Prepubertal children born large for gestational age have lower serum DHEAS concentrations than those with a lower birth weight

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BACKGROUND: Children born small for gestational age (SGA) have higher serum dehydroepiandrosterone sulfate (DHEAS) concentrations than children born appropriate for gestational age (AGA). The overall metabolic risk associated with birth weight is U-shaped, but it is not known whether children born large for gestational age (LGA) have elevated serum DHEAS levels.

METHODS: A cohort of 49 children born LGA, 56 children born AGA, and 23 children born SGA were studied at 5–8 years of age. Anthropometric data at birth, at the age of 2 years, and at examination were recorded. Fasting blood samples were collected for serum analyses of DHEAS, insulin-like growth factor 1 (IGF-1), and insulin concentrations.

RESULTS: The children born LGA had lower serum DHEAS levels adjusted for body mass index (BMI) standard deviation score (SDS) and age than the rest of the children. Lower birth weight SDS and higher weight gain during the first 2 years of life predicted higher serum DHEAS levels. Higher serum IGF-1 levels were also associated with higher prevalence of adrenarchal DHEAS levels.

CONCLUSION: Being born LGA was associated with lower DHEAS levels, whereas small birth size and early catch-up growth predicted higher levels. This suggests that genetic or early epigenetic factors have an impact on adrenarche. IGF-1 may be a mediator in this process.

Children born small for gestational age (SGA) have higher serum dehydroepiandrosterone sulfate (DHEAS) concentrations than children born appropriate for gestational age (AGA) (1,2). High prepubertal DHEAS levels are related to premature adrenarche (PA), defined as androgenic clinical signs appearing before the age of 8 years in girls and 9 years in boys in the presence of elevated serum DHEAS levels for age (reviewed in (refs 3–5)). PA has been associated with several metabolic disturbances including hyperinsulinemia/decreased insulin sensitivity (6,7), adverse lipid profile (8), and increased fat mass and body fat percentage (9).

It is also well known that both children born SGA and those born large for gestational age (LGA) have an increased

cardiometabolic disease risk (10,11). They may develop obesity, type 2 diabetes, the metabolic syndrome, and hypertension later in life (11–16). However, it has not been studied whether LGA children have elevated serum DHEAS levels in childhood and/or an increased prevalence of PA.

PA has been associated with increased body weight (9,17), and girls with PA have accelerated statural growth already during the first 2 years of life (18,19). Early rapid weight gain of children with normal birth weight predicts higher DHEAS levels at the age of 8 years (20).

The purpose of this study was to investigate the influence of large birth size on serum DHEAS levels and the prevalence of adrenarche in prepubertal children.

METHODS

A cohort of 128 Caucasian children (67 boys) born singleton at term between 2004 and 2007 in Eastern Finland was studied (21). In brief, the children were enrolled according to their birth size and studied at 5.0–8.7 years of age (mean (95% CI), 6.9 (6.8–7.1) years) (Table 1). SGA was defined as gender-specific birth weight ≤ -2.0 SDS, LGA as birth weight $\geq +2.0$ SDS, and AGA as birth weight and length being between -1.0 and $+1.0$ SDS. Anthropometric data at birth, at the age of 2 years, and at examination were recorded (Table 1).

BMI was calculated as the body weight divided by the square of the height (kg/m^2). Sex- and age-specific SDS for height and BMI were calculated according to the recently published Finnish growth reference (22). The following BMI SDS cutoff points for overweight and obesity were used corresponding to BMI of 25 and 30 at the age of 18 years: for boys, 0.78 and 1.70, and for girls, 1.16 and 2.11, respectively (22). Catch-up or catch-down growth was defined as an increase or a decrease in weight SDS > 0.67 during the first 2 years of life, respectively (23).

Clinical signs of adrenarche (adult-type body odor, oily hair, acne or comedones, and appearance of pubic and axillary hair) and pubertal status (breast development in girls, testicular size in boys, and pubic hair in both sexes) were recorded. Children were defined prepubertal when girls had no palpable breast tissue or boys had a testicular volume ≤ 3 ml.

