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Serum Dehydroepiandrosterone Sulfate Levels and Pubarche in Short Children Born Small for Gestational Age before and during Growth Hormone Treatment

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It has been suggested that the programming of the endocrine axes occurs during critical phases of fetal development and will be affected by intrauterine growth retardation. As a result, children born small for gestational age (SGA) might have several hormonal disturbances. In later life, one of the questions that might arise is: Do short children born SGA have higher serum dehydroepiandrosterone sulfate (DHEAS) levels than their peers? Therefore, we compared serum DHEAS levels of 181 short prepubertal children aged 3–9 yr born SGA [birth length (SD score) below −2 for gestational age] with a control group of 170 prepubertal age-matched, normal-statured children born appropriate for gestational age (birth length between −2 and +2 SD score). Because relatively high serum DHEAS levels at a young age might result in a premature pubarche, we investigated the incidence of premature pubarche. We also investigated the association between serum DHEAS levels and bone maturation. In addition, we analyzed whether 1 yr of GH treatment with 1 and 2 mg/m^2·d (≈0.035 and 0.070 mg/kg·d, respectively) had an effect on serum DHEAS levels of prepubertal short SGA children.

Serum DHEAS levels of the SGA group were comparable with those of age-matched appropriate for gestational age controls. The incidence of premature pubarche was comparable with that of the normal population. There was a weak negative correlation between serum DHEAS levels and bone maturation after the age of 7 yr. After 1 yr of GH treatment, the increase of serum DHEAS levels was the same for both GH dosage groups and the untreated group.

In conclusion, this study shows that small size at birth, which might be a feature of fetal growth restriction, has no effect on serum DHEAS levels before the age of 9 yr. The incidence of premature pubarche is comparable with the normal population. Finally, 1 yr of GH treatment has no effect on serum DHEAS levels. (*J Clin Endocrinol Metab* 89: 712–717, 2004)

EPIDEMIOLOGICAL STUDIES HAVE shown a correlation between low birth weight and hypertension, diabetes mellitus type II, hyperlipidemia, and cardiovascular disease at a relatively young age (1). It has been suggested that the programming of the endocrine axes occurs during critical phases of fetal development, which will be affected by intrauterine growth retardation (2–4). As a result, children born small for gestational age (SGA) might have several hormonal disturbances during later life.

One of the unresolved questions is whether children born SGA without catch-up growth have a disturbed adrenarche, the prepubertal rise in the secretion of the adrenal steroids dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione, and whether these children are at increased risk for a premature pubarche. Premature pubarche is defined as the appearance of pubic hair growth before the age of 8 yr in girls and 9 yr in boys and is mostly accompanied by axillary hair, acne, and pubertal odor (5, 6). Some studies have reported higher DHEAS levels in children born SGA (7, 8), but other studies did not confirm these results (9). A possible explanation for these discrepancies could be that various definitions for low birth weight, SGA, and catch-up growth were used. Premature pubarche might be caused by relatively high serum DHEAS levels at a young age. Studies in adolescent girls indicated associations between low birth weight and the occurrence of premature adrenarche, pubarche, hyperandrogenism, polycystic ovarian syndrome, and hyperinsulinism (10). These findings might have serious consequences for later life.

DHEAS arises primarily from the adrenal cortex, has a relatively long half-life in the circulation, and, therefore, does not exhibit a circadian rhythm (6, 11–13). For that reason, determination of serum DHEAS levels is appropriate for evaluation of adrenarche.

In the first part of our study, we assessed whether short prepubertal children aged 3–9 yr born SGA had serum DHEAS levels that differ from those in normal-statured, age-matched children born appropriate for gestational age (AGA). In addition, we investigated the incidence of premature pubarche in short children born SGA and whether there was an association between serum DHEAS levels and bone maturation in SGA children.

Many children born SGA without a catch-up growth are being treated with GH. Therefore, in the second part of this

Abbreviations: AGA, Appropriate for gestational age; BA, bone age; BMI, body mass index; CA, chronological age; DHEA, dehydroepiandrosterone; DHEAS, DHEA sulfate; SDS, SD score; SGA, small for gestational age.

