Association of Plasma Cortisol Levels with Gestational Age and Anthropometric Values at Birth in Preterm Infants

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Association of Plasma Cortisol Levels with Gestational Age and Anthropometric Values at Birth in Preterm Infants

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Abstract: There are no study reports to clarify the association between gestational age (GA) or anthropometric values at birth, and plasma cortisol levels in the blood of preterm infants at birth and at one month of age. This hospital-based retrospective cohort study included infants born at < 37 weeks' gestation between 2019 and 2021. First, the association between plasma cortisol level and GA or anthropometric values at birth (birth weight standard deviation score [SDS], birth length SDS, and birth head circumference SDS) was identified by regression and multiple regression analyses. Second, plasma cortisol levels in the umbilical cord at birth and at one month of age were compared between small-for-gestational age (SGA) and non-SGA infants. Sixty-one preterm infants were enrolled (SGA: 24 and non-SGA: 37). Plasma cortisol levels at birth were significantly associated with GA. Plasma cortisol levels at one month of age were associated with GA and birth head circumference SDS. Plasma cortisol levels at birth were significantly higher in SGA than non-SGA ($p = 0.010$). GA was an independent determinant of plasma cortisol levels at birth. SGA infants had a high plasma cortisol level at birth; resulting in speculation that a high plasma cortisol level at birth may predict abnormal neurological outcomes.

Keywords: anthropometric value; birth head circumference; birth weight; cortisol; preterm infant; gestational age; small-for-gestational age

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1. Introduction

Cortisol is an essential hormone for the maintenance of human health. During the fetal period, cortisol promotes organ maturation, whereas excess cortisol suppresses organ development. During the fetal period, maternal active cortisol is converted into inactive cortisone by 11β-hydroxysteroid dehydrogenase-2 (11βHSD2) in the placenta to prevent the influx of maternal active cortisol into the fetus. However, under stresses, such as poor nutrition and hypoxia, 11βHSD2 activity in the placenta is suppressed and maternal active cortisol flows into the fetus [1]. In preterm infants, 11βHSD2 activity is generally low, and maternal active cortisol flows directly into the infant via the placenta [2]. Elevated fetal cortisol is associated with cardiovascular, metabolic, and endocrine disorders in adulthood in some animal studies [3,4].

Fetal growth parameters, such as the body weight standard deviation score (SDS) and head circumference SDS, have been used as indicators to assess poor intrauterine nutrition [5]. Previous studies examined the relationship between cortisol levels and prematurity, small-for-gestational-age (SGA), and some neonatal diseases [6–12]. Iwata et al. reported that salivary cortisol levels in infants born at 31–39 weeks' gestational age (GA) were higher in SGA infants than in non-SGA infants within 5 days of age and lower in SGA infants than in non-SGA infants within 14 days of age [6]. Grunau et al. evaluated plasma cortisol levels at 8–18 months of age in full-term or preterm infants born at < 28 weeks' gestation, and found higher plasma cortisol levels in preterm infants than in full-

term infants [7]. Cortisol levels in preterm infants have also been associated with neonatal complications, such as chronic lung disease (CLD) [8,9], respiratory distress syndrome (RDS) [10,11], and late-onset circulatory collapse (LCC) [12]. Although there are a few reports regarding cortisol levels in neonates, no study has evaluated the association between plasma cortisol levels and GA or anthropometric parameters measured at birth in preterm infants. This study aimed to clarify the association between GA or anthropometric values at birth and plasma cortisol levels in umbilical cord blood at birth and at one month of age in preterm infants (Study 1) and to compare plasma cortisol levels between small-for-gestational age (SGA) and non-SGA infants (Study 2).

2. Materials and Methods

2.1. Eligible Infants

This retrospective cohort study was approved by the Ethics Committee of Nihon University Itabashi Hospital (approval no: RK-190910-3; date: 20 November 2019). All preterm infants born by cesarean section at Nihon University Itabashi Hospital between September 2019 and June 2021 were enrolled in the study. Written informed consent was provided by the parents. Blood samples of the infants at birth (umbilical cord blood) and at 1 month of age were obtained for routine laboratory tests for various medical reasons. After the relevant laboratory tests were performed, the residual blood samples were used to measure plasma cortisol levels. The exclusion criteria were prenatal diagnosis of monochorionic twins, severe congenital heart malformation, and chromosomal abnormalities.

Preterm infants, who were born between 22 and 36 weeks after conception, were then divided into three groups based on Japanese neonatal anthropometric charts for GA at birth [13]: birth weight (BW) less than the 10th percentile (small-for-gestational age [SGA]), BW between the 10th and 90th percentile (appropriate-for-gestational age [AGA]), and BW more than the 90th percentile (large-for-gestational age [LGA]).

2.2. Blood Sample Collection and Plasma Cortisol Measurement

Blood samples were collected from the umbilical vein immediately after birth and from vein puncture at 1 month of age (median [minimum-maximum]: 28 (25–49) days after birth), and blood samples at 1 month of age were collected between 8 and 9 a.m. before feeding. Plasma cortisol levels were measured using the electrochemiluminescence immunoassay method, as previously reported [14]. The difference between the plasma cortisol levels at 1 month of age and birth (umbilical cord blood) was defined as Δ cortisol.

2.3. Nutrition Policy from Birth to One-Month of Age

Shortly after birth, a 10% sugar solution was initiated at a water quantity (WQ) of 50–60 mL/kg/day. Thereafter, the WQ was increased by approximately 10 mL/kg/day, considering daily weight gain or loss, urine output, and insensible excretion. In the case of infusion alone, the WQ was maintained at 100–120 mL/kg/day. Depending on the infant's condition, enteral feeding (exclusive breast feeding) was initiated, the infusion was tapered and the feeding volume was maintained at a WQ of 130 mL/kg/day with enteral feeding alone. After 35 weeks of corrected GA, infants were fed independently if possible.

2.4. Clinical Characteristics and Disease Definitions

Maternal clinical factors included maternal age at birth, pre-pregnancy body mass index (BMI), weight gain during pregnancy, maternal height, placental weight, multiple births, the development of hypertensive disorder of pregnancy (HDP) and gestational diabetes mellitus (GDM), presence of chorioamnionitis, and prepartum intramuscular betamethasone use (two intramuscular injections of 12 mg are administered 24 h apart to pregnant women at high risk of preterm birth before 33 weeks and 6 days according to

our management policy). HDP is defined as hypertension (blood pressure ≥ 140/90 mmHg) during pregnancy [15]. GDM is defined as glucose intolerance with onset or first recognition during pregnancy. GDM was diagnosed when an oral glucose tolerance test (OGTT) was performed and one or more of the following criteria were met: fasting blood glucose ≥ 92 mg/dL, 1-h value ≥ 180 mg/dL, or 2-h value ≥ 153 mg/dL in the 75-g OGTT [16,17] Regarding multiple births, monochorionic twins were excluded because the umbilical cord blood was affected due to blood flow traffic between the twins. Chorioamnionitis was defined as placental pathology with a grade 1–3 Blanc classification [18]. Neonatal clinical factors included sex, GA, BW, birth length (BL), birth head circumference, BW SDS, BL SDS, birth head circumference SDS, and development of RDS, CLD, and LCC. RDS was defined as the presence of reticular granular shadows on plain chest radiographs [19]. CLD was defined as respiratory distress symptoms requiring oxygen supply continuing beyond 28 days of age due to lung abnormalities, excluding congenital respiratory malformations, based on the Japanese criteria [20]. LCC was defined as a sudden disorder that manifested as hypotension and oliguria at one week or more after birth [12]. Patent ductus arteriosus was defined when surgical ligation was performed. Sepsis was defined as an elevated serum C-reactive protein level, bacterial pathogen detected in culture, and antibiotic treatment. Premature retinopathy was defined when photocoagulation was required. Intracranial hemorrhage and periventricular leukomalacia were diagnosed using cranial ultrasonography and magnetic resonance imaging. Necrotizing enteritis was defined based on the pathological findings after surgery. Meconium disease was defined when treated by contrast agent [21].

2.5. Statistical Analysis

Study 1: To clarify the association between GA or anthropometric values (BW SDS, BL SDS, and head circumference SDS) at birth with plasma cortisol levels at birth and at 1 month of age in preterm infants, regression analysis was performed to linearly compare GA or each anthropometric SDS at birth and plasma cortisol levels at birth and at 1 month of age. Δ cortisol levels, coefficient of determination (R^2), and *p*-values were calculated. Multiple regression analysis was performed using plasma cortisol levels at birth and at 1 month of age and Δ cortisol levels as objective variables, and GA and each anthropometric SDS at birth as explanatory variables.

Study 2: To compare the following between SGA and non-SGA infants, the Mann—Whitney U test and Fisher's exact test were performed: maternal and neonatal clinical factors, cord blood plasma cortisol levels, plasma cortisol levels at 1 month of age, and Δ cortisol levels.

