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

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Disclosure statement: Nothing to disclose

BACKGROUND

Children born small for gestational age (SGA) have higher serum dehydroepiandrosterone sulfate (DHEAS) concentrations than children born appropriate for gestational age (AGA) (1, 2). Premature adrenarche (PA) has been associated with several metabolic disturbances including hyperinsulinemia / decreased insulin sensitivity (3, 4), adverse lipid profile (5), and increased fat mass and body fat percentage (6). The overall metabolic risk associated with birth weight is U-shaped, but it is not known if children born large for gestational age (LGA) have elevated serum DHEAS levels.

OBJECTIVE

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

METHODS

A cohort of 128 children (67 boys) was studied. The children were enrolled according to their birth size and studied at 5.0-8.7 years of age (mean ± SD, 6.9 ± 0.9 years). SGA was defined as gender-specific birth weight ≤ –2.0 standard deviation scores (SDS), LGA as birth weight ≥ +2.0 SDS, and AGA as birth weight and length being between –1.0 and +1.0 SDS. Sex- and age-specific SDS for height and BMI were calculated according to the current Finnish growth reference. Catch-up or catch-down growth was defined as an increase or decrease in weight SDS more than 0.67 during the first two years of life, respectively. Fasting blood samples were collected at the examination. Analyses were performed using SPSS statistical software (version 22; SPSS, IBM Corp., Armonk, NY). One-way analysis of variance (ANOVA) 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 -adjusted analysis of covariance (ANCOVA) and predictors of serum DHEAS levels were explored by linear regression analysis. Association of insulin or IGF-1 levels (tertiles) with the absence / presence of biochemical adrenarche [DHEAS < 37 µg/dL (1.0 µmol/L); DHEAS ≥ 37 µg/dL (1.0 µmol/L)] were analyzed using the Chi-square test.