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study we evaluated the effect of GH treatment (1 or 2 mg/m^2·d) on serum DHEAS levels in short children born SGA.

Patients and Methods

Study groups

The SGA group was comprised of 181 prepubertal children (91 boys and 90 girls) with short stature born SGA. They were enrolled between 1991 and 2001 in two Dutch multicenter GH trials in which short children born SGA were treated with GH. The following inclusion criteria were used: 1) birth length below −2 SD for gestational age according to the standards of Usher and McLean (14); 2) an uncomplicated neonatal period; 3) height SD score (SDS) for chronological age (CA) below −2.00 according to Dutch references (15); 4) height velocity SDS for CA less than or equal to zero to exclude children presenting spontaneous catch-up growth (15, 16); 5) normal liver, kidney, and thyroid functions; 6) prepubertal stage defined as Tanner breast stage I for girls, and testicular volume less than 4 ml for boys (17); and 7) age between 3 and 9 yr. Exclusion criteria were: endocrine or metabolic disorders, chromosomal disorders, growth failure caused by other disorders (emotional deprivation, severe chronic illness, chondrodysplasia) or syndromes (with the exception of the Silver Russell syndrome), and previous or present use of drugs that could interfere with growth and GH treatment. Mean birth length (SDS) was −3.4 ± 1.6; birth weight (SDS), −2.5 ± 1.1; gestational age, 36.4 ± 3.7 wk; and body mass index (BMI), (SDS) −1.3 ± 1.2.

The control group was comprised of 170 healthy age-matched prepubertal children (94 boys and 76 girls) with a normal stature born AGA who were referred to the hospital for a minor surgical procedure. Blood was obtained before anesthesia was given. Normal stature was defined as a height between −2 and +2 SDS according to Dutch references (15). All children were between 3 and 9 yr of age. None of the children had a syndrome or chromosomal abnormality, endocrine or metabolic disorder, or any other illness or use of drugs that might have affected DHEAS levels.

The study was approved by the Ethics Committee of each participating center. Written informed consent was obtained from the parents or custodians of each child.

Study design

In the first part of this study, the serum DHEAS levels were compared between the SGA group and the AGA controls. Venous blood samples were obtained for determination of serum DHEAS levels. In the SGA group, blood was obtained before the start of GH treatment, the incidence of premature pubarche was assessed, and bone maturation was determined.

In the second part of this study, the 1-yr effect of GH treatment (1 or 2 mg GH/m^2·d) on serum DHEAS levels was evaluated in the SGA group in comparison with changes after 1 yr in a randomized untreated SGA group. The SGA group consisted of participants of two Dutch GH trials who met the same inclusion and exclusion criteria. All patients had a GH stimulation test to exclude GH deficiency. The first study consisted of 56 short SGA children who were 1:1 randomly and blindly assigned to a group receiving either 1 mg or 2 mg GH/m^2·d (≈0.035 and 0.070 mg/kg·d, respectively) (18). The second study consisted of 125 short SGA children who were 1:2 randomly assigned to either a group without GH treatment (untreated group) or a group receiving 1 mg GH/m^2·d (≈0.035 mg/kg·d). Together, this resulted in three study groups: an untreated control group (n = 42), a group that received 1 mg GH/m^2·d (n = 111), and a group treated with 2 mg GH/m^2·d (n = 28). Biosynthetic GH (recombinant human GH Norditropin; Novo Nordisk A/S, Bagsvaerd, Denmark) was given sc once daily at bedtime with a pen injection system (Nordiject 24; Novo Nordisk A/S). Every 3 months, the total GH dose was adjusted to the calculated body surface. Venous blood samples were obtained after 1 yr of GH treatment or nontreatment. All samples were frozen at −80 C until assayed.

Physical examination

Before the start of GH treatment and every 3 months after the start of GH treatment, SGA children had a physical examination including measurement of standing height, weight, and pubertal stage. Height was measured according to Cameron (19) using a Harpenden (Cambridge, MD) stadiometer. Height and weight were expressed as SDS (15). Pubertal stages were assessed according to Tanner (17) using an orchidometer in boys. Premature pubarche was defined as the appearance of pubic hair stage II or more before the age of 8 yr in girls and 9 yr in boys.