Statistical analyses were performed using JMP ver14.0 (JMP Statistical Discovery LLC. Tokyo, Japan), and $p < 0.05$ was considered significant.

3. Results

3.1. Study 1

3.1.1. Clinical Characteristics

During the study period, 61 (SGA: 24, non-SGA: 37) preterm infants were enrolled. Of the non-SGA infants, 35 were AGA and 2 were LGA. The clinical characteristics of the enrolled infants and their mothers are presented in Table 1. Since six mothers with four di- and two tri-chorionic births were included, the clinical characteristics of 53 mothers are shown.

Table 1. Clinical characteristics of mothers and infants.

Mothers	***N* = 53**
Age at delivery, years	31 (24–36)
Pre-pregnancy BMI, kg/m^2	21.5 (15.6–33.8)

Weight gain during pregnancy, kg	5.9 (0.0–24.4)
Height, cm	156.9 (144.6–172.0)
Placenta weight, g	348 (136–804)
Di- and tri-chorionic births, *n* (%)	6 (11.3)
Hypertensive disorders of pregnancy, *n* (%)	16 (30.2)
Gestational diabetes mellitus, *n* (%)	1 (1.9)
Chorioamnionitis, *n* (%)	28 (52.8)
Prepartum use of betamethasone, *n* (%)	37 (69.8)
Last use of betamethasone, days before delivery, *n* = 37	6 (0–35)
Infants	***N* = 61**
Male sex, *n* (%)	22 (36)
GA, weeks	31 (24–36)
BW, g	1424 (464–2834)
BW SDS	−0.91(−4.23–1.69)
BL, cm	39.0 (28.0–47.0)
BL SDS	−0.9 (−4.23–1.69)
Birth head circumstance, cm	28.8 (20.0–34.5)
Birth head circumstance SDS	−0.16 (−2.48–1.92)
Respiratory distress syndrome, *n* (%)	26 (42.6)
Chronic lung disease, *n* (%)	14 (23.0)
Late-onset circulatory collapse, *n* (%)	5 (8.2)
Patent ductus arteriosus, *n* (%)	0 (0)
Sepsis, *n* (%)	1 (1.6)
Retinopathy of prematurity, *n* (%)	2 (3.3)
Necrotizing enterocolitis, *n* (%)	0 (0)
Meconium disease, *n* (%)	2 (3.3)
Intraventricular hemorrhage, *n* (%)	0 (0)
Periventricular leukomalacia, *n* (%)	2 (3.3)

Data are shown as the median (range) or number (percentage); BMI, body mass index; BL, birth length; BW, birth weight; GA, gestational age at birth; SDS, standard deviation score.

3.1.2. Plasma Cortisol Levels at Birth and at 1 Month of Age

Figure 1 shows the relationship between GA and plasma cortisol levels at birth and at 1 month of age. GA was significantly correlated with plasma cortisol levels at birth and at 1 month of age ($R^2 = 0.154$, $p = 0.0018$ and $R^2 = 0.146$, $p = 0.0024$, respectively).

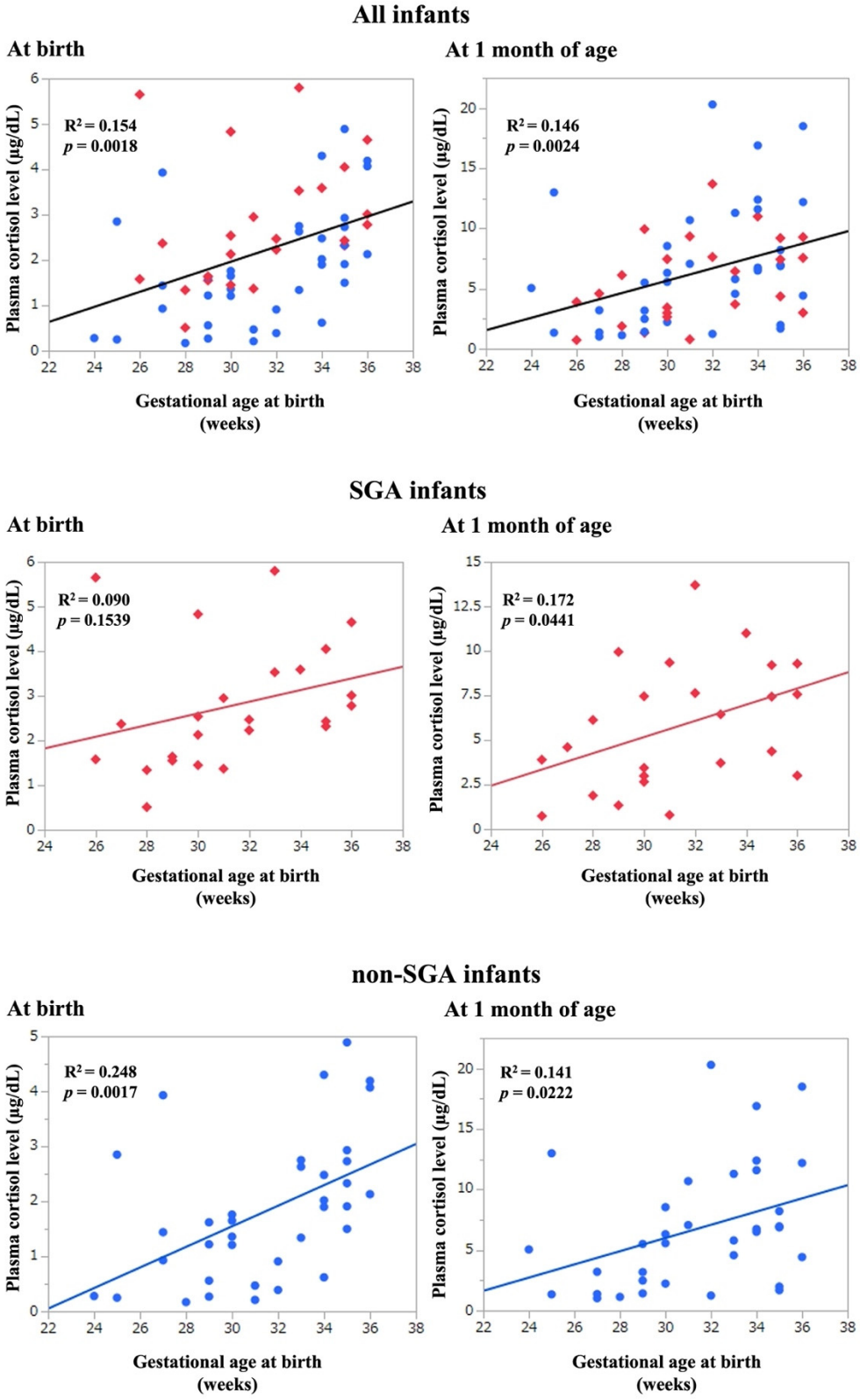

Figure 1. Gestational age at birth and plasma cortisol levels at birth or at 1 month of age. Red rhombus: small-for-gestational age (SGA), Blue circle: non-SGA.

3.1.3. Association between Plasma Cortisol Levels and GA, and Anthropometric Values at Birth

Plasma cortisol levels in umbilical blood and at 1 month of age, and Δ cortisol levels were significantly positively correlated with GA (Table 2A–C). Δ cortisol levels were significantly correlated with head circumference SDS ($R^2 = 0.078$, $p = 0.029$; Table 2C). In multivariate analyses, plasma cortisol levels of umbilical blood and Δ cortisol were significantly positively correlated with GA ($p < 0.05$, Table 3 A–C). Plasma cortisol levels at 1 month of age exhibited a significantly positive correlation with not only GA, but also birth head circumference SDS (partial correlation coefficient = 2.533, $p = 0.015$).

Table 2. Regression analysis.

A. Cortisol Level at Birth		
	Coefficient of Determination	***p*-Value**
GA, weeks	0.154	0.002
BW SDS	0.057	0.063
BL SDS	0.063	0.051
Birth head circumference SDS	0.015	0.344
B. Cortisol Level at 1 Month of Age		
	Coefficient of Determination	***p*-Value**
GA, weeks	0.146	0.002
BW SDS	0.014	0.370
BL SDS	0.010	0.453
Birth head circumference SDS	0.058	0.062
C. Δ Cortisol		
	Coefficient of Determination	***p*-Value**
GA, weeks	0.067	0.044
BW SDS	0.037	0.137
BL SDS	0.031	0.172
Birth head circumference SDS	0.078	0.029

BL, birth length; BW, birth weight; CI, confidence interval; GA, gestational age at birth; SDS, standard deviation score.

Table 3. Multivariate regression analysis.

