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Birth weight and postnatal growth in preterm born children are associated with cortisol in early infancy, but not at age 8 years

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ABSTRACT

Background: Preterm birth has been associated with altered hypothalamic-pituitary-adrenal (HPA-) axis activity as well as cardiometabolic diseases and neurodevelopmental impairments later in life. We assessed cortisol from term age to age 8 y in children born preterm, to explore the development of HPA-axis activity in association with intrauterine and early-postnatal growth until 6 mo. corrected age.

Methods: In 152 children born at a gestational age ≤32 wks. and/or with a birth weight ≤1,500 g, random serum cortisol was assessed at term age (n = 150), 3 mo. (n = 145) and 6 mo. corrected age (n = 144), and age 8 y (n = 59). Salivary cortisol was assessed at age 8 y (n = 75): prior to bedtime, at awakening, 15 min after awakening, and before lunch. Cortisol was analyzed in association with birth weight-standard deviation score (SDS), being born small for gestational age (SGA), and combinations of intrauterine and postnatal growth: appropriate for gestational age (AGA) with or without growth restriction (AGA GR+ or AGA GR−) at 6 mo. corrected age, and SGA with or without catch-up growth (SGA CUG+ or SGA CUG−) at 6 mo. corrected age. Cross-sectional associations at all time points were analyzed using linear regression, and longitudinal associations were analyzed using generalized estimating equations.

Results: Longitudinally, birth weight-SDS was associated with cortisol (β [95%CI]): lower cortisol over time was seen in infants with a birth weight ≤ −2 SDS (−50.69 [−94.27; −7.11], p = 0.02), infants born SGA (−29.70 [−60.58; 1.19], p = 0.06), AGA GR+ infants (−55.10 [−106.02; −4.17], p = 0.03) and SGA CUG− infants (−61.91 [−104.73; −19.10], p = 0.01). In cross-sectional analyses at age 8 y, no associations were found between either serum or salivary cortisol and birth weight-SDS, SGA-status, or growth from birth to 6 mo. corrected age.

Conclusion: In children born preterm, poor intrauterine and postnatal growth were associated with lower cortisol in early infancy, but not at age 8 y. Even though HPA-axis activity no longer differed between groups at age 8 y, or differences could not be confirmed due to attrition, it is unknown whether the differences found in early infancy could attribute to increased health risks later in life.

1. Introduction

In infants born very preterm, i.e., born at a gestational age ≤32 wks., the hypothalamic-pituitary-adrenal (HPA-) axis is not yet fully maturated. Relative adrenal insufficiency is common in this group during the first weeks of life, and is characterized by relatively low basal and stress-induced cortisol levels, and increased risks of hypotension, hypoglycemia and bronchopulmonary dysplasia (Bolt et al., 2002; Finken et al., 2016; Ng, 2011; Watterberg, 2004). This is partly attributable to the sudden disruption of the maturation of the fetal HPA-axis, which in full-term pregnancies is stimulated in the third trimester by an increase in the secretion of placental corticotropin-

Abbreviations: AGA, appropriate for gestational age; BMI, body mass index; CAR, cortisol awakening response; CRH, corticotropin-releasing hormone; CUG, catch-up growth; GEE, generalized estimating equation; GR, growth restriction; HELLP, Hemolysis Elevated Liver enzymes and Low Platelets; HPA-axis, hypothalamic-pituitary-adrenal axis; LLOQ, lower limit of quantitation; NTISS, neonatal therapeutic intervention scoring system; SDS, standard deviation score; SGA, small for gestational age; STEP, Study Towards the Effect of Postdischarge nutrition

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releasing hormone (CRH) and alterations in the expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) by the placenta (Watterberg, 2004). Conversely, there is some evidence suggesting that HPA-axis activity is upregulated years after preterm birth (Finken et al., 2016), which might contribute to the association between prematurity and long-term sequelae like cardiometabolic diseases and neurodevelopmental impairments.

Little is known about the impact of intrauterine and early-postnatal growth patterns on these associations in preterm infants. Intrauterine growth restriction is accompanied by a reduced expression and activity of the placental barrier enzyme 11β-HSD2, which converts cortisol to inert cortisone (Kajantie et al., 2003). The subsequent fetal overexposure to maternal cortisol has been suggested to permanently alter HPA-axis settings (Duthie and Reynolds, 2013), initially by suppressing the axis, followed by increased activity later in life. This is strengthened by animal studies suggesting that the presence of abundant glucocorticoids in-utero, could result in a reduced expression of glucocorticoid receptors in tissues, and thereby, a compensatory upregulation of HPA-axis activity (Cottrell and Seckl, 2009; de Kloet et al., 2014; Sebaai et al., 2002).

Moreover, animal studies suggest that fetal growth restriction as well as early-postnatal growth restriction may predispose to cardiometabolic diseases later in life. Also, rapid postnatal growth after being born with a low birth weight has been associated with cardiometabolic disease risk, and alterations in HPA-axis functioning have been suggested to explain these associations (Guilloteau et al., 2009; Sebaai et al., 2002).