Hormone assays

DHEAS levels were determined in one central laboratory and measured using a chemiluminescence-based competitive immunoassay (Immulite1, Diagnostic Products Corporation, Los Angeles, CA). The interassay coefficient was 8%. The limit of detection was 0.2 μmol/liter. Values below this limit of detection were considered to be 0.1 μmol/liter.

Bone maturation

For the SGA children, an x-ray of the left hand was made before the start of GH therapy and after 1 yr of GH treatment. All bone ages (BAs) were determined by one investigator according to the radius, ulna, and short bone scores of Tanner *et al.* (20).

Statistical analyses

Serum DHEAS levels are presented as median and interquartile range; BAs are presented as mean ± SD. The SGA children and the AGA controls were divided into various age groups: group I, 3.00–4.99 yr; group II, 5.00–6.99 yr; and group III, 7.00–8.99 yr.

Differences in serum DHEAS levels between the SGA children and AGA controls were tested per subgroup of age and gender. In case of a non-Gaussian-shaped DHEAS distribution, the Mann-Whitney *U* test was used. If the DHEAS distribution within a group was Gaussian-shaped, the analysis of covariance was used with age as covariate. Differences in BA and CA were tested using the paired-samples *t* test. The Spearman rank correlation test was used to test the correlations between serum DHEAS levels and age, BMI, and difference between CA and BA. The correlations between DHEAS, birth weight, and birth length were tested with the partial correlation test corrected for age at time of study. A *P* value of less than 0.05 was considered significant.

TABLE 1. Age and serum DHEAS levels for boys and girls per age group in SGA children and AGA controls and BMI SDS for SGA children

	Age group	SGA children				AGA controls		
		n	Age (yr)	DHEAS (μmol/liter)	BMI SDS	n	Age (yr)	DHEAS (μmol/liter)
Boys	I	26	3.9 (3.7–4.6)	0.1 (0.1–0.3)	−1.5 (1.2)[a]	30	3.7 (3.3–4.3)	0.1 (0.1–0.1)
	II	29	6.0 (5.4–6.7)	0.1 (0.1–0.7)	−1.0 (1.0)[a]	30	6.0 (5.4–6.4)	0.3 (0.1–0.8)
	III	36	7.7 (7.2–8.3)	1.0 (0.2–2.3)	−1.0 (1.1)[a]	34	7.9 (7.4–8.5)	0.5 (0.3–0.9)
Girls	I	23	4.0 (3.5–4.5)	0.1 (0.1–0.3)	−1.9 (1.6)[a]	26	4.3 (3.6–4.6)	0.1 (0.1–0.2)
	II	37	6.2 (5.3–6.6)	0.3 (0.1–0.5)	−1.5 (1.2)[a]	30	5.9 (5.4–6.3)	0.3 (0.2–0.4)
	III	30	7.9 (7.4–8.6)	0.5 (0.2–1.2)	−0.9 (1.0)[a]	20	7.9 (7.5–8.6)	1.2 (0.4–2.0)[b]

Data are expressed as median (interquartile range) except BMI SDS, which is mean (SD). Age group I, 3.00 to 4.99 yr; II, 5.00–6.99 yr; III, 7.00–8.99 yr.

[a] $P < 0.01$ *vs.* 0 SDS.

[b] $P < 0.05$, AGA *vs.* SGA.

All analyses were performed using SPSS version 10.0 (SPSS, Inc., Chicago, IL).

Results

Untreated SGA children vs. *AGA controls*

Table 1 shows the serum DHEAS levels and age in the various age groups for the SGA children compared with the age-matched AGA controls for boys and girls. For both the SGA children and AGA controls, we found higher serum DHEAS levels with increasing age. There was no significant difference in age between the SGA group and AGA controls. The serum DHEAS levels per age group were not higher for the SGA group compared with AGA controls. SGA girls aged 7.00–8.99 yr had significantly lower serum DHEAS levels compared with age-matched AGA girls (Table 1). Table 1 also shows the BMI SDS for the SGA children. In all age groups, the mean BMI SDS for the SGA children was significantly lower than zero. Only one SGA boy in age group III had a BMI SDS above 2.