A. Cortisol Level at Birth		
	Partial Correlation Coefficient (95% CI)	***p*-Value**
GA, weeks	0.191 (0.092–0.290)	< 0.001
BW SDS	−0.459 (−0.934–0.015)	0.058
BL SDS	−0.127 (−0.581–0.328)	0.580
Birth head circumference SDS	0.495 (−0.125–1.114)	0.115
B. Cortisol Level at 1 Month of Age		
	Partial Correlation Coefficient (95% CI)	***p*-Value**
GA, weeks	0.558 (0.236–0.881)	0.001
BW SDS	−1.151 (−2.700–0.398)	0.142
BL SDS	0.095 (−1.389–1.578)	0.899
Birth head circumference SDS	2.533 (0.514–4.552)	0.015
C. Δ Cortisol		
	Partial Correlation Coefficient (95% CI)	***p*-Value**
GA, weeks	0.367 (0.028–0.707)	0.034
BW SDS	−0.692 (−2.323–0.939)	0.399
BL SDS	0.221 (−1.341–1.783)	0.778
Birth head circumference SDS	2.039 (−0.876–4.165)	0.060

BL, birth length; BW, birth weight; CI, confidence interval; GA, gestational age at birth; SDS, standard deviation score.

3.2. Study 2

3.2.1. Clinical Characteristics

Mothers who delivered at least one SGA infant were included in the SGA group. Maternal complications, such as multiple births, HDP, GDM, and chorioamnionitis were not significantly different between the two groups (Table 4). No significant difference was found between the two groups regarding maternal betamethasone use (SGA 69.6% vs. non-SGA 70.0%, $p = 1.000$). No significant difference between the two groups was found with respect to the timing of betamethasone use ($p = 0.113$). In the SGA group, fetal distress was the most common cause for delivery (13 / 23 cases, 56.5%). In the non-SGA group, threatened preterm delivery was the most common cause for delivery (21 / 30 cases, 70.0%).

As expected, BW, BL, and birth head circumference were significantly lower in the SGA group than in the non-SGA group. No significant differences were found in the GA (Table 4).

Table 4. Clinical characteristics of SGA and non-SGA groups.

Mothers *N* = 53	**SGA** *N* = 23	**Non-SGA** *N* = 30	***p*-Value**
Age at delivery, years	31 (26–36)	32 (24–36)	0.212
Pre-pregnancy BMI, kg/m²	22.2 (16.7–33.8)	20.9 (15.6–26.6)	0.049
Weight gain during pregnancy, kg	7.1 (1.0–24.4)	5.8 (0.0–14.8)	0.543
Height, cm	157.6 (149.0–172.0)	156.2 (144.6–168.0)	0.287
Placenta weight, g	311 (136–480)	420 (242–804)	< 0.001
Di- and tri-chorionic births, *n* (%)	3 (13.0)	3 (10.0)	1.000
Hypertensive disorders of pregnancy, *n* (%)	12 (52.2)	4 (13.3)	0.006
Gestational diabetes mellitus, n (%)	1 (4.3)	0 (0.0)	0.434
Chorioamnionitis, *n* (%)	10 (43.5)	18 (60.0)	0.276
Prepartum use of betamethasone, *n* (%)	16 (69.6)	21 (70.0)	1.000
Last use of betamethasone, days before delivery, *n* = 37	14 (0–35), *n* = 16	4 (0–28), *n* = 21	0.113
Infants *N* = 61	**SGA** *N* = 24	**Non-SGA** *N* = 37	
Male sex, *n* (%)	11 (45.8)	11 (29.7)	0.068
GA, weeks	31 (26–36)	32 (24–36)	0.796
BW, g	1051 (464–1900)	1575 (578–2834)	< 0.001
BW SDS	−2.5 (–4.23–−1.29)	−0.23 (−1.27–1.69)	< 0.001
BL, cm	36.4 (28.0–46.5)	40.5 (30.0–47.0)	0.001
BL SDS	−2.2 (−4.17–0.33)	−0.31 (−1.89–1.71)	< 0.001
Birth head circumstance, cm	26.7 (20.7–31.0)	29.2 (20.0–34.5)	0.013
Birth head circumstance SDS	−1.0 (−2.48–0.50)	0.14 (−1.07–1.92)	< 0.001
Respiratory distress syndrome, *n* (%)	11 (45.8)	15 (40.5)	0.793
Chronic lung disease, *n* (%)	7 (29.2)	7 (18.9)	0.370
Late-onset circulatory collapse, *n* (%)	3 (12.5)	2 (5.4)	0.373
Sepsis, *n* (%)	0 (0)	1 (2.7)	1.000
Retinopathy of prematurity, *n* (%)	1 (4.2)	1 (2.7)	1.000
Meconium disease, *n* (%)	1 (4.2)	1 (2.7)	1.000
Periventricular leukomalacia, *n* (%)	1 (4.2)	1 (2.7)	1.000

Data are shown as the median (range) or number (percentage). BMI, body mass index; BL, birth length; BW, birth weight; GA, gestational age at birth; SDS, standard deviation score.

3.2.2. Plasma Cortisol Levels

Plasma cortisol levels at birth and at 1 month of age were plotted based on GA in SGA and non-SGA infants (Figure 1). A comparison of plasma cortisol levels between SGA and non-SGA infants is presented in Table 5. Plasma cortisol levels at birth were significantly higher in the SGA group than in the non-SGA group ($p = 0.010$). However,

there were no significant differences in plasma cortisol levels at 1 month of age and Δ cortisol levels between the two groups.

Table 5. Comparison of plasma cortisol levels between SGA and non-SGA infants.

	All Infants $N = 61$	SGA $N = 24$	Non-SGA $N = 37$	p-Value
At birth, μg/dL	2.02 (0.17–5.80)	2.45 (0.51–5.80)	1.62 (0.17–4.89)	0.010
1 month of age, μg/dL	5.80 (0.74–20.3)	5.37 (0.74–13.7)	5.80 (1.03–20.3)	0.816
Δ cortisol, μg/dL	4.21 (−4.91–19.39)	2.28 (−4.91–11.47)	4.61 (−2.55–19.39)	0.181

Data are shown as medians (ranges).

4. Discussion

In the present study, we observed that in preterm infants, plasma cortisol levels at birth and at 1 month of age were positively correlated with GA. Importantly, plasma cortisol levels at 1 month of age were positively correlated with head circumference SDS at birth. SGA infants had significantly higher plasma cortisol levels at birth than non-SGA infants; however, this significant difference disappeared at 1 month of age.

4.1. Maternal Steroid Administration and Fetal Cortisol Levels

Most of the cortisol in maternal blood is inactivated by 11βHSD2 in the placenta to maintain fetal blood cortisol levels at approximately 10% of the maternal levels [22]. Hence, the fetus develops in an environment with low cortisol concentrations before delivery, but the high concentrations affect the hypothalamic–pituitary–adrenal axis (HPA-axis) [23]. Thus, the regulation of fetal cortisol concentration involves placental 11βHSD2 [3] and the fetal HPA axis [23]. Prepartum synthetic steroid administration, intrauterine infection, and HDP are also known to affect fetal cortisol concentrations [22]. Synthetic steroids (betamethasone or dexamethasone) are commonly used for pulmonary maturation in preterm infants before delivery, and are not inactivated in the placenta. However, they are known to accumulate in the fetus and affect fetal cortisol levels [22]. In Study 1, because approximately 70% of the mothers received betamethasone, plasma cortisol levels were affected in some infants. In Study 2, the use and timing of maternal betamethasone did not differ significantly between the SGA and non-SGA groups.

4.2. Factors Affecting Plasma Cortisol Levels and Physique

GA is known to affect fetal cortisol levels [24,25]. Similar results were obtained in Study 1. Importantly, we found that plasma cortisol levels at 1 month of age were associated with birth head circumference SDS, as well as GA. There have been several reports regarding physique and cortisol levels [7,24,26,27], but they vary in background; cortisol specimens included hair, serum, and saliva. The GA and age at the time of measurement were not considered.

In fetal growth restriction, blood flow to the limbs decreases, height decreases, and weight gain decreases. However, vital organs, such as the brain and adrenal glands, are prioritized [28]. SGA infants with severely small head circumferences do not maintain their height and weight [29,30]. As such, height and weight are affected earlier than the head circumference. When the head circumference can no longer be maintained, the adrenal function, as well as the brain also declines. Cortisol levels might be more closely associated with head circumference, rather than weight or height. There is a possibility that studies conducted with larger cohorts may reveal an association between BW or BL and plasma cortisol levels. However, because it does not affect the adrenal glands at the time at which BL and BW are affected, the association between BL and BW is not clinically significant. Plasma cortisol levels in the first month of life reflect an infant's adrenal function. Infants with small head circumferences may have low plasma cortisol levels at 1 month of age. Further studies are required to confirm this hypothesis.