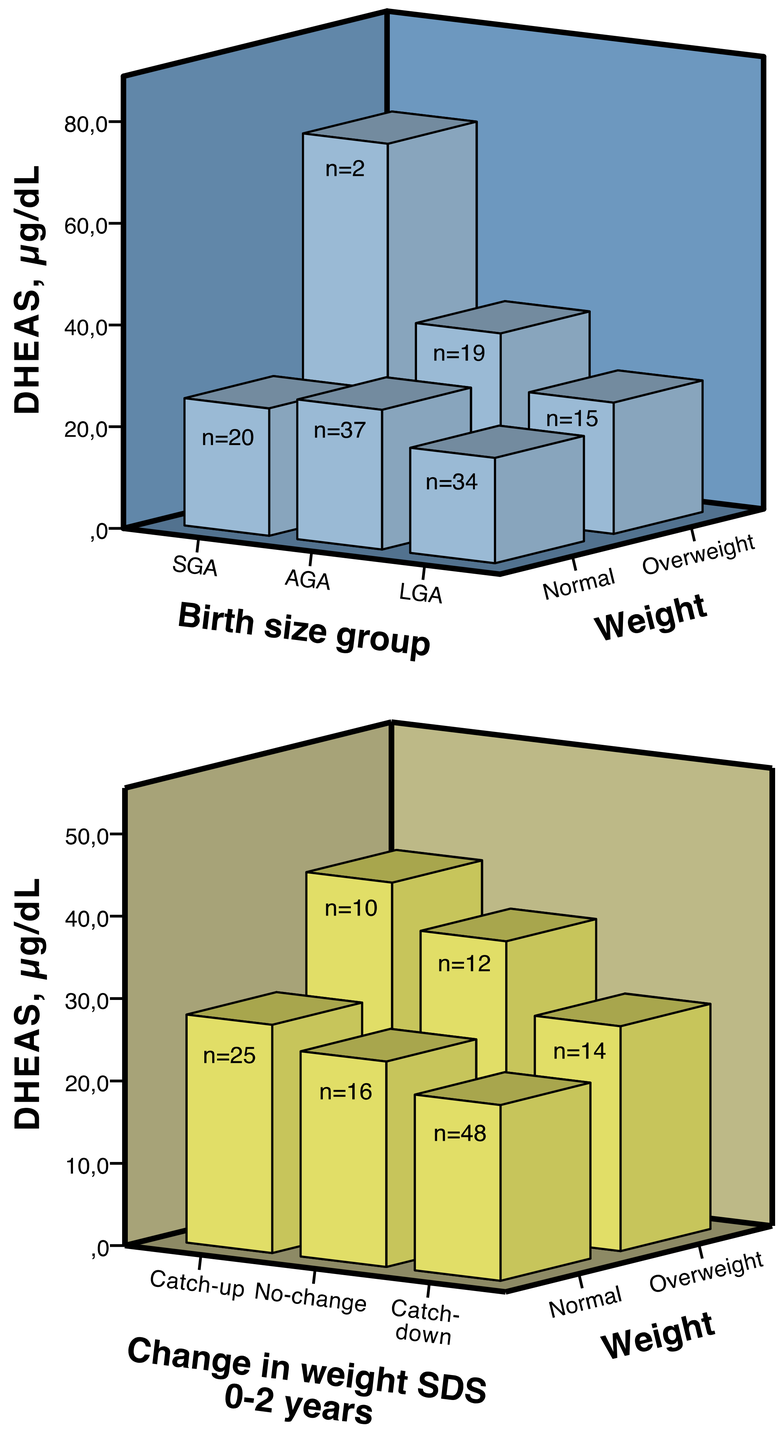

Figure 1. DHEAS levels (mean) at prepuberty, by birth size/early childhood weight development and current weight. Normal and overweight defined as BMI SDS corresponding to adult BMI < 25 and ≥ 25, respectively.

Table 1. Anthropometric and biochemical characteristics of the study groups. Data are presented as mean (95% confidence interval (CI)), except DHEAS, IGF-1, and insulin as geometric mean (95% CI).

	LGA	AGA	SGA	*P*
N (boys)	49 (25)	56 (29)	23 (13)	
At Birth				
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**
At the age of 2 years				
Weight, SDS	0.65 (0.41–0.90)	0.16 (-0.14–0.45)	-0.95 (-1.37– -0.53)	**<0.001**
Height, SDS	0.40 (0.17–0.63)	-0.05 (-0.34 –0.24)	-0.98 (-1.33– -0.63)	**<0.001**
At examination				
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	17.9 (13.4–23.0)	26.2 (21.0–31.9)	27.9 (19.3–38.1)	**0.046**
IGF-1, ng/mL	195.4 (178.2–214.3)	200.4 (184.5–218.3)	187.1 (162.2–215.3)	0.69
Insulin, µIU/mL	4.46 (3.91–5.08)	4.81 (4.27–5.42)	4.79 (3.92–5.86)	0.67

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

	Independent variables	Standardized B	*P*
Model 1	Weight SDS (at birth)	-0.27	**0.002**
n=125	BMI SDS	0.11	0.22
P<0.001	Serum IGF-1	0.16	0.09
R^2 0.27	Serum Insulin	0.03	0.73
	Age	0.39	**<0.001**
Model 2	Δ Weight SDS 0-2 yr	0.26	**0.001**
n=123	BMI SDS	0.02	0.78
P<0.001	Serum IGF-1	0.14	0.12
R^2 0.28	Serum Insulin	0.03	0.78
	Age	0.39	**<0.001**

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

Biochemical adrenarche	**IGF-1 tertiles (*P*=0.007)**					
	1		2		3	
	n	%	n	%	n	%
Yes	7	21.9	7	21.9	18	56.3
No	34	36.6	35	37.6	24	25.8
	Insulin tertiles (*P*=0.57)					
	1		2		3	
	n	%	n	%	n	%
Yes	9	28.1	10	31.3	13	40.6
No	33	34.7	33	34.7	29	30.5

RESULTS

All girls had prepubertal breast stage (Tanner B1), all boys prepubertal genital stage (Tanner G1), and no child had pubic hair. Three girls and 1 boy (3%) had both clinical signs of PA and DHEAS level ≥ 37 µg/dL (1.0 µmol/L) and were thus diagnosed with PA. The LGA children had lower serum DHEAS levels compared to the AGA children (the post hoc test (Sidak correction) *P*=0.075 and BMI SDS –adjusted ANCOVA *P*=0.029 for DHEAS between the LGA and AGA groups, Table 1, Figure 1). Weight at birth, early weight SDS change (0-2 years) and age were positively associated with DHEAS levels (Table 2, Figure 1), and the Chi-square test indicated a significant association between biochemical adrenarche and IGF-1 (*P*=0.007), but not insulin levels (*P*=0.57) (Table 3). There was no difference in the DHEAS levels between the sexes in BMI SDS -adjusted ANCOVA (*P*=0.99).

CONCLUSIONS

Being born LGA associated with decreased 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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55ESPE 4--P1

Adrenal

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DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS