Intrauterine growth and the maturation process of adrenal function

Sachiko Iwata[1], Masahiro Kinoshita[2], Hisayoshi Okamura[2],
Kennosuke Tsuda[1], Mamoru Saikusa[2], Eimei Harada[2], Shinji Saitoh[1]
and Osuke Iwata[1]

[1] Center for Human Development and Family Science, Department of Pediatrics and Neonatology,
Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi, Japan
[2] Centre for Developmental and Cognitive Neuroscience, Department of Paediatrics and Child Health,
Kurume University School of Medicine, Kurume, Fukuoka, Japan

ABSTRACT

Backgrounds: Environmental factors during early life alter the hypothalamus-
pituitary-adrenal (HPA) axis regulation and increase the risk of diseases in later life.
However, adrenal function at each developmental stage has not fully been
investigated in relation to pathological antenatal conditions. Cortisol levels of
newborns with intrauterine growth restriction (IUGR) are elevated during the
neonatal period; however, when studied during early childhood, cortisol levels are
reduced compared with their peers, suggesting that the HPA axis regulation might be
altered from activation to suppression, the timing of which remains uncertain.
Aim: The aim of this study was to assess the presence of an interaction between
intrauterine growth and postnatal age on cortisol levels in newborns hospitalised at a
neonatal intensive care unit.
Methods: We performed a secondary analysis using a dataset from saliva samples of
62 newborns collected between 30 and 40 weeks corrected age. Interactions between
postnatal age and clinical variables with regard to cortisol levels were assessed.
Results: The z-score of the birth weight and IUGR showed significant interactions
with postnatal age on cortisol levels; cortisol levels were higher ≤5 days of birth and
lower >14 days of birth than those in their peers without IUGR.
Conclusion: The adrenal function of newborns with IUGR might be altered
from activation to suppression within the first several weeks of life. Longitudinal
studies need to address when/how IUGR alters adrenal functions, and how these
responses are associated with diseases during adulthood.

Subjects Diabetes and Endocrinology, Pediatrics
Keywords Salivary cortisol, Hypothalamus-pituitary-adrenal axis, Placental 11-β-hydroxysteroid
dehydrogenase 2, Preterm infant, Intrauterine growth restriction

INTRODUCTION

During pregnancy, plasma cortisol levels markedly change with gestational stage
(*Mastorakos & Ilias, 2003*). However, the influence of maternal glucocorticoid on the
foetus is limited because of the activation of placental 11-β-hydroxysteroid dehydrogenase
2 (11-β-HSD2) and subsequent conversion of cortisol to biologically inactive cortisone
(*Benediktsson et al., 1997*). Clinical conditions such as maternal infection, strict diet,

hypoxia, and foetal stress attenuate placental 11-β-HSD2 activity (*Hardy & Yang, 2002*), which may increase foetal cortisol levels. Foetal exposure to excessive cortisol might induce pathological conditions such as intrauterine growth restriction (IUGR) and preterm labour (*Kajantie et al., 2003*; *Stewart, Rogerson & Mason, 1995*), which are associated with increased risks of short-term mortality and a range of long-term morbidities (*Hack et al., 2002*; *Hutchinson et al., 2013*; *Murray et al., 2015*; *Pallotto & Kilbride, 2006*). Increasing evidence suggests that homeostatic regulation is modified by environmental factors during early life, which is recognised as antenatal programming (*Barker et al., 1990*). Physiological stress response systems, particularly the hypothalamus-pituitary-adrenal (HPA) axis, have been suggested to play a central pathophysiological role in antenatal programming. Although stress-response actions may provide short-term benefits, the resultant alteration of the HPA axis may yield modified responses that result in the development of disease later in life.

Several studies have shown associations between perinatal physiological stress and attenuated adrenal function during childhood. For example, IUGR and preterm birth are associated with attenuated cortisol secretion at ages between 6 months and 7 years (*Brummelte et al., 2015*; *Fattal-Valevski et al., 2005*; *Ruys et al., 2017*). In contrast, when studied during the neonatal period, paradoxically increased cortisol levels were observed in association with IUGR and preterm birth (*Heckmann et al., 1999*; *Kajantie et al., 2003*; *Mericq et al., 2009*; *Stewart, Rogerson & Mason, 1995*), suggesting that the HPA axis regulation might be altered from activation to suppression at some point during infancy or early childhood. However, thus far, few studies have addressed temporal changes in adrenal function following birth in association with exposure to pathological conditions in utero.