4.3. Plasma Cortisol Levels in Preterm SGA Infants

SGA infants had significantly higher plasma cortisol levels at birth than non-SGA infants; fetal distress was the most common cause of preterm birth in SGA infants, which was more common than in non-SGA infants. Previous studies reported that the HPA axis is affected by fetal distress, undernutrition, maternal infection, and strict diet [22,31]. Excessive fetal cortisol exposure may also induce fetal growth restriction and preterm birth [32]. In a previous report, salivary cortisol levels within 5 days of age in SGA at 31–39 GA were significantly higher than those in non-SGA [6] In the present study, SGA preterm infants were considered to be exposed to low nutrition or fetal distress, which caused HPA-axis activity and high plasma cortisol levels at birth. Furthermore, this result was implicated to be important in relation to long-term neurological outcome. In the Cochrane library, Doyle et al. reported long-term neurological outcome in preterm infants who had steroids at < 8 days of age to prevent or treat CLD in meta-analyses; resulting in the view that dexamethasone treatment at an early age was associated with increased risk of an abnormal neurological examination, developmental delay, and cerebral palsy [33]. A high plasma cortisol level at birth in preterm SGA infants may, therefore, be associated with abnormal neurological outcome. Plasma cortisol level at birth may be a predictive factor for long-term abnormal neurological outcome. Further prospective cohort studies are required to investigate long-term neurological outcomes in preterm SGA infants with a high plasma cortisol level.

Our results revealed that plasma cortisol levels at 1 month of age were not significantly different between the SGA and non-SGA groups. Iwata et al. reported that cortisol levels in saliva were higher in the non-SGA group than in the SGA group after 14 days of age [6]. The reason for this might be that their report involved a mixture of preterm and full-term infants. Furthermore, there was no consideration of GA in the comparison between SGA and non-SGA infants. SGA infants have high plasma cortisol levels at birth and fetal distress. The HPA axis, and placental 11βHSD2, associated with low nutrition and fetal distress, are profoundly involved, but this effect disappears at 1 month of age.

4.4. Limitations

Our study had some limitations. First, because this was a single-center study with a short duration, the number of infants in the cohort was limited. Second, this study included all preterm infants born by cesarean section with a high percentage of prenatal dexamethasone administrations to pregnant women, which was a major limitation,. Słabuszewska-Jóźwiak et al. reported that there was no difference in umbilical cord blood cortisol levels between cesarean and vaginal delivery, but umbilical cord blood cortisol levels were significantly lower in scheduled cesarean section delivery than in vaginal delivery, possibly due to less distress involved in uterine contractions during delivery compared to vaginal delivery [34]. In this study, the differences in delivery were not examined. The activation of the HPA-axis is preparation for birth and the optimal and physiological reactions occur in a vaginal birth. Further studies using preterm infants born by vaginal delivery are needed to confirm our results.

5. Conclusions

GA is an independent determinant of plasma cortisol levels at birth. SGA infants had a high plasma cortisol level at birth; resulting in speculation that a high plasma cortisol level at birth may be associated with abnormal neurological outcome. Further follow-up studies using a large cohort are required to confirm this result.

Author Contributions: M.A., T.U., N.N., and I.M. conceived and designed the study, acquired, analyzed, and interpreted the data; and drafted the manuscript. M.A., T.U., N.N., R.A., and I.M. were involved in the implementation of the study and data collection. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Ethics Committee of Nihon University School of Medicine (approval no.: RK-190910-3, date: 20 November 2019). This study was conducted in accordance with the relevant guidelines and regulations.

Informed Consent Statement: Written informed consent for publication was obtained from the parents of all enrolled newborns.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no competing interests in this study.

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主論文の和文の要約

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論文題名： Association of Plasma Cortisol Levels with Gestational Age and Anthropometric Values at Birth in Preterm Infants

（早産児における血漿コルチゾール値と在胎週数や体格との関連について）

1. 背景

コルチゾールは人間の生命維持に不可欠なホルモンであり、胎児期に臓器の成熟を促進するが、過剰になると胎児発育を抑制する[1]。母体血中のコルチゾールの大部分は胎盤中の 11β-hydroxysteroid dehydrogenase-2（11βHSD2）によって不活型のコルチゾンに変換され、胎児への活性型コルチゾールの流入を抑えている。そのため胎児は通常出生前はコルチゾール濃度が低い環境(母体環境の 10%）で発育する。しかし、低栄養、低酸素などのストレスがあると、この 11βHSD2 が働かなくなるためコルチゾールに変換されず、活性型コルチゾールが胎児に流入してしまう[2]。視床下部-下垂体-副腎系 Hypothalamic-Pituitary- Adrenal（HPA-axis)は副腎から分泌されるコルチゾールの分泌を調節し、コルチゾールが高いと視床下部や下垂体にネガティブフィードバックがかかり、コルゾ―ル分泌が抑制される。逆にコルチゾールが低いと視床下部や下垂体にポジティブフィードバックがかかり、コルゾ―ル分泌が亢進する。このように胎児コルチゾール濃度の調節には、胎盤の 11βHSD2 と胎児 HPA-axis が関与している(Figure1)。何らかの原因（感染や胎盤、母体要因）によって規定よりも早く出生する早産児はストレスが多いため 11βHSD2 の低下により、より多くのステロイド暴露をうけることとなる。

Small-for-gestational age（SGA）とは、出生時の体重が在胎週数相当の 10 パーセンタイル未満で出生時した児のことをいう[3]。子宮内で胎児の発育が障害されて在胎週数相当の発育ができない胎児発育不全である。母体のやせや高齢出産、多胎児の増加により SGA 出生は増加傾向にある。SGA 児では低酸素や低栄養などのストレスにさらされてその環境適応として臓器の組織構造に変化を与え、出生後環境とのミスマッチにより SGA 児は将来、肥満、糖尿病、高血圧症などのメタボリック症候群のリスクがある。ラットの研究では子宮内胎児発育不全があるとネフロン数が減少して慢性腎臓病のリスクとなり[4]、同じくラットの研究で子宮内胎児発育不全があると神経細胞の遊走に関与する分子生物学的変化により大脳の狭小化がおこり注意欠陥多動性障害、認知・学習障害のリスクが報告されている[5]。このようにコルチゾールは生命維持や成長などの臓器成熟だけでなく、代謝疾患や精神発達にも深く関わるホルモンである。

コルチゾールはホルモンの中でもストレスや日内変動の影響が大きいため研究は容易ではない。これまでもコルチゾールと早産・低出生体重児、SGA、および新生児疾患との関連について報告されている[6,7,8,9]がその背景（対象、測定時の在胎週数や年齢、時間）は様々

であり、検体も毛髪、血清、唾液など報告によって異なり結論も一定でない。そこで我々は対象や検体、採取時期・タイミングを統一して早産児に限定して血漿コルチゾール値と在胎週数および身体測定値との関連を検討することとした。

2. 目的

早産児において出生時および生後 1 か月の血漿コルチゾール値と、在胎週数、出生時の体格との関連を明らかにすること（研究 1)、SGA 児と non-SGA 児の出生時と生後 1 ヶ月の血漿コルチゾール値を比較すること（研究 2)。

3. 対象と方法

3.1 対象児

本研究は、日本大学医学部附属板橋病院臨床研究倫理審査委員会の承認を得た（承認番号：RK-190910-3、日付：2019 年 11 月 20 日)。2019 年から 2021 年に日本大学医学部附属板橋病院において帝王切開で出生した早産児(在胎 22 週 0 日-36 週 6 日)を対象とした。一卵性双胎児、重度の先天性心奇形、染色体異常児は除外した。出生時の体重が在胎週数相当の 10 パーセンタイル未満を SGA 児、10 パーセンタイル以上を non-SGA 児とした。

3.2. 血液サンプルの採取と血漿コルチゾール値の測定

出生直後は臍帯静脈から、生後 1 か月は授乳前の午前 8 時から 9 時に静脈から血液サンプルを採取した。Δ コルチゾール値は生後 1 か月と出生時の差と定義した。

3.3. 出生から生後 1 か月までの栄養方針

生後まもなく 10%糖液の投与を開始し、水分率 50～60mL/kg/日とした。その後日々の体重増減、尿量、不感蒸泄量を考慮し水分率 10mL/kg/日ずつ増量し、100～120 mL/kg/日を維持した。児の状況に応じて経腸栄養（基本的に母乳）を開始し、輸液を減量、経腸栄養のみの場合は水分率 130mL/kg/日で維持した。修正 35 週以降は自律哺乳とした。