Fasting blood samples were collected for serum analyses of DHEAS, IGF-1, and insulin concentrations. DHEAS level of $1.0 \mu\text{mol}/\text{l}$ ($37 \mu\text{g}/\text{dl}$) was referred as a cutoff for biochemical adrenarche (24,25). Serum DHEAS and insulin concentrations were analyzed using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Serum IGF-1

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Table 1. Anthropometric and biochemical characteristics of the study groups

	LGA	AGA	SGA	P
Total number (boys)	49 (25)	56 (29)	23 (13)	
<i>At birth</i>				
Gestational age (weeks)	39.8 (39.5–40.1)	39.9 (39.6–40.2)	39.7 (39.2–40.3)	0.81
Weight (g)	4722 (4631–4812)	3561 (3484–3637)	2476 (2345–2607)	<0.001
Weight (SDS)	2.63 (2.46–2.79)	–0.02 (–0.16–0.12)	–2.39 (–2.53– –2.25)	<0.001
Length (cm)	53.0 (52.6–53.4)	50.0 (49.7–50.4)	46.2 (45.5–46.9)	<0.001
Length (SDS)	1.58 (1.40–1.76)	–0.11 (–0.24–0.03)	–2.16 (–2.43– –1.88)	<0.001
<i>At the age of 2 years</i>				
Weight (SDS)	0.65 (0.41–0.90)	0.16 (–0.14–0.45)	–0.95 (–1.37– –0.53)	<0.001 ^a
Height (SDS)	0.40 (0.17–0.63)	–0.05 (–0.34–0.24)	–0.98 (–1.33– –0.63)	<0.001 ^a
<i>At examination</i>				
Age (years)	6.89 (6.62–7.16)	7.09 (6.86–7.33)	6.65 (6.22–7.07)	0.13
Weight (kg)	27.6 (26.2–29.0)	27.5 (25.7–29.4)	21.8 (19.8–23.7)	<0.001
Weight (SDS)	0.68 (0.38–0.97)	0.39 (0.11–0.67)	–0.80 (–1.26– –0.33)	<0.001
Height (cm)	126.1 (124.0–128.3)	125.7 (123.8–127.7)	119.0 (115.6–122.4)	<0.001
Height (SDS)	0.54 (0.30–0.78)	0.20 (–0.07–0.46)	–0.64 (–1.01– –0.27)	<0.001
BMI (SDS)	0.56 (0.22–0.89)	0.36 (0.05–0.67)	–0.65 (–1.18– –0.12)	<0.001
DHEAS (μg/dl)	18.3 (14.1–23.0)	24.7 (20.2–29.8)	30.5 (22.2–40.2)	0.028 ^b
IGF-1 (ng/ml)	196.3 (179.1–214.8)	198.6 (182.4–216.3)	190.1 (165.2–218.8)	0.87
Insulin (μIU/ml)	4.47 (3.92–5.09)	4.79 (4.24–5.40)	4.84 (3.94–5.93)	0.70

AGA, appropriate for gestational age; ANOVA, analysis of variance; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; CI, confidence interval; IGF-1; insulin-like growth factor 1; LGA, large for gestational age; SDS, standard deviation score; SGA, small for gestational age.

Data are presented as mean (95% CI), except DHEAS, IGF-1, and insulin (geometric mean (95% CI)).

ANOVA between the three study groups, except DHEAS, IGF-1, and insulin (BMI SDS and age-adjusted ANCOVA).

^aThe *post hoc* test (Sidak correction) $P < 0.001$ between SGA and AGA/LGA groups; $P < 0.05$ between LGA and AGA groups.

^bThe *post hoc* test (Sidak correction) $P = 0.041$ between the LGA and SGA groups.

concentrations were determined using an ELISA kit (Mediagnost, Reutlingen, Germany).

A written informed consent was obtained from all the parents and from participating children aged ≥ 6 years. The study protocol was approved by the Committee on Research Ethics of the Hospital District of Northern Savo.

Statistical Analyses

Data are presented as mean (95% CI). Analyses were performed using SPSS statistical software (version 22; SPSS, IBM, Armonk, NY). A significance level of 0.05 was used in all analyses. Analysis of variance was used for comparisons between groups on anthropometric measures. Differences in serum DHEAS, IGF-1, and insulin concentrations between the three groups were analyzed by the BMI SDS and age-adjusted analysis of covariance and predictors of serum DHEAS levels (model 1: weight SDS at birth; model 2: the change in weight SDS from birth to the age of 2 years; both models: BMI SDS at examination, serum IGF-1, serum insulin, and age at examination) were explored by linear regression analysis. Skewed data were either logarithm- or square-root-transformed before parametric analyses. Obtained estimated means (BMI SDS and age-adjusted) were power-transformed to geometric means for presentation. Association of insulin or IGF-1 levels (tertiles) with the absence/presence of biochemical adrenarche (blood samples obtained at the same age;

DHEAS < 37 μg/dl (1.0 μmol/l); DHEAS ≥ 37 μg/dl (1.0 μmol/l)) was analyzed using the χ^2 -test.

