Table 1: Characteristics of the study population and cortisol levels.

	Group 1	Group 2
n	89	56
Maternal age (years)	27 ± 8	31 ± 8
Type of birth	C: 32	C: 36
	V: 57	V: 20
Pregnancy week	38 ± 2	35 ± 4
Birth weight (g)	3155 ± 535	2606 ± 1054
APGAR 5/10	9/10	<7 (in both times)
Maternal cortisol (ug/dL)	18.1 (1.6–50.0)	15.5 (1.1–50.0)
Umbilical cord blood cortisol (ug/dL)	11.3 (2.5–32.6)	5.6 (2.3–43.3)

adjusting for birth weight. In group 2 we found a correlation between maternal cortisol concentrations and birth weight (r=0.313, p=0.021) and pregnancy week (r=0.364, p=0.006) (Figure 2). After performing a linear regression analysis an association between maternal cortisol and birth weight was found (F=6.574, p=0.013).

Discussion

In this study, we found that umbilical cord blood cortisol concentrations correlated with pregnancy week, birth weight and maternal cortisol concentrations. Previous research reported that during fetal life, cortisol produced by adrenal cortex definitive zone correlates directly with gestational age [28]. Several studies have shown an association between higher maternal cortisol levels and shorter gestation as well as with low birth weight [4,29].

Maternal cortisol levels during pregnancy could influence through stimulation of placental corticotropin-releasing hormone, which in turn would stimulate fetal cortisol production [30-32]. Accordingly, positive correlations between maternal cortisol and cortisol in the fetal compartment have been reported [31,33,34]. There is increasing evidence that changes in the maternal HPA axis lead to lower birth weight and long-term adverse health outcomes for the offspring [4]. In addition, the correlation between hair cortisol levels in mothers and their children suggests a heritable trait or maternal calibration of the child's HPA axis [35]. Paarlberg et al. [36] showed that placental CRH, cortisol and other hormones when crossing the placenta could be used to slow growth rate, reduce birth weight and precipitate preterm labor in prenatally stressed infants.

In this study, no significant differences were found in maternal cortisol concentrations when dividing the population based on the type of birth. Stjernholm et al., showed that spontaneous birth (vaginal delivery) generated higher maternal cortisol than elective (cesarean section), indicating higher stress levels. In that study, they also found a lack of correlation between maternal cortisol and body mass index (BMI), parity, gestational age and duration of labor [37,38]. Interestingly, other studies show a lack of correlation between maternal ACTH and cortisol levels at this stage, newborn weight and duration of delivery [37-40]. Cortisol levels in cord plasma were higher after spontaneous vaginal delivery than after elective cesarean section. Earlier, spontaneous vaginal delivery was found to increase cortisol levels both in maternal and fetal plasma [41].

In mothers with different pathologies (hypo and hyperthyroidism, diabetes, preeclampsia) we found a correlation of maternal cortisol concentrations with birth weight and pregnancy week. A recent study revealed that placental expression of the 11βHSD2 gene was reduced in preeclampsia [42]. Furthermore, other research reported that in preeclampsia, elevated umbilical cord cortisol levels resulting from reduced 11βHSD2 activity may contribute to impaired fetal growth [43].

A question to be answered is whether psychosocial stress during pregnancy and high maternal cortisol levels could affect fetal HPA axis, resulting in higher cortisol levels at birth. A possible way could be given by changes in placental functioning caused by exposure to prenatal psychosocial stress.

A better understanding of the mechanisms by which maternal prenatal stress programs the fetus could provide essential information for the development of effective interventions that can generate substantial benefits for the health and well-being of future generations.

Conclusion

The correlation found between maternal cortisol and umbilical cord blood cortisol levels might be related to a probable fetal programming of the hypothalamic-pituitary-adrenal axis.

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