3.4. 臨床的特徴および疾患の定義 （Table1）

母体因子は、出産時年齢、妊娠前 BMI、妊娠中の体重増加、身長、胎盤重量、双胎または品胎出産、妊娠高血圧症、妊娠糖尿病、絨毛膜羊膜炎、分娩前のベタメタゾン筋注（33 週 6 日以前の早産リスクの高い妊婦に 12mg の筋注を 24 時間おきに 2 回実施）の有無を検討した。児因子は、性別、在胎週数、出生時の体重・身長・頭囲、それぞれの SDS：standard deviation score、呼吸窮迫症候群、慢性肺疾患*、晩期循環不全、動脈管開存症、敗血症、未熟児網膜症、壊死性腸炎、胎便関連腸閉塞、脳室内出血、脳室周囲白質軟化症の合併の有無を検討した。

＊慢性肺疾患とは、「先天奇形を除く肺の異常により、酸素投与を必要とするような呼吸窮迫症状が新生児期に始まり日齢 28 日を越えて続くもの」と定義し、慢性肺疾患を「胸部Ｘ線写真で、びまん性不透亮像、泡沫状陰影など明らかな異常所見を伴う慢性肺障害のある場合」とした[10]。原因は、外因性因子（人工呼吸器による圧損傷など）と Wilson-Mikity

症候群に代表される内因性因子（肺の未熟性、子宮内感染および脆弱性）に分類されるが[11]、臨床的にも胸部レントゲン的にも判別は不可能であり両者を含めて慢性肺疾患と定義されている。

胎盤機能不全とは胎盤機能が低下して胎児が低酸素・低栄養となり発育不良、仮死状態となることである。原因としては母体因子（妊娠高血圧症候群、糖尿病、腎炎、加齢、抗リン脂質症候群など）、胎児因子（染色体異常）、胎盤因子（前置胎盤、常位胎盤早期剥離）があり、母体側の要因であることが多い[12]。

4. 統計解析

JMP ver14.0 を用いて行い、$p<0.05$ を有意とした。

研究 1：在胎週数、出生時の身体測定 SDS と、出生時と生後 1 か月の血漿コルチゾール値との関連を明らかにするため回帰分析を行い、決定係数、 p 値を算出した（Table2）。また出生時および生後 1 か月の血漿コルチゾール値と在胎週数の関連について、SGA 群と non-SGA 群それぞれで線形回帰分析を用いて検討した（Figure2）。最後に出生時および生後 1 か月の血漿コルチゾール値、Δコルチゾール値を目的変数、在胎週数および出生時の身体測定 SDS を説明変数として重回帰分析を行った（Table3）。

研究 2：SGA 群と non-SGA 群の比較のため Mann-Whitney U 検定および Fisher の正確確率検定を用いて以下の解析を行った：母体および児の臨床背景の比較（Table4）、出生時と生後 1 か月の血漿コルチゾール値、Δコルチゾール値の比較（Table5）、SGA 群と non-SGA 群の早産に至った原因について検討した。

5. 結果：

研究 1：早産児 61 名（SGA 群 24 名、non-SGA 群 37 名）が対象となり、母親のうち 4 名が双胎、2 名が品胎を出産しているため、母親は 53 名が対象となった（Table1）。出生時・生後 1 か月の血漿コルチゾール値、Δコルチゾール値いずれも在胎週数と正の相関を認め（Table2A-C）、重回帰分析では、出生時とΔコルチゾールは在胎週数と正の相関を示し、生後 1 か月の血漿コルチゾール値は在胎週数だけでなく出生時の頭囲 SDS とも正の相関を示した（Table3A-C）。全児だと、出生時・生後 1 か月の血漿コルチゾール値は在胎週数と正の相関を示したが、SGA 群のみの検討では出生時血漿コルチゾールは在胎週数と相関を認めなかった（Figure2）。

研究 2：SGA 出産母体は non-SGA 出産母体に比較して有意に胎盤重量が小さいが、妊娠高血圧症、妊娠糖尿病、絨毛膜羊膜炎などの合併症や、ベタメタゾン使用と使用時期に有意差は認めなかった。新生児の臨床因子については、SGA 群は non-SGA 群よりも有意に体格が小さいが、早産に伴う合併症（呼吸窮迫症候群、慢性肺疾患、晩期循環不全、敗血症など）については両者に有意差を認めなかった（Table4）。SGA 群は non-SGA 群と比較して血漿コルチゾールは出生時には有意に高値だが、生後 1 か月になると有意差を認めなかった

（Table5）。また、SGA 群と non-SGA 群の分娩に至った原因について検討したところ、SGA 群では胎盤機能不全（56.5%）、non-SGA 群では切迫早産（70.0%）が最多だった。

6. 考察

本研究では、早産児全体において出生時および生後 1 か月の血漿コルチゾール値は、在胎週数と正の相関があるが、SGA 群のみの検討では、出生時の血漿コルチゾールは在胎週数と相関を認めず高値であることを明らかにした。コルチゾールと体格指数との関連については、早産児において生後 1 か月の血漿コルチゾールは出生時の頭囲 SDS と正の相関があることを明らかにした。また、SGA 群と non-SGA 群を比較した検討では、SGA 群は出生時の血漿コルチゾール値が有意に高く、生後 1 か月では non-SGA 群と差を認めなくなった。

コルチゾールはストレスや日内変動の影響をうける。在胎週数は胎児のコルチゾールに影響を与えることは既報でも知られており[7,13]、研究 1 でも同様の結果が得られた。早産児とコルチゾールに関する報告はいくつかあるが（Table.6）[6,7,8,9]、その背景は様々で、採取された検体には毛髪、血清、唾液などがあり、測定時の在胎週数や年齢、時間などが一定でないため結論も一致していない。唾液検体と血漿検体でのコルチゾール値の精度を比較検討すると唾液は血漿に比較してコルチゾール値の感度や特異度が低く、また量の確保が難しく適切な検体でないと報告されている[14]。コルチゾールは針の穿刺へのストレスでも正確な値がでないこと、また早産児対象にしているため体格が小さいほど採血量が多いと容易に貧血になる。そこで本研究では児にストレスを与えず、量も確保可能で純粋に胎児血として評価できる臍帯血を出生時の血漿検体として採用した。臍帯血とは、児と母体を繋ぐ胎児側の組織である臍帯の中に含まれる胎児血のことであり、臍帯血での血液ガス検査の pH で児の状態を把握できるとされ[15]、臍帯血は児の状態を正確に反映する。本研究では、出生時は臍帯血、生後 1 か月はミルクまたは母乳哺乳の 1 時間前で午前 8-9 時と条件を統一して採血していること、また出生時・生後 1 ヶ月ともに血漿コルチゾールが採取できてより生理的で新規性がある。また対象も既報では早産児と正期産児、SGA と non-SGA 児が混同されていたが、本研究は早産児に限定し SGA と non-SGA 児を区別して検討を行った。そのため本研究は既報と比較しても対象と方法の設定を整えて検討を行っているため、結果は信頼性が高いと考える。

コルチゾールと体格指数との関連について、早産児において生後 1 か月の血漿コルチゾールは、出生時の頭囲 SDS と正の相関があることが明らかとなった。ヒトでは重要臓器である脳、心臓と同様に副腎も血流が優先される臓器である[16]。これらの重要臓器の血流確保のため四肢への血流が減少し身長、体重が小さくなる（身長と体重は、頭囲よりも早く影響を受ける）。しかし、いよいよ脳(頭囲)、副腎が保たれなくなるころには身長および体重も維持できなくなる。つまり出生時の頭囲が小さい乳児は、生後 1 か月のコルチゾールが低い可能性があるといえる。

研究 1（Figure2）と研究 2（Table5）の結果では、SGA 群は、non-SGA 群よりも出生時の血漿コルチゾール値が在胎週数によらず有意に高く、ストレスの影響と思われた。SGA 群では non-SGA 群に比較して胎盤重量が優位に小さかった。これはストレスによりコルチゾールが上昇して胎盤発育が抑制されたと考えられた（SGA ではストレスが多い➔コルチゾール上昇➔胎盤の発育が抑制）。逆に早産の理由として SGA 群は non-SGA 群よりも胎盤機能不全が最多であり、このストレスによりコルチゾールが高値となった可能性も否定できない (SGA では胎盤機能不全が多い➡ストレス上昇➔コルチゾール高値)。以上より SGA 児、胎盤重量、出生時コルチゾールは相互に関与していると考えられる。

胎児のコルチゾールの分泌を調整する HPA-axis や 11β HSD-2 は胎盤機能不全、低栄養、母体感染症の影響を受けることが報告されている[17,18]。在胎週数や陣痛による 11β-HSD2 への影響を検討した研究によると[19]、胎盤における 11β-HSD2 mRNA の存在量は、在胎週数や陣痛によって変化なく、11β-HSD2 のタンパク質量は妊娠年齢や陣痛の開始とともに減少傾向だが有意ではなかった。38 週から 40 週にかけて 11β-HSD2 活性の有意な減少が見られたが、陣痛による 11β-HSD2 活性の有意な変化は見られなかった。以上より 11β-HSD2 活性は在胎週数と無関係であることが分かった。