RESULTS

All girls had prepubertal breast stage (Tanner B1), all boys had prepubertal genital stage (Tanner G1), and no child had pubic hair. Nine girls (prevalence 14.8%) and two boys (3.0%) had some clinical sign of PA (six girls and two boys—adult-type body odor, two girls—oily hair, and one—comedones). Thirty-two children (25%, 17 boys; 8 LGA, 18 AGA, and 6 SGA ($P = 0.17$, the χ^2 -test between the groups)) had DHEAS level ≥ 37 μg/dl (1.0 μmol/l). Three girls and one boy (3%) had both clinical signs of PA and DHEAS level ≥ 37 μg/dl (1.0 μmol/l).

Serum DHEAS levels did not differ between the sexes ($P = 0.50$). There was a significant difference in serum DHEAS levels between the three study groups (Table 1). The *post hoc* test (Sidak correction) showed significantly lower serum DHEAS levels in the LGA than in the SGA group (Table 1). A significant difference was also found in body mass index (BMI) standard deviation score (SDS) and

Table 2. Determinants of serum DHEAS levels (linear regression analysis) in the whole study population at examination

	Independent variables	Standardized <i>B</i>	<i>P</i> (variables)	<i>P</i> (model)	<i>R</i> ²
Model 1 (<i>n</i> = 125)	Weight SDS (at birth)	−0.27	0.002	<0.001	0.27
	BMI SDS	0.11	0.22		
	Serum IGF-1	0.16	0.09		
	Serum insulin	0.03	0.73		
Model 2 (<i>n</i> = 123)	Δ Weight SDS 0–2 years	0.26	0.001	<0.001	0.28
	BMI SDS	0.02	0.78		
	Serum IGF-1	0.14	0.12		
	Serum insulin	0.03	0.78		

Adjusted for age at examination

age-adjusted serum DHEAS levels between the LGA and the rest of the study population ($P = 0.015$; mean (95% confidence interval (CI)), 18.4 (14.2–23.1); 26.2 (22.2–30.6), respectively). A trend toward lower DHEAS levels adjusted for BMI SDS and age was seen in children born LGA compared with those in children born AGA, but the difference was not statistically significant ($P = 0.06$; [Table 1](#)). There were no significant differences in serum insulin-like growth factor 1 (IGF-1) and insulin concentrations between the study groups ([Table 1](#)).

Lower birth weight SDS (model 1) and higher weight gain during the first 2 years of life (model 2) predicted higher serum DHEAS concentrations in linear regression analyses ([Table 2](#)). The same trend was also seen when the children were arranged by their birth size or weight gain during the first 2 years of life and their weight SDS at examination ([Figure 1](#)). A significant association was found between biochemical adrenarche and IGF-1 levels ($P = 0.007$), but not between biochemical adrenarche and insulin levels ($P = 0.57$; [Table 3](#)).

DISCUSSION

As far as we know, there are no previously published reports on DHEAS levels or early adrenarche in LGA-born children. In this study, the prepubertal children born LGA had lower serum DHEAS levels compared with children born SGA or children born SGA and AGA combined. Low birth weight SDS and early weight SDS change (0–2 years) were associated with DHEAS levels, and the prevalence of biochemical adrenarche was highest among the children with the highest IGF-1 levels. There was no difference in the DHEAS levels between the sexes.

Previous studies have shown an association between low birth size and increased serum DHEAS levels in later childhood (1,2,26). In addition, the Avon Longitudinal Study of Parents and Children study with a large population-based sample of children showed that the negative relationship between birth weight and later prepubertal serum DHEAS levels is continuous throughout the normal birth weight range (20). Our study shows that the trend toward low prepubertal DHEAS levels extends to the LGA-born children. Consequently, children born LGA are not prone to develop PA that has been linked to a later metabolic risk (6–9).