Using a cohort of newborns hospitalised in a neonatal intensive care unit (NICU), we have previously reported that lower cortisol levels were associated with clinical events suggestive of unfavourable foetal/postnatal conditions such as exposure to maternal pregnancy-induced hypertension (PIH), caesarean delivery, and preterm birth (*Kinoshita et al., 2016*). Using the same dataset with these studies, we performed a secondary analysis to assess whether maturational changes in cortisol levels after birth vary with the presence of IUGR and other clinical variables suggestive of foetal physiological stress.

MATERIAL AND METHODS

Ethics approval and consent

This study was conducted in compliance with the Declaration of Helsinki and with the approval of the Ethics Committee of Kurume University School of Medicine (13142). Written informed consent was obtained from one parent of each participating newborn.

This cross-sectional observational study was conducted as part of a project that investigated the independent variables of cortisol levels and their diurnal patterns (*Kinoshita et al., 2016, 2018*). In an exploratory analysis of the dataset, the foetal-type diurnal pattern was observed on the basis of salivary cortisol levels, which were entrained in antiphase to the adult rhythm. Furthermore, the analysis found that lower cortisol levels were associated with older postnatal age, maternal PIH, caesarean delivery, preterm

delivery, mechanical ventilation required at birth, and independence from ventilation support on the study day (*Kinoshita et al., 2016*). Feeding-induced elevation of cortisol levels was also noted, which was more prominent following oral feeding and was reduced with prolonged feeding (*Kinoshita et al., 2018*).

Study population

Detailed data on patient recruitment, sample collection, and cortisol assays have been reported previously (*Kinoshita et al., 2016*, *2018*). In brief, 65 newborns hospitalised in a tertiary NICU were recruited between 30 and 40 weeks (corrected age). Newborns, who were diagnosed with major congenital anomalies or chromosomal aberrations, who had undergone phototherapy within 24 h previously, who had not been weaned from invasive mechanical ventilation and continuous intravenous infusion, and who had received glucocorticoid replacement therapy within 1 week previously, were excluded. Data collection was repeated up to two times for each patient, with a minimum interval of 7 days.

Sample collection and assay

Saliva was collected before and 1 h after regular feeding at 10:00 and 19:00 using an absorbent swab (SalivaBio; Salimetrics LLC, State College, PA, USA). A cortisol assay was performed using an enzyme immunoassay kit (high-sensitivity salivary cortisol enzyme-linked immunosorbent assay kit; Salimetrics LLC, State College, PA, USA). The limit of detection of this assay in our laboratory was 0.19 nmol/L, and the intra- and inter-assay coefficients of variation were 5.43% and 6.41%, respectively.

Clinical variables

Clinical information was obtained from electronic patient records, including maternal age, maternal body weight, and body-mass index at the time of delivery, gestational age, delivery mode, intravenous tocolysis, premature rupture of membranes, histopathologically confirmed chorioamnionitis, PIH, multiple gestations, antenatal glucocorticoid administration, birth weight, and its standard score calculated against the standard Japanese birth weight for gestational age (*Itabashi et al., 2014*), IUGR less than the 10th percentile of the norm, sex, Apgar scores, requirement for respiratory support at birth, and predominant type of milk (formula or breast milk) on the day of saliva collection.

Data analysis

Values are presented as mean (standard deviation), unless otherwise specified. In the current study, only saliva samples collected before (but not after) feeding at 10:00 and 19:00 were considered because of the known influence of feeding on the cortisol levels (*Kinoshita et al., 2018*). Interactions between the clinical variables and postnatal age at saliva collection and their relation to salivary cortisol levels were assessed using the generalised estimating equations with gamma distribution modelling (SPSS ver. 20; IBM, Armonk, NY, USA). To minimise the potential influence of adrenal diurnal patterns and the bias from repeated sampling, the timing of saliva sampling (morning/evening and

Iwata et al. (2019), *PeerJ*, DOI 10.7717/peerj.6368

3/11

Table 1 Clinical backgrounds of the study cohort.	
Variables during pregnancy	
Maternal and antenatal variables	
Intravenous tocolysis	51 (82.3)
Pregnancy-induced hypertension	10 (16.1)
Antenatal glucocorticoid	29 (46.8)
Premature rupture of membranes	22 (35.5)
Chorioamnionitis	18 (29.0)
Maternal age (years)	31.0 ± 6.2
Maternal height (cm)	158.2 ± 5.1
Maternal body weight (kg)	61.1 ± 11.1
Maternal body-mass index	24.4 ± 4.1
Variables at birth	
Vaginal delivery	26 (41.9)
Multiple births	15 (24.2)
Male	27 (43.5)
Gestational age (weeks)	32.3 ± 3.7
Birth weight (g)	1671 ± 579
Standard score of the birth weight	−0.55 ± 1.13
Intrauterine growth restriction	20 (32.3)
Apgar score (1 min)	6.4 ± 2.5
Apgar score (5 min)	8.1 ± 1.5
Need for mechanical ventilation	31 (50.0)
Postnatal glucocorticoid	7 (11.3)
Variables on the day of saliva sampling	
Postnatal age (days)	24.3 ± 22.6
Corrected age (weeks)	35.8 ± 1.3
Predominant breast milk feeding	37 (59.7)

Note:
Values are shown as number (%) or mean ± standard deviation.

the study date when studied on two different days) was incorporated as a within-subject factor. Statistical significance was assumed when $p < 0.003$, after correcting for multiple comparisons of 18 variables. For combinations of categorical variables with significant interactions, the simple effect test was performed for cortisol levels among three postnatal ages of ≤5 days, between 6 and 14 days, and >14 days (defined by the upper and lower quartile) for better clinical translation.

RESULTS

Out of the 65 newborns, two with an insufficient volume of saliva and one who was subsequently diagnosed with a major chromosomal aberration were excluded from the analysis. Subsequently, 124 samples from 62 cumulative newborns (corrected age, 31.7–39.5 weeks; postnatal age, 1–92 days) who were hospitalised because of low birth weight ($n = 55$), maternal hyperthyroidism or hypothyroidism ($n = 2$), or maternal gestational diabetes mellitus ($n = 5$) were considered (Table 1; Dataset S1).

The main effects of potential antenatal and postnatal physiological stressors on the cortisol levels have been reported previously (See the second paragraph of the Material and Methods section for the brief summary of findings) (*Kinoshita et al., 2016*). Significant interactions were observed between postnatal age and the standard score of the body weight (standardised partial regression coefficient, 1.008; 95% confidence interval, 1.004–1.012; $p < 0.001$), and postnatal age and IUGR (standardised partial regression coefficient, 0.981; 95% confidence interval, 0.968–0.993; $p = 0.002$) (Table 2).

When the simple effect test was performed for newborns with/without IUGR, the cortisol levels were associated with postnatal age in newborns with (but not without) IUGR; cortisol levels at >14 days were lower than those at ≤5 days and between 6 and 14 days (Fig. 1). Subsequently, IUGR newborns showed higher cortisol levels at ≤5 days and paradoxically lower cortisol levels at >14 days than their peers (both $p < 0.001$).

DISCUSSION

Our study suggested that foetal growth is associated with the relationship between postnatal age and cortisol levels in NICU newborns; cortisol levels of newborns with IUGR were higher soon after birth and lower after two weeks compared to those in their peers without IUGR. These findings build on our previous observations from the same dataset, that maternal PIH, caesarean delivery, and preterm birth are associated with lower cortisol levels in newborns hospitalised in the NICU (*Kinoshita et al., 2016*).

IUGR and adrenal function after birth

Intrauterine growth restriction is associated with an increased incidence of both short-term and long-term morbidities (*Murray et al., 2015*, *Pallotto & Kilbride, 2006*). In newborns with IUGR, the expression of placental 11-β-HDS2 is decreased (*Stewart, Rogerson & Mason, 1995*), leading to increased cord blood cortisol levels in newborns with low body/placental weight (*Heckmann et al., 1999*; *Mericq et al., 2009*). Increased plasma cortisol levels and angiotensin II receptor subtype 1 expression induce constriction of peripheral vessels, leading to growth restriction of the foetal organs (*Lanz et al., 2003*). Studies further highlighted that antenatal exposure of the foetus to increased cortisol levels contributes to antenatal programming of the HPA axis and other systems, the influence of which is observed throughout (and even after) the developmental process (*Barker et al., 1990*; *Hales et al., 1991*).