For both the SGA group and AGA controls, a positive correlation was found between serum DHEAS levels and age ($r = 0.47$, $P < 0.001$; $r = 0.56$, $P < 0.001$, respectively). A weak but significant negative correlation was found between serum DHEAS levels and birth weight SDS and birth length SDS in children born SGA ($r = -0.30$, $P < 0.01$; $r = -0.29$, $P < 0.01$, respectively), but after correction for age at the time of study the correlations disappeared. No correlation was found between serum DHEAS levels and BMI SDS at the time of study.

Of the 90 SGA girls, two girls had first signs of pubarche before the age of 8 yr. Because pubic hair development at a stage greater than stage I was not an exclusion criterion for the GH trials, these girls were enrolled in the study at the age of 8.5 yr. At that age serum DHEAS levels were 1.60 and 3.00 μmol/liter, respectively, and BAs were 9.8 and 9.6 yr, respectively. The normal interval range for serum DHEAS for girls aged 7.0–8.9 yr is 1.19 (0.37–2.00) μmol/liter. None of the boys had signs of pubarche before the age of 9 yr.

TABLE 2. BA compared with CA in 164 SGA children

Age group (yr)	n	CA (yr)	BA (yr)[a]
I (3–4.99)	43	4.0 ± 0.6	3.2 ± 0.9[b]
II (5–6.99)	59	6.0 ± 0.7	5.0 ± 1.3[b]
III (7–8.99)	62	7.9 ± 0.6	6.9 ± 1.7[b]

Data expressed as mean ± SD.

[a] Bone age according to the radius, ulna, and short bones scores of Tanner *et al.* (20).

[b] $P < 0.001$.

Table 2 shows that all age groups of SGA children had a BA delay (ΔCA − BA), with a significantly lower mean BA than CA ($P < 0.001$). Until the age of 7 yr, we did not find a correlation between serum DHEAS levels and degree of BA delay, but after the age of 7 yr, a weak negative correlation was found between serum DHEAS levels and degree of BA delay ($r = -0.34$; $P < 0.001$).

Effect of 1 yr of GH treatment vs. no treatment

Table 3 shows that baseline clinical data were comparable for the three study groups. The mean age of the children receiving 2 mg GH/m^2·d was 11 months older than that of the untreated group, but this age difference was not significant. Table 4 shows the age, serum DHEAS levels, and progression of BA after 1 yr of GH treatment or no treatment. In the oldest age group, the age was significantly different between the three study groups. We, therefore, used the analysis of covariance test adjusted for age. After adjusting for age, the serum DHEAS levels of the three study groups per age group were not significantly different between the three SGA study groups. The progression of bone maturation (the increase of BA divided by the increase of CA) in age group II was significantly faster in the group receiving 2 mg GH/m^2·d compared with the groups without GH treatment and the group receiving 1 mg GH/m^2·d.

Discussion

We investigated the serum DHEAS levels in a large group of 181 short prepubertal children aged 3–9 yr born SGA in comparison with 171 age-matched AGA controls. Our data show that short prepubertal children born SGA have normal serum DHEAS levels, and 1 yr of GH treatment had no influence on the serum DHEAS levels. Premature pubarche was found in 2.2% of the girls and in none of the boys. Age was positively correlated with serum DHEAS levels. After the age of 7 yr, a weak negative correlation was found between serum DHEAS levels and BA delay. No correlation was found between serum DHEAS levels and BMI SDS.

Normal serum DHEAS levels were found in short prepubertal SGA children compared with age-matched AGA controls. SGA girls aged 7.00–8.99 yr had significantly lower serum DHEAS levels compared with their AGA controls. Previously, other studies reported higher serum DHEAS levels in individuals born SGA (2, 7, 8, 21, 22). However, most of these studies were much smaller and used different definitions. For example, some studies included individuals with low birth weight not corrected for

TABLE 3. Clinical data at start of GH trial in 181 short SGA children

	SGA study groups		
	Untreated group	1 mg GH/m^2·d	2 mg GH/m^2·d
Male/female	19/23	57/54	15/13
Gestational age (wk)	36.3 ± 3.5	36.6 ± 3.7	35.6 ± 4.1
Birth length SDS	−3.7 ± 2.3	−3.3 ± 1.2	−3.6 ± 1.7
Birth weight SDS	−2.8 ± 1.0	−2.3 ± 1.1	−2.7 ± 1.2
CA (yr)	5.8 ± 1.5	6.1 ± 1.6	6.7 ± 1.9
Height SDS	−3.1 ± 0.6	−3.0 ± 0.7	−3.1 ± 0.7

Data expressed as mean ± SD.

