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Exaggerated Adrenarche and Hyperinsulinism in Adolescent Girls Born Small for Gestational Age

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ABSTRACT Serum dehydroepiandrosterone-sulfate (DHEAS) is a classic marker for adrenarche and, subsequently, for the individual hormonal milieu. We have tested the hypothesis that prenatal growth reduction is followed by exaggerated adrenarche. Serum DHEAS, androstenedione and insulin concentrations were determined together with fasting glycemia in matched populations of asymptomatic, non-obese, post-menarcheal girls (mean age 14 yr) who were born either with a strictly appropriate weight for gestational age (AGA) or small for gestational age (SGA). When compared to AGA girls, the SGA girls had identical glucose levels, higher values for insulin and androstenedione ($p < 0.01$), and a two-fold rise of DHEAS concentrations ($p < 0.0001$). In conclusion, girls with prenatal growth reduction were found to be prone to develop, besides hyperinsulinism, a variant of exaggerated adrenarche. It remains to be verified whether the exaggerated adrenarche in adolescence is followed by adrenal hyperandrogenism throughout adulthood and senescence.

INTRODUCTION

Circulating dehydroepiandrosterone-sulfate (DHEAS) is a classic marker for adrenarche and for the individual hormonal milieu (1).

There is preliminary evidence indicating that prenatal growth reduction may be followed by exaggerated adrenarche, as judged by DHEAS (2-4). However, these data were obtained in potentially biased groups of children who either were born after a discordant twin pregnancy (2), maintained a short stature (3) or presented with precocious pubarche (4).

We have now tested the hypothesis that prenatal growth reduction is followed by exaggerated adrenarche by assessing whether serum DHEAS concentrations are indeed elevated in a population of asymptomatic, non-obese, post-menarcheal girls born small for gestational age, when compared to those of healthy girls with a strictly normal birthweight.

STUDY POPULATION & METHODS

The study population consisted of 63 healthy girls (age 14.0 ± 1.7 yr; range 11.4-19.0 yr) who had been recruited for this study at the time of discharge from the hospital after an intercurrent, minor illness.

The inclusion criteria were: [1] A birthweight that was either appropriate (AGA; between −1 and +1 SD) or small for gestational age (SGA; below −2 SD), [2] Menarche between 1.5 and 3 yr prior to the study, [3] Regular menstrual cycles lasting 21-45 days, and [4] normal body mass index (5).

The exclusion criteria were: evidence for a syndromatic, chromosomal, or infectious etiology of low birthweight; hirsutism [defined as a score of 8 or more on the Ferriman and Gallwey scale (6)]; thyroid dysfunction; Cushing syndrome; hyperprolactinemia; previous or current use of oral contraceptive medication, and a family or personal history of diabetes mellitus.

Blood sampling for measurement of glucose, serum insulin, estradiol, DHEAS and androstenedione concentrations was performed in fasting state during the follicular phase (range: day 5 ± 3) of the cycle.

Birthweight and gestational age data were obtained from hospital records and transformed into Standard Deviation (SD) scores, as described (4).

Glycemia was measured by glucose oxidase method. Immunoreactive insulin was assayed by IMX (Abbott Diagnostics, Santa Clara, CA), mean intra- and inter-assay coefficients of variation being 4.7 and 7.2 %. Serum DHEAS, androstenedione and estradiol levels were determined by RIA, as described (7).

Results are expressed as mean ± SEM. Mann-Whitney U-test was used for comparisons with a p-value of 0.05 as threshold for statistical significance.

The study protocol was approved by the Institutional Review Board of the Barcelona Hospital. Informed consent was obtained from the parents and assent from the girls.

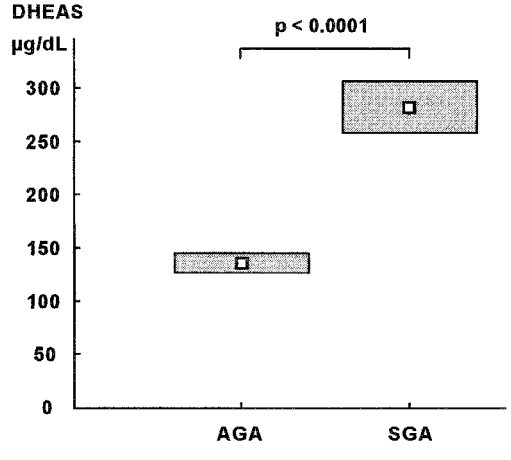
RESULTS

The Table summarizes the clinical characteristics and endocrine results.

	AGA n = 40	SGA n = 23
Birthweight (Kg)	3.21 ± 0.03	2.13 ± 0.08
Birthweight SD score	0.0 ± 0.1	-2.9 ± 0.1**
Age (yr)	14.0 ± 0.3	13.9 ± 0.3
Age at menarche (yr)	12.1 ± 0.1	12.2 ± 0.2
Height (cm)	158.0 ± 1.1	152.4 ± 1.5*
Body Mass Index (Kg/m^2)	21.8 ± 0.4	20.8 ± 0.6
DHEAS (μg/dL)	136 ± 9	282 ± 25**
Androstenedione (ng/dL)	177 ± 9.9	229 ± 18*
Insulin (μU/mL)	11 ± 0.8	18 ± 2.7*
Glucose (mg/dL)	80 ± 2	79 ± 3
Estradiol (pg/mL)	21 ± 3.3	22 ± 4.4

*p < 0.01; **p ≤ 0.0001

When compared to AGA adolescents, the SGA girls were found to have strikingly increased serum DHEAS concentrations (see Figure), as well as higher androstenedione and fasting insulin levels, while glycemia and serum estradiol were similar.



DISCUSSION

The present results, obtained in a cohort of non-symptomatic, non-obese girls matched for interfering factors, such as age and BMI, support the concept that a low weight at birth is a risk factor for adrenal hyperandrogenism in adolescence. These results are compatible with those from previous studies that suggested a link between prenatal growth reduction and adrenarche, but were either based on assessments of urinary metabolites (8) or on serum DHEAS levels in selected clinical conditions, such as twinning, short stature or precocious pubarche (2-4).

The pathophysiological mechanisms underpinning the described relationship are currently unknown, but will presumably prove to be multiple and mutually non-exclusive. One of the possibly involved factors is corticotropin-releasing hormone as the fetal serum concentrations of this peptide are high in case of fetal growth reduction (9), and as corticotropin-releasing hormone is an adrenal androgen secretagogue that may be involved in the regulation of adrenarche (10). Alternatively, the SGA girls in this cohort may have a hitherto unidentified genetic defect – for example, causing insulin resistance – that is responsible for both the initially reduced growth and the subsequently exaggerated adrenarche.

In conclusion, girls with prenatal growth reduction seem prone to develop, besides hyperinsulinism, a variant of exaggerated adrenarche. It remains to be verified whether the exaggerated adrenarche of SGA adolescents, who also seem to be at risk for developing ovarian hyperandrogenism (4), will be followed by adrenal hyperandrogenism throughout adulthood and senescence.

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