Studies involving children and adults found associations between low birth weight and increased basal cortisol levels (*Clark et al., 1996*; *Martinez-Aguayo et al., 2012*). However, when assessed during early childhood, there were conflicting findings, showing no association (*Dahlgren et al., 1998*; *Kajantie et al., 2002*; *Tenhola et al., 2002*) or positive associations (*Elhassan et al., 2015*; *Fattal-Valevski et al., 2005*) between body size at birth and cortisol levels. These inconsistent findings may be derived from the relatively wide age range when cortisol levels were assessed, and the heterogeneous backgrounds of the population, for which the influence of the birth weight was evaluated without incorporating gestational age. Our current data suggest the potential presence of dynamic temporal changes in the adrenal function of IUGR newborns.

Table 2 Effect of antenatal stressors on cortisol levels according to postnatal age.

Clinical conditions		Cortisol (nmol/L) Mean (SD)	Main effects Condition *p*	PNA *p*	Interaction with PNA β Mean	95% CI Lower	Upper	*p*
Intravenous tocolysis	Yes	8.79 (8.76)	0.144	0.738	0.987	0.968	1.006	0.183
	No	8.03 (5.04)						
PROM	Yes	9.24 (9.52)	0.393	0.006	0.994	0.979	1.009	0.457
	No	8.14 (6.51)						
PIH	Yes	6.10 (4.21)	0.259	*<0.001*	0.994	0.982	1.005	0.269
	No	9.00 (8.12)						
Maternal age			0.442	0.598	1.000	0.999	1.001	0.962
Maternal body-mass index			0.027	0.004	1.002	1.000	1.003	0.023
Maternal body weight			0.051	0.014	1.000	1.000	1.001	0.074
Chorioamnionitis	Yes	8.41 (6.65)	0.541	0.003	1.009	0.997	1.022	0.151
	No	8.58 (8.11)						
Antenatal glucocorticoid	Yes	7.29 (6.15)	0.819	0.008	0.993	0.979	1.008	0.367
	No	9.62 (8,72)						
Postnatal glucocorticoid	Yes	6.43 (4.42)	0.870	0.112	1.005	0.985	1.026	0.618
	No	8.80 (7.99)						
Standard score of the birth weight			0.022	0.004	1.008	1.004	1.012	*<0.001*
IUGR	Yes	9.23 (7.92)	0.144	*<0.001*	0.981	0.968	0.993	*0.002*
	No	8.20 (7.60)						
Multiple pregnancy	Yes	8.84 (8.74)	0.756	0.182	1.004	0.982	1.026	0.744
	No	8.29 (6.83)						
Vaginal delivery	Yes	10.37 (9.52)	0.641	0.013	1.009	0.997	1.020	0.140
	No	7.20 (5.76)						
Male sex	Yes	8.29 (6.83)	0.286	0.005	0.989	0.976	1.003	0.121
	No	8.84 (8.74)						
Gestational age			0.346	0.784	1.000	0.997	1.002	0.748
5-min Apgar score <7	Yes	6.30 (4.56)	0.295	0.059	1.008	0.992	1.024	0.338
	No	8.86 (8.02)						
Mechanical ventilation	Yes	6.76 (5.07)	0.632	0.896	0.989	0.954	1.026	0.571
	No	10.30 (9.34)						
Breast milk	Yes	6.88 (5.52)	0.061	0.032	1.006	0.992	1.020	0.371
	No	10.97 (9.64)						

Notes:
The *p*-values are from the generalised estimating equation (see "Data analysis" in "Material and Methods" for detail), and are presented for the main effects of each independent variable and postnatal age and their interaction. Statistical significance was assumed when *p* < 0.003, after correcting for multiple comparisons of 18 variables (indicated in bold and italic).
β, standardised partial regression coefficient; IUGR, intrauterine growth restriction; PIH, pregnancy-induced hypertension; PNA, postnatal age; PROM, premature rupture of membranes; SD, standard deviation.