11β-HSD-2 や HPA-axis 以外にも胎盤 Corticoid releasing hormone（CRH）が胎児期のコルチゾールの調節を担っている、胎盤 CRH は妊娠 8-10 週から胎盤で産生され、構造的・免疫活性的に視床下部 CRH と同一であり、母体と胎児の両方から分泌される。HPA-axis だとコルチゾールが高いとネガティブフィードがかかるので、CRH や ACTH は抑制される。一方で胎盤 CRH については、ポジティブフィードバックするので、コルチゾール高値だと胎盤 CRH が亢進する。例えば胎盤機能不全により胎児ストレスがあると胎児胎盤 CRH、下垂体 ACTH、副腎の順で刺激されてコルチゾールが分泌亢進する。一方で母体にもストレスがあると、母体胎盤 CRH、下垂体 ACTH、副腎の順でコルチゾールが分泌亢進する[20]。また胎盤機能不全そのものにより 11β-HSD2 が阻害されて胎児にコルチゾールが流入する。胎盤機能不全の多くは母体側要因であるが、ストレス負荷は母児ともにかかるためコルチゾール高値の由来は、母体と胎児両方からと考えられる。このように ACTH は胎盤 CRH の影響もうけており、コルチゾールに対する純粋な視床下部-下垂体-副腎系（HPA-axis）の反応の評価が難しいため、今回の研究では ACTH の測定は行っていない。またコルチゾールと同様に新生児期の正常値が規定されていない。

本研究では、SGA 群と non-SGA 群の比較において母体の合併症や児の合併症に有意差を認めず、SGA 群における早産の最大の原因は胎盤機能不全（56.5%）だった。このことより SGA では胎盤機能不全により、出生前から前記の機序で高ステロイドの環境下で出生時の血漿コルチゾールの高値を引き起こす可能性が考えられた。胎盤機能不全を示すバイオマーカーは今のところないが、本研究によって出生時のコルチゾール高値が胎盤機能不全の存在を示唆する可能性がある。

一方で生後 1 ヶ月になると SGA 群と non-SGA 群でのコルチゾール値に有意差は認めな

くなった。これは出生時のコルチゾールが優位に高値である SGA 群において生後 1 か月にはストレスが解除されるためと考えられた。しかし早産児のなかでも超早産児において、生後 1 か月以降にコルチゾール高値が持続することがあり、これは胎児期により多くのステロイドに暴露された影響で HPA-axis のセットポイントが上昇した結果といわれている[6]。胎児期のストレスや長期のコルチゾール高値は認知能力に悪影響を及ぼし[21]、情動や不安を増加させる[22,23]。その理由としてグルココルチコイド受容体は海馬に存在し、HPA 活性のフィードバック制御の重要な箇所であり影響をうけやすい。早産児の神経画像研究において、海馬の体積が減少しているという報告もある[24,25]。

本研究は早産児を対象としているため肺成熟を目的とした分娩前のベタメタゾン投与が高頻度である(SGA 群 69.6%、non-SGA 群 70.0%)。ベタメタゾンやデキサメタゾンなどの合成ステロイド以外のステロイドだと 11βHSD2 によって不活化型のコルチゾンに変換されるため活性型は 10%程度しか胎盤を通過しない（胎児は母体ステロイド濃度の 10%)。しかし合成ステロイドは CBG(corticosteroid-binding globulin)を要せず、また 11β-HSD 2 の作用を受けないので、胎盤で不活化されずほぼ胎児まで移行する。規定量だと問題がないことが多いが大量投与であると新生児期の合併症（慢性肺疾患、呼吸窮迫症候群、晩期循環不全）と関連する[26]。ベタメタゾン投与の出生時コルチゾール値への影響をみるために投与群と非投与群での出生時のコルチゾールについて検討した[Table.7]。分娩前ベタメタゾン投与群で出生時コルチゾール中央値 1.62μg/dL、非投与群で出生時コルチゾール中央値 2.90μg/dL、p 値<0.01 であり非投与群で有意に高値だった。この理由として非投与群は分娩日がベタメタゾン投与の適応にならない 34 週 0 日以降の週数であり、本研究により明らかなことだが、出生時コルチゾールは在胎週数に依存するため、非投与群（在胎週数が長い群）でコルチゾールが高値を示したと考えられた（例外的に切迫早産でベタメタゾンの筋肉注射をやらない間に緊急帝王切開で出生した児が含まれている)。以上より、本研究では分娩前ベタメタゾンの投与は出生時のコルチゾール値には影響を与えていないと考えられた。

Doyle らは、早産児とコルチゾールの関係について、慢性肺疾患の予防や治療のために生後 8 日未満でステロイドを使用した早産児の長期神経学的転帰をメタ解析で報告し、早期のデキサメタゾン投与は神経学的検査異常、発達遅延、脳性麻痺のリスク上昇と関連すると報告している[27]。ステロイド投与の短期的(修正 36 週の時点)な神経学的検査異常としては脳室内出血、脳室周囲白質軟化症、未熟児網膜症、短期的な身体発育はで体重と頭囲が小さいと報告している[28]。長期的な神経学的異常は注意欠陥多動性障害、うつ病、統合失調症[29]、身体発育への影響は、生後 1 ヶ月までは対象患者と比較して体重と頭囲の発育が不良になる[30]が、それ以降報告はなく将来の低身長との因果関係は報告されていない[31]。以上より早産 SGA 児の出生時の血漿コルチゾール高値は、長期的な神経学的転帰の異常と関連している可能性があり、その予測因子としての有用性を示唆する。出生時血漿コルチゾールが高値である早産 SGA 児の長期神経学的転帰を調べるために、さらなる前向きコホート研究が必要である。

6. Limitation

経腟分娩の生理的反応として HPA-axis の活性化が起こるが本研究では全例帝王切開の早産児が対象であるため、分娩法による違いが検討されていない（しかし帝王切開で条件を統一して検討ができた利点はある)。また研究期間が短く長期予後がおえていない。

11βHSD は胎盤やその他の組織にみとめる。胎盤ではコルチゾール（活性型）からコルチゾン（不活性型）に変換することで胎児へのコルチゾ―ルの流入をおさえている。11βHSD2 の活性をみるには遺伝子発現を確認する必要があるが本研究では行っていない。11βHSD-2 活性とよく相関するのがコルチゾール/コルチゾン比である[32]。11βHSD 2 活性が悪いとこの比は上昇し、活性が良いとこの比は低下する。本研究ではコルチゾンの測定は行っていないので各症例で 11βHSD2 活性の評価はできていない。

7. 結論

早産において在胎週数は出生時の血漿コルチゾールの独立した決定因子であるが、SGA 児ではその関連が破綻する。SGA 児は non-SGA 児と比較して、出生時の血漿コルチゾール値が高く、それが長期的な神経学的転帰の異常と関連しているか更なる検討が必要である。

＜本研究の新規性と社会への貢献について＞

手法としての新規性：コルチゾールの検体が唾液や毛髪ではなく出生時、生後 1 か月ともにより生理的である血漿で検討していることと、コルチゾールはストレスや日内変動の影響をうけやすいが対象すべてにそのようなバイアスを排除して検討を行った。また既報では早産と正期産、SGA と non-SGA 児が混同されていて結果が正確でない（一定していない）が、本研究は早産児に限定して更に SGA と non-SGA 児を区別して検討を行った。

結果の新規性：早産児において在胎週数は出生時の血漿コルチゾールの独立した決定因子であるが、SGA 児ではその関連が破綻し、在胎週数によらず出生時のコルチゾールが高い。早産 SGA 児は、胎内でコルチゾール暴露（強いストレス下にある）を受けている影響で、将来の神経学的予後が悪い可能性がある。早産児の臍帯血コルチゾールは新たな予後予測マーカーとなる可能性がある。また、出生時の頭囲ＳＤが小さい早産児は、生後 1 か月の副腎機能が出生時の頭囲 SD が保たれている児と比較して悪い可能性がある。

社会への貢献について：SGA 児は出生時の血漿コルチゾール値が高く長期的な神経学的転帰の異常と関連している可能性が高く、綿密にフォローアップすることで早期介入、治療が可能となり予後改善につながる。