Table 3. Association of biochemical adrenarche with IGF-1 and insulin levels at examination

Biochemical adrenarche	1		2		3	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
<i>IGF-1 tertiles</i>						
Yes	7	21.9	7	21.9	18	56.3
No	34	36.6	35	37.6	24	25.8
<i>Insulin tertiles</i>						
Yes	9	28.1	10	31.3	13	40.6
No	33	34.7	33	34.7	29	30.5

The χ^2 -test between IGF-1 tertiles, $P = 0.007$, and insulin tertiles, $P = 0.57$.Biochemical adrenarche: serum DHEAS ≥ 37 $\mu\text{g/dl}$ (≥ 1 $\mu\text{mol/l}$).

Adrenal androgen levels do not have the U-shaped association with birth size as some other metabolic risks and outcomes may have (10,11). As no follow-up studies exist, the later significance of lower DHEAS levels in children born LGA remains unknown.

Metabolic programming during fetal (e.g., intrauterine growth restriction) and early postnatal development, as well as increased IGF-1 and insulin levels in SGA-born children with catch-up growth, has been linked to increased prepubertal adrenal androgen secretion (20). These factors could at least partly explain the negative association between birth weight and later serum DHEAS levels, as the majority of the SGA- and LGA-born children experience catch-up and catch-down growth, respectively. This might indicate a greater impact of the early childhood growth pattern than the birth size itself on later adrenal androgen production and its consequences.

Our data did not show difference in the DHEAS levels between the sexes. In a previous study, girls had higher DHEAS than boys had, but, in that study, DHEAS was not adjusted for BMI or age (27). When these factors are taken into account, no difference in serum DHEAS between the sexes is expected (24).

In our study, children born SGA and AGA did not have a significant difference in their DHEAS levels, but birth weight was negatively associated with prepubertal DHEAS levels in the whole study population, supporting the previously described association (1,2). One reason for the relatively high

Figure 1. Dehydroepiandrosterone sulfate (DHEAS) levels (mean) at prepuberty, by birth size/early childhood weight development, and current weight. Normal and overweight defined as body mass index (BMI) standard deviation score (SDS) corresponding to adult BMI <25 and ≥25, respectively (22).

DHEAS levels in our children born AGA may be their BMI SDS being above the population mean (21) at the examination. Early catch-up growth and weight in childhood seem to have a strong impact on DHEAS levels in prepuberty (20,28), which was also noticeable in our study.

No child in this study had pubic or axillary hair, which is permissible as the appearance of the clinical signs of PA is related to the level of androgen effect (ascending order: adult-type body odor, oily hair, comedones, and pubic or axillary hair) (25), although variation may occur because of ethnicity. The prevalence of children with some clinical sign of PA and of girls with both clinical signs of PA and DHEAS level ≥37 µg/dl was lower in our study than in the previous Finnish study of larger population (24). Participants being younger in our study could explain the difference. In addition, the proportion of children with biochemical adrenarche was higher in our study compared with that in the data by Mäntyselkä *et al* (24). Increased body weight is associated with PA (9,17), and the children belonging to LGA and AGA groups were somewhat heavier in our study than the children in the previous study (24). Our findings are thus well coherent with the previously published Finnish data, although some differences could originate from the relatively small sample size in the current study.

Increased IGF-1 concentrations were previously demonstrated in prepubertal girls (19,29) and boys (27) with PA compared with those in age-matched controls. IGF-1 stimulates steroidogenesis in adrenocortical cells, and its serum concentrations increase with overweight and hyperinsulinism (reviewed in (refs 3,4)). In our study, linear regression analysis showed a trend between serum IGF-1 and DHEAS levels, and the highest prevalence of biochemical adrenarche was detected in children with the highest IGF-1 serum levels. Hyperinsulinism has also

been suggested to contribute to PA (4). However, our study showed no association of insulin with DHEAS. In our previous study, prepubertal girls with PA had slightly higher oral glucose tolerance test-stimulated serum insulin concentrations than control girls had, but basal insulin concentrations were similar (7).

The strengths of this study include the detailed physical examination including the clinical signs of adrenarche and the pubertal stage. In addition, the study participants were enrolled strictly according to the birth size, and the AGA group was selected to represent the children close to the mean birth weight and length. Furthermore, to reduce the influence of confounding factors, we adjusted our analyses for BMI SDS and age. The main limitation of this study is the relatively small sample size, affecting the statistical power of the study.

In conclusion, being born LGA was associated with lower prepubertal DHEAS levels, whereas small birth size and early catch-up growth predicted increased DHEAS levels. This suggests that genetic or early epigenetic factors have an impact on adrenal androgen secretion and adrenarche. IGF-1 may be a mediator in this process.

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