Spontaneous adrenal functioning might be suppressed in growth-restricted foetuses, which causes plasma cortisol levels to diminish rapidly after birth when maternal cortisol is no longer provided.
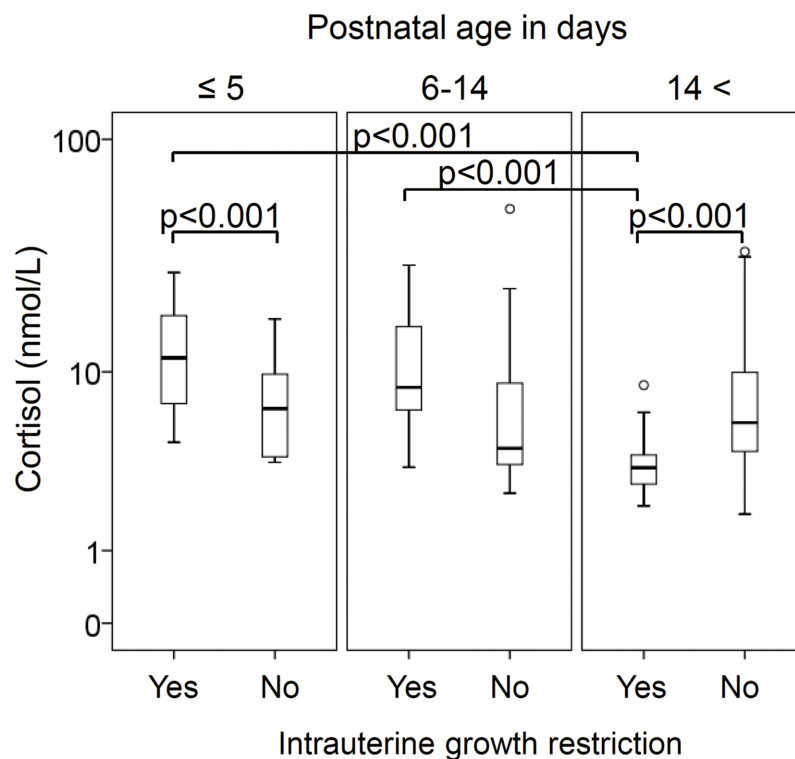
Figure 1 Box plot depicting the interaction between postnatal age and intrauterine growth restriction on cortisol levels. IUGR newborns showed higher cortisol levels at ≤5 days and lower cortisol levels at >14 days compared with their peers. Association between postnatal age and cortisol levels was observed for newborns with IUGR, but not for those without IUGR. Statistical findings are from the simple effect test with Bonferroni correction. Symbols: box, first and third quartiles; bold line, median; perpendicular line, range without outliers; and open circle, extreme outlier less than 1.5 times the interquartile range from the first quartile. Abbreviation: IUGR, intrauterine growth restriction.

Full-size 🖼 DOI: 10.7717/peerj.6368/fig-1

Because of the observations suggesting accelerated organ maturation of IUGR newborns (*Amiel-Tison et al., 2004*), the rapid postnatal decrease in cortisol levels in IUGR newborns might merely be a hint of the precocious maturation of the HPA axis that occurs with the earlier-than-usual physiological postnatal decrease in cortisol levels. This speculation might be relevant considering previous findings of attenuated HPA functioning during infancy and activated HPA functioning during adolescence and thereafter in IUGR newborns (*Clark et al., 1996*; *Fattal-Valevski et al., 2005*; *Martinez-Aguayo et al., 2012*).

Limitations of the study

We did not serially obtain multiple saliva samples; temporal changes in cortisol levels were only extrapolated from cross-sectional findings. Because newborns were recruited when their feeding was established, preterm newborns had older postnatal ages than did their near-term/term peers at the time of the study. Our findings need to be re-assessed in future studies, which serially collect saliva samples from the first day of life to at least four weeks. IUGR newborns in the current study cohort exclusively had asymmetrical

IUGR, presumably because symmetrical IUGR was excluded from the study cohort when newborns with major congenital anomalies were excluded.

CONCLUSIONS

Cortisol levels of newborns were associated with both postnatal age and intrauterine growth. Cortisol levels of newborns with IUGR were higher soon after birth and lower after two weeks than their peers without IUGR. It is possible to speculate that intrauterine growth may alter age-specific cortisol levels via deactivation of the HPA axis within first weeks of life. Future studies should address the impact of IUGR and other perinatal physiological stressors (and their level and duration) on the adrenal function and the development of diseases during adulthood. The potential benefits of care designed to minimise perinatal physiological stressors in these vulnerable newborns also need to be evaluated.

ADDITIONAL INFORMATION AND DECLARATIONS

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Sachiko Iwata conceived and designed the experiments, performed the experiments, analysed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Masahiro Kinoshita performed the experiments, analysed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, approved the final draft.