Table 1. 母体と児の臨床背景

母体	***n* = 53**
出産時年齢（歳）	31 (24–36)
妊娠前 BMI, kg/m^2	21.5 (15.6–33.8)
妊娠中の体重増加, kg	5.9 (0.0–24.4)
身長, cm	156.9 (144.6–172.0)
胎盤重量, g	348 (136–804)
双胎または品胎出産, n (%)	6 (11.3)
妊娠高血圧症, n (%)	16 (30.2)
妊娠糖尿病, n (%)	1 (1.9)
絨毛膜羊膜炎, n (%)	28 (52.8)
分娩前のベタメタゾン使用, n (%)	37 (69.8)
最終ベタメタゾン使用-分娩までの日数, *n* = 37	6 (0–35)
児	**n = 61**
男児, n (%)	22 (36)
在胎週数, 週	31 (24–36)
体重, g	1424 (464–2834)
体重 SDS	-0.91(-4.23–+1.69)
身長, cm	39.0 (28.0–47.0)
身長 SDS	-0.9 (-4.23–+1.69)
頭囲, cm	28.8 (20.0–34.5)
頭囲 SDS	-0.16 (-2.48–+1.92)
呼吸窮迫症候群, n (%)	26 (42.6)
慢性肺疾患, n (%)	14 (23.0)
晩期循環不全, n (%)	5 (8.2)
動脈管開存症, n (%)	0 (0)
敗血症, n (%)	1 (1.6)

未熟児網膜症, n (%)	2 (3.3)
壊死性腸炎, n (%)	0 (0)
胎便関連腸閉塞, n (%)	2 (3.3)
脳室内出血, n(%)	0 (0)
脳室周囲白質軟化症, n (%)	2 (3.3)

データは中央値（範囲）または数値（%）で示す。

BMI, body mass index; SDS, standard deviation score

Table 2. 回帰分析

A. 出生時コルチゾール値

	決定係数	***p*-値**
在胎週数, 週	0.154	0.002
体重 SDS	0.057	0.063
身長 SDS	0.063	0.051
頭囲 SDS	0.015	0.344

B. 生後 1 か月コルチゾール値

	決定係数	***p*-値**
在胎週数, 週	0.146	0.002
体重 SDS	0.014	0.370
身長 SDS	0.010	0.453
頭囲 SDS	0.058	0.062

C. Δ コルチゾール値

	決定係数	***p*-値**
在胎週数, 週	0.067	0.044
体重 SDS	0.037	0.137
身長 SDS	0.031	0.172
頭囲 SDS	0.078	0.029

SDS, standard deviation score

Table 3. 重回帰分析

A. 出生時コルチゾール値

	偏相関係数（95% 信頼区間）	***p*-値**
在胎週数，週	0.191 (0.092–0.290)	<0.001
体重 SDS	-0.459 (-0.934–0.015)	0.058
身長 SDS	-0.127 (-0.581–0.328)	0.580
頭囲 SDS	0.495 (-0.125–1.114)	0.115

B. 生後 1 か月コルチゾール値

	偏相関係数（95% 信頼区間）	***p*-値**
在胎週数，週	0.558 (0.236–0.881)	0.001
体重 SDS	-1.151 (-2.700–0.398)	0.142
身長 SDS	0.095 (-1.389–1.578)	0.899
頭囲 SDS	2.533 (0.514–4.552)	0.015

C. Δコルチゾール値

	偏相関係数（95% 信頼区間）	***p*-値**
在胎週数，週	0.367 (0.028–0.707)	0.034
体重 SDS	-0.692 (-2.323–0.939)	0.399
身長 SDS	0.221 (-1.341–1.783)	0.778
頭囲 SDS	2.039 (-0.876–4.165)	0.060

SDS, standard deviation score

Table 4. SGA 群と non-SGA 群の母体と児の臨床背景の比較

母体　　*n* = 53	**SGA** ***n* = 23**	**non-SGA** ***n* = 30**	***p*-値**
出産時年齢，歳	31 (26–36)	32 (24–36)	0.212
妊娠前 BMI, kg/m^2	22.2 (16.7–33.8)	20.9 (15.6–26.6)	0.049
妊娠中体重増加, kg	7.1 (1.0–24.4)	5.8 (0.0–14.8)	0.543
身長, cm	157.6 (149.0–172.0)	156.2 (144.6–168.0)	0.287
胎盤重量, g	311 (136–480)	420 (242–804)	<0.001
双胎または品胎出産, n (%)	3 (13.0)	3 (10.0)	1.000
妊娠高血圧症, n (%)	12 (52.2)	4 (13.3)	0.006
妊娠糖尿病, n (%)	1 (4.3)	0 (0.0)	0.434
絨毛膜羊膜炎, n (%)	10 (43.5)	18 (60.0)	0.276
分娩前のベタメタゾン使用, n (%)	16 (69.6)	21 (70.0)	1.000
最終ベタメタゾン使用-分娩までの日数, *n* = 37	14 (0–35), *n* = 16	4 (0–28), *n* = 21	0.113
児　　*n* = 61	**SGA** ***n* = 24**	**non-SGA** ***n* = 37**	***p*-値**
男児, n (%)	11 (45.8)	11 (29.7)	0.068
在胎週数，週	31 (26–36)	32 (24–36)	0.796
体重, g	1051 (464–1900)	1575 (578–2834)	<0.001
体重 SDS	-2.5 (-4.23–-1.29)	-0.23 (-1.27–+1.69)	<0.001
身長, cm	36.4 (28.0–46.5)	40.5 (30.0–47.0)	0.001
身長 SDS	-2.2 (-4.17–+0.33)	-0.31 (-1.89–+1.71)	<0.001
頭囲, cm	26.7 (20.7–31.0)	29.2 (20.0–34.5)	0.013
頭囲 SDS	-1.0 (-2.48–+0.50)	0.14 (-1.07–+1.92)	<0.001
呼吸窮迫症候群, n (%)	11 (45.8)	15 (40.5)	0.793
慢性肺疾患, n (%)	7 (29.2)	7 (18.9)	0.370
晩期循環不全, n (%)	3 (12.5)	2 (5.4)	0.373
敗血症, n (%)	0 (0)	1 (2.7)	1.000
未熟児網膜症, n (%)	1 (4.2)	1 (2.7)	1.000
胎便関連腸閉塞, n (%)	1 (4.2)	1 (2.7)	1.000
脳室周囲白質軟化症, n (%)	1 (4.2)	1 (2.7)	1.000

データは中央値(範囲)または数値(%)で示す。BMI, body mass index; SDS, standard deviation score

Table 5. SGA 群と non-SGA 群の血漿コルチゾール値の比較

	全児 ***n* = 61**	SGA ***n* = 24**	non-SGA ***n* = 37**	*p*-値
出生時, μg/dL	2.02 (0.17–5.80)	2.45 (0.51–5.80)	1.62 (0.17–4.89)	0.010
生後 1 か月, μg/dL	5.80 (0.74–20.3)	5.37 (0.74–13.7)	5.80 (1.03–20.3)	0.816
Δ コルチ―ル, μg/dL	4.21 (-4.91–+19.39)	2.28 (-4.91–+11.47)	4.61 (-2.55–+19.39)	0.181

データは中央値（範囲）で示す。

Table 6.　早産児・SGA 児におけるコルチゾールの報告

報告者	対象	測定検体	年齢	コルチゾール値
Buske-Kirschbaum, A. 2007	早産26-36週 正期産39-41週	唾液	8-14歳	早産、正期産で有意差なし
Grunau R.E. 2007	早産28-32週 正期産37-42週	唾液	3,6,8,18か月	生後3か月は早産＜正期産 8,18か月は早産＞正期産
Stoye,D.Q 2021	早産<32週 正期産 >37週	毛髪	日齢10 生後6週	生後6週は早産＜正期産
Iwata, S 2018	31-39週の SGA 体重1,092-2,250g	唾液	日齢5未満 日齢14以上	日齢5未満は SGA＞non-SGA 日齢14日以上は SGA＜non-SGA

- ✓ 測定検体や対象年齢が一定でない。
- ✓ 早産に限定してSGA児とnon-SGA児を比較した検討されていない。
- ✓ コルチゾールと在胎週数や出生時の体格との関連は十分に解明されていない。