In term born subjects, there are few studies that have explored whether the HPA-axis could explain part of the association between low birth weight and cardiometabolic disease (Krishnaveni et al., 2014; Phillips et al., 2000). In preterm born infants, rapid early-postnatal and childhood growth have been associated with risks of cardiometabolic diseases (Embleton et al., 2016; Ong et al., 2015), but their relation with HPA-axis activity throughout the lifespan has never been described.

To study the development of HPA-axis activity after preterm birth in association with intrauterine and early-postnatal growth, we assessed cortisol levels of infants who were born very preterm and/or with a very low birth weight (≤1500g), from term age until the age of 8 y.

2. Methods

All subjects were originally included in a nutritional RCT ('Study Towards the Effect of Postdischarge nutrition' [STEP-1]) that compared the effects of postdischarge formula, term formula, and human milk on growth and body composition of very preterm (gestational age ≤32 wks.) and/or very low birth weight (≤1500g) infants, as described previously (Amesz et al., 2010). Exclusion criteria were congenital malformations or other conditions known to affect growth or body composition. At term age, infants fed formula were randomized to receive either protein- and mineral-enriched postdischarge formula or term formula between term age and 6 mo. corrected age. Corrected age is the age of the preterm born child calculated from the term date (i.e., 40 wks gestation), and not from birth. This correction is usually maintained until the corrected age of 24 months.

At the age of 8 y, parents from the STEP-1 study participants were asked to participate in the follow-up study, STEP-2. Exclusion criteria were incomplete follow-up, severe physical impairment or other conditions known to affect growth or body composition.

2.1. Data collection

For STEP-1, the following data were extracted from medical records: birth weight, birth length, gestational age and gender. The neonatal therapeutic intervention scoring system (NTISS), an indicator for neonatal illness severity and mortality risk (Gray et al., 1992), was calculated, and parents were asked to report their ethnicity, which was categorized as Caucasian or non-Caucasian. At term age, 3 mo. and 6 mo. corrected age, weight was measured with a digital scale to the nearest 1.0 g, and length with a length board to the nearest 0.1 cm. Standard deviation scores (SDS's), which quantify the deviation from a reference population, were calculated for all auxological parameters. At birth and at term age, this was done by the use of neonatal anthropometric charts, adjusting for sex and gestational age (Niklasson et al., 1991). At 3 and 6 mo. corrected age, this was done by the use of postnatal growth curves, adjusting for sex and corrected age (Fredriks et al., 2000). At term age, 3 mo. and 6 mo. corrected age, fasting venous blood samples were collected. Mean fasting duration was recorded as the interval between blood sampling and the last feed before blood sampling. Mean fasting duration was 3.4 ± 0.7 h at term age, 3.6 ± 0.7 h at 3 mo. corrected age, and 3.5 ± 0.7 h at 6 mo. corrected age.

We used the following definitions (van de Lagemaat et al., 2014):

1 Appropriate for gestational age (AGA): birth weight and birth length > −2SDS.
2 Growth restriction (AGA GR+): weight and/or length ≤ −2SDS at 6 mo. corrected age, after being born AGA.
3 Small for gestational age (SGA): birth weight and/or birth length ≤ −2SDS.
4 Catch-up growth (SGA CUG+): weight and length > −2SDS at 6 mo. corrected age, after being born SGA.

For STEP-2, children aged 8 y visited the outpatient clinic in the morning. Venous blood samples were obtained after an overnight fast, and anthropometric measurements were performed. Weight was measured to the nearest 0.05 kg with an electronic scale (Seca) and standing height was measured to the nearest 0.1 cm using a digital stadiometer (DGI 250D, De Grood Metaaltechniek, Nijmegen, the Netherlands), and expressed as SDS based on Dutch growth curves adjusted for gender and age (Fredriks et al., 2000). Salivary samples for cortisol measurement were collected at 4 moments: prior to bedtime at the evening before the study visit, immediately after awakening at the morning of the study visit, 15 min after awakening, and before lunch during the study visit. Participants were instructed to refrain from eating and drinking at least 30 min before sampling.

Parents were asked to report their education level, which was categorized as neither, one, or both parent(s) having finished higher education.

The study protocols were approved by the ethics committee of VU University Medical Center, Amsterdam. All parents of subjects gave written informed consent.

2.2. Laboratory parameters

Serum was stored at −80 °C and thawed only once just before the analyses.

In STEP-1, total serum cortisol (nmol/L) was measured using 2 different methods as the assay changed during the course of the study. In 90 infants, total serum cortisol at term age, 3 mo. and 6 mo. corrected age was measured using a competitive immunoassay (Advantage, Nichols Institute Diagnostics, San Juan Capistrano, USA) with an intra-assay coefficient of variation (CV) of 3%, 3% and 4% (at levels of 100, 500 and > 600 nmol/L, respectively), an inter-assay CV of 8%, 7% and 6% (at levels of 140, 400 and 850 nmol/L, respectively), and a lower limit of quantitation (LLOQ) of 30 nmol/L. In 62 infants, total serum cortisol at term age, 3 mo. and 6 mo. corrected age was measured using a competitive immunoassay (DPC, Los Angeles, USA) with an inter-assay CV of 8%, 7% and 6% (at levels of 150, 400 and 900 nmol/L, respectively).

In STEP-2, total serum cortisol was measured using a competitive immunoassay (Luminescence Advia Centaur, Siemens Medical