- Hisayoshi Okamura performed the experiments, analysed the data, authored or reviewed drafts of the paper, approved the final draft.
- Kennosuke Tsuda performed the experiments, analysed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Mamoru Saikusa performed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Eimei Harada performed the experiments, analysed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Shinji Saitoh conceived and designed the experiments, authored or reviewed drafts of the paper, approved the final draft.
- Osuke Iwata conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the paper, approved the final draft.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

This study was conducted in compliance with the Declaration of Helsinki and with the approval of the Ethics Committee of Kurume University School of Medicine (13142).

Data Availability

The following information was supplied regarding data availability:

Raw data are available as a Supplementary File.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.6368#supplemental-information.

REFERENCES

Amiel-Tison C, Cabrol D, Denver R, Jarreau PH, Papiernik E, Piazza PV. 2004. Fetal adaptation to stress. Part I: acceleration of fetal maturation and earlier birth triggered by placental insufficiency in humans. *Early Human Development* **78(1)**:15–27 DOI 10.1016/j.earlhumdev.2004.03.002.

Barker DJ, Bull AR, Osmond C, Simmonds SJ. 1990. Fetal and placental size and risk of hypertension in adult life. *BMJ* **301(6746)**:259–262 DOI 10.1136/bmj.301.6746.259.

Benediktsson R, Calder AA, Edwards CRW, Seckl JR. 1997. Placental 11 beta-hydroxysteroid dehydrogenase: a key regulator of fetal glucocorticoid exposure. *Clinical Endocrinology* **46(2)**:161–166 DOI 10.1046/j.1365-2265.1997.1230939.x.

Brummelte S, Chau CM, Cepeda IL, Degenhardt A, Weinberg J, Synnes AR, Grunau RE. 2015. Cortisol levels in former preterm children at school age are predicted by neonatal procedural pain-related stress. *Psychoneuroendocrinology* **51**:151–163 DOI 10.1016/j.psyneuen.2014.09.018.

Clark PM, Hindmarsh PC, Shiell AW, Law CM, Honour JW, Barker DJ. 1996. Size at birth and adrenocortical function in childhood. *Clinical Endocrinology* **45(6)**:721–726 DOI 10.1046/j.1365-2265.1996.8560864.x.

Dahlgren J, Boguszewski M, Rosberg S, Albertsson-Wikland K. 1998. Adrenal steroid hormones in short children born small for gestational age. *Clinical Endocrinology* **49(3)**:353–361 DOI 10.1046/j.1365-2265.1998.00514.x.

Elhassan ME, Miller AL, Vazquez DM, Lumeng JC. 2015. Associations of prenatal and perinatal factors with cortisol diurnal pattern and reactivity to stress at preschool age among children living in poverty. *Journal of Clinical Research in Pediatric Endocrinology* **7(2)**:114–120 DOI 10.4274/jcrpe.1685.

Fattal-Valevski A, Toledano-Alhadef H, Golander A, Leitner Y, Harel S. 2005. Endocrine profile of children with intrauterine growth retardation. *Journal of Pediatric Endocrinology and Metabolism* **18(7)**:671–676 DOI 10.1515/jpem.2005.18.7.671.

Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. 2002. Outcomes in young adulthood for very-low-birth-weight infants. *New England Journal of Medicine* **347(2)**:141–143 DOI 10.1056/nejm200207113470214.

Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. 1991. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* **303(6809)**:1019–1022 DOI 10.1136/bmj.303.6809.1019.

Hardy DB, Yang K. 2002. The expression of 11β-hydroxysteroid dehydrogenase type 2 is induced during trophoblast differentiation: effects of hypoxia. *Journal of Clinical Endocrinology & Metabolism* **87(8)**:3696–3701 DOI 10.1210/jcem.87.8.8720.

Heckmann M, Wudy SA, Haack D, Pohlandt F. 1999. Reference range for serum cortisol in well preterm infants. *Archives of Disease in Childhood–Fetal and Neonatal Edition* **81(3)**:F171–F174 DOI 10.1136/fn.81.3.f171.

Hutchinson EA, De Luca CR, Doyle LW, Roberts G, Anderson PJ, for the Victorian Infant Collaborative Study Group. 2013. School-age outcomes of extremely preterm or extremely low birth weight children. *Pediatrics* **131(4)**:e1053–e1061 DOI 10.1542/peds.2012-2311.

Itabashi K, Miura F, Uehara R, Nakamura Y. 2014. New Japanese neonatal anthropometric charts for gestational age at birth. *Pediatrics International* **56(5)**:702–708 DOI 10.1111/ped.12331.