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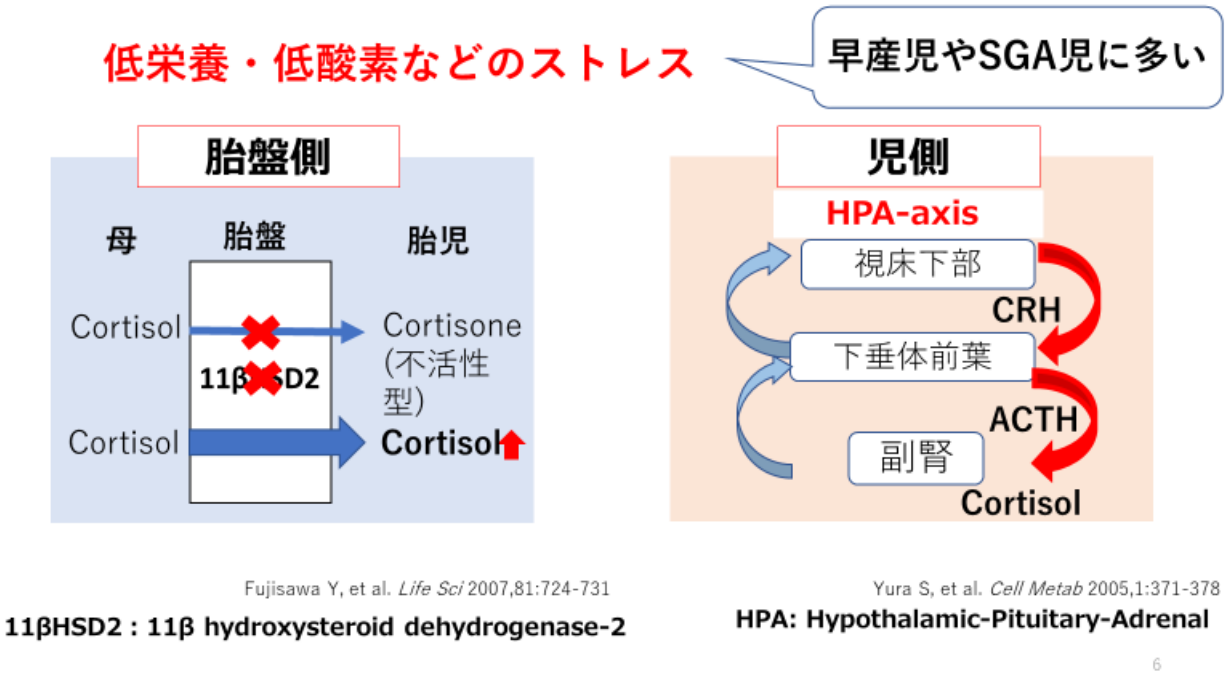
Table 7.　ベタメタゾン投与の有無と出生時のコルチゾール値

	ベタメタゾン投与群 n=45 (74%)	ベタメタゾン非投与群 n=16 (26%)	*p*値
出生時コルチゾール値（μg/dL）	1.62 (0.17-5.65)	2.9 (0.62-5.80)	<0.001
在胎週数	30週2日 （25週4日-36週0日）	34週4日 （25週4日-36週6日）	

Figure 1.　子宮内環境とコルチゾール



Fujisawa Y, et al. *Life Sci* 2007,81:724-731

11βHSD2 : 11β hydroxysteroid dehydrogenase-2

Yura S, et al. *Cell Metab* 2005,1:371-378

HPA: Hypothalamic-Pituitary-Adrenal

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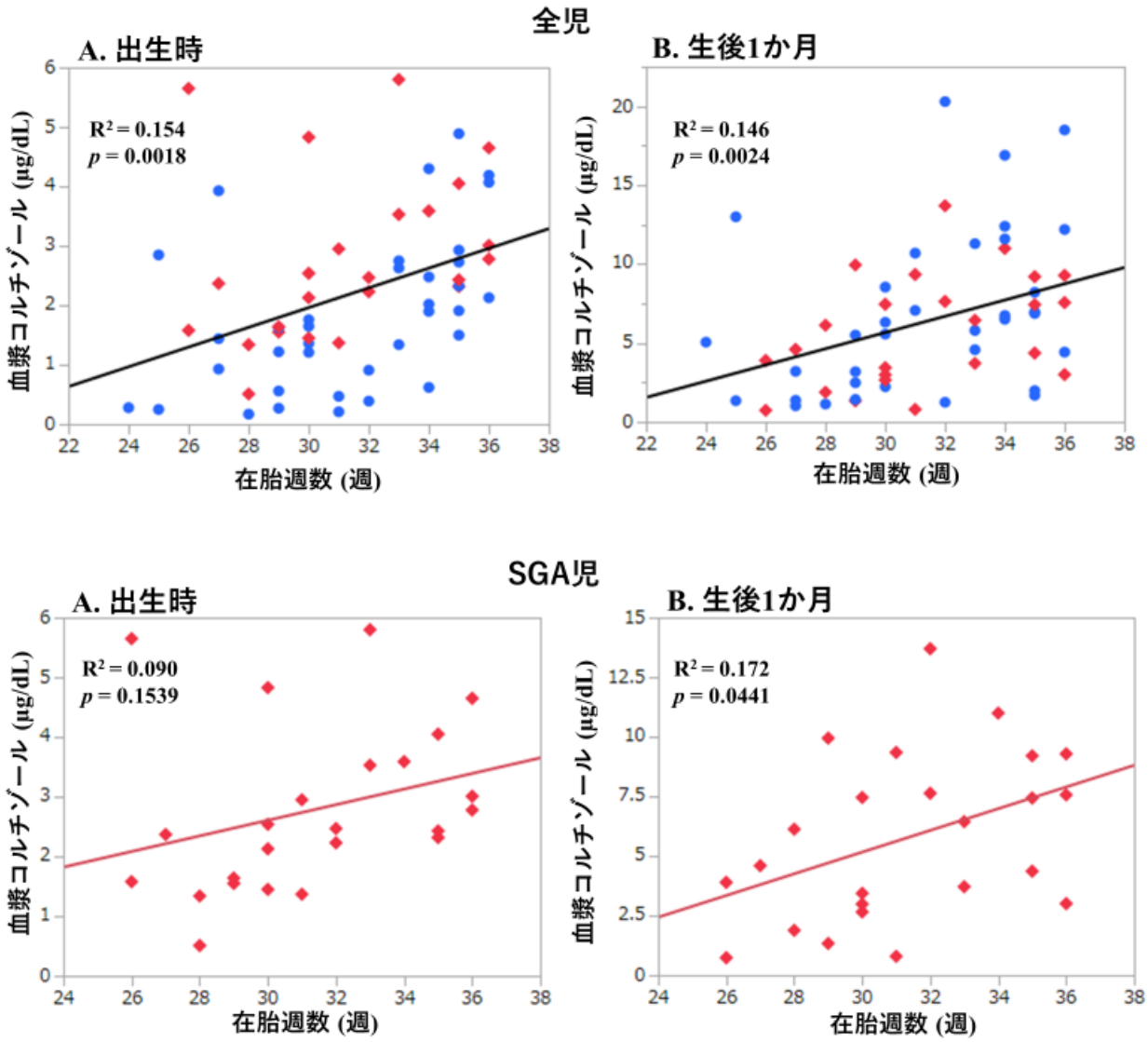
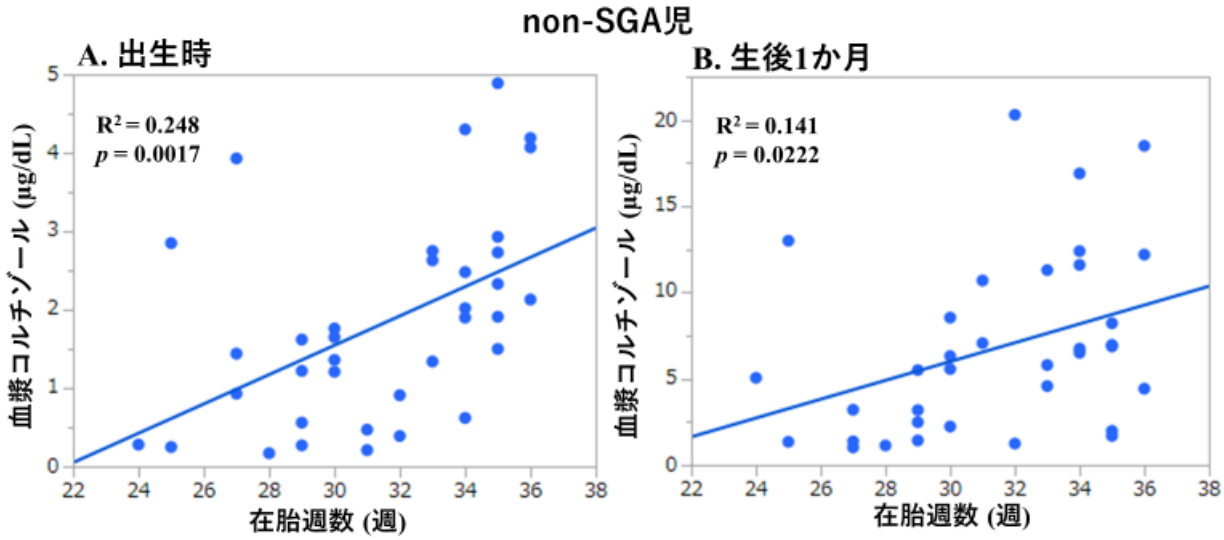
Figure 2.　在胎週数と出生時と生後 1 か月の血漿コルチゾールの関係

ひし形-赤；small-for-gestational age (SGA)，青-丸：non-SGA




non-SGA児
A. 出生時
B. 生後1か月
R² = 0.248
p = 0.0017
R² = 0.141
p = 0.0222
血漿コルチゾール (μg/dL)
在胎週数 (週)

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