Kajantie E, Dunkel L, Turpeinen U, Stenman UH, Wood PJ, Nuutila M, Andersson S. 2003. Placental 11β-hydroxysteroid dehydrogenase-2 and fetal cortisol/cortisone shuttle in small preterm infants. *Journal of Clinical Endocrinology & Metabolism* **88(1)**:493–500 DOI 10.1210/jc.2002-021378.

Kajantie E, Phillips DIW, Andersson S, Barker DJP, Dunkel L, Forsen T, Osmond C, Tuominen J, Wood PJ, Eriksson J. 2002. Size at birth, gestational age and cortisol secretion in adult life: foetal programming of both hyper- and hypocortisolism? *Clinical Endocrinology* **57(5)**:635–641 DOI 10.1046/j.1365-2265.2002.01659.x.

Kinoshita M, Iwata S, Okamura H, Saikusa M, Hara N, Urata C, Araki Y, Iwata O. 2016. Paradoxical diurnal cortisol changes in neonates suggesting preservation of foetal adrenal rhythms. *Scientific Reports* **6(1)**:35553 DOI 10.1038/srep35553.

Kinoshita M, Iwata S, Okamura H, Tsuda K, Saikusa M, Harada E, Yamashita Y, Saitoh S, Iwata O. 2018. Feeding-induced cortisol response in newborn infants. *Journal of Clinical Endocrinology & Metabolism* **103(12)**:4450–4455 DOI 10.1210/jc.2018-01052.

Lanz B, Kadereit B, Ernst S, Shojaati K, Causevic M, Frey BM, Frey FJ, Mohaupt MG. 2003. Angiotensin II regulates 11β-hydroxysteroid dehydrogenase type 2 via AT2 receptors. *Kidney International* **64(3)**:970–977 DOI 10.1046/j.1523-1755.2003.00192.x.

Martinez-Aguayo A, Aglony M, Bancalari R, Avalos C, Bolte L, Garcia H, Loureiro C, Carvajal C, Campino C, Inostroza A, Fardella C. 2012. Birth weight is inversely associated with blood pressure and serum aldosterone and cortisol levels in children. *Clinical Endocrinology* **76(5)**:713–718 DOI 10.1111/j.1365-2265.2011.04308.x.

Mastorakos G, Ilias I. 2003. Maternal and fetal hypothalamic-pituitary-adrenal axes during pregnancy and postpartum. *Annals of the New York Academy of Sciences* **997(1)**:136–149 DOI 10.1196/annals.1290.016.

Mericq V, Medina P, Kakarieka E, Marquez L, Johnson MC, Iniguez G. 2009. Differences in expression and activity of 11β-hydroxysteroid dehydrogenase type 1 and 2 in human placentas of term pregnancies according to birth weight and gender. *European Journal of Endocrinology* **161(3)**:419–425 DOI 10.1530/EJE-09-0308.

Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. 2015. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. *BJOG: An International Journal of Obstetrics & Gynaecology* **122(8)**:1062–1072 DOI 10.1111/1471-0528.13435.

Pallotto EK, Kilbride HW. 2006. Perinatal outcome and later implications of intrauterine growth restriction. *Clinical Obstetrics and Gynecology* **49(2)**:257–269 DOI 10.1097/00003081-200606000-00008.

Ruys CA, Van Der Voorn B, Lafeber HN, Van De Lagemaat M, Rotteveel J, Finken MJJ. 2017. Birth weight and postnatal growth in preterm born children are associated with cortisol in early infancy, but not at age 8 years. *Psychoneuroendocrinology* **82**:75–82 DOI 10.1016/j.psyneuen.2017.05.007.

Stewart PM, Rogerson FM, Mason JI. 1995. Type 2 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid and activity in human placenta and fetal membranes: its relationship to birth weight and putative role in fetal adrenal steroidogenesis. *Journal of Clinical Endocrinology & Metabolism* **80(3)**:885–890 DOI 10.1210/jcem.80.3.7883847.

Tenhola S, Martikainen A, Rahiala E, Parviainen M, Halonen P, Voutilainen R. 2002. Increased adrenocortical and adrenomedullary hormonal activity in 12-year-old children born small for gestational age. *Journal of Pediatrics* **141(4)**:477–482 DOI 10.1067/mpd.2002.126923.