TABLE 4. Age, serum DHEAS levels, and ΔBA/ΔCA after 1 yr of GH treatment in SGA children

Age group	GH treatment groups								
	0 mg/m^2·d (n = 42)			1 mg/m^2·d (n = 111)			2 mg/m^2·d (n = 28)		
	Age (yr)	DHEAS (μmol/liter)	ΔBA/ΔCA	Age (yr)	DHEAS (μmol/liter)	ΔBA/ΔCA	Age (yr)	DHEAS (μmol/liter)	ΔBA/ΔCA
I	4.9 (4.4–5.0)	0.2 (0.1–0.7)	0.9 (0.6–1.4)	5.1 (4.7–5.6)	0.3 (0.1–0.5)	1.3 (0.9–1.8)	4.8 (4.3–5.6)	0.2 (0.1–0.5)	1.0 (0.9–1.9)
II	7.0 (6.3–7.4)	0.6 (0.4–1.4)	0.9 (0.6–1.4)	6.9 (6.3–7.7)	0.4 (0.2–1.3)	1.4 (0.9–2.2)	7.5 (6.6–7.8)	1.2 (0.4–2.9)	2.8 (1.8–3.1)[d,e]
III	8.2 (8.1–8.7)	0.8 (0.3–1.1)	1.1 (0.4–1.5)	8.8 (8.4–9.3)[a]	1.3 (0.6–1.8)	1.5 (0.7–1.8)	9.6 (9.0–9.7)[b,c]	2.0 (1.4–2.5)	1.2 (0.1–2.5)

Data are expressed as median (interquartile range).
[a] $P < 0.05$, 0 *vs.* 1 mg.
[b] $P < 0.05$, 1 *vs.* 2 mg.
[c] $P < 0.001$, 0 *vs.* 2 mg.
[d] $P < 0.05$, 1 *vs.* 2 mg.
[e] $P < 0.05$, 0 *vs.* 2 mg.

gestational age or evaluated the effect of birth weight or length in a group of children born AGA. In most studies, serum DHEAS levels were studied in individuals during or after puberty or in SGA children who underwent a spontaneous catch-up growth after birth. Our results are in agreement with those of a French study of normal-statured adult women born SGA that found no differences in serum DHEAS levels between women born SGA and an AGA control group (9). Dahlgren *et al.* (23) also did not find significantly different serum DHEAS levels in 33 short SGA children (defined as a weight or a length at birth below −2 SDS) compared with 35 normal-statured AGA children. However, this study included both prepubertal and pubertal children aged between 2.8 and 15.5 yr. To our knowledge, our study is the first one investigating serum DHEAS levels in a large group of prepubertal short SGA children.

Serum DHEAS levels were positively correlated with age. However, we did not find a correlation between birth weight (SDS), birth length (SDS), and serum DHEAS levels in SGA children after correction for age at the time of study. Dahlgren *et al.* (23) found a negative correlation between serum DHEAS levels and birth weight in SGA and AGA children together, but this correlation disappeared after the age of 9 yr. A possible explanation for this discrepancy is that these authors did not correct for age at investigation below the age of 9 yr, although they also found a significant correlation between serum DHEAS levels and age.

Ibanez *et al.* (24) reported a significantly lower birth weight in girls with ovarian hyperandrogenism who also had a premature pubarche. It was concluded that girls with a premature pubarche born SGA are at higher risk of getting polycystic ovarian syndrome (10). However, these studies were performed in a relatively small patient group from a specific part of Spain. Their patients presented with abnormalities, and the association with low birth weight was found retrospectively. We feel that selection based on low birth weight is more appropriate for studying the consequences of a small size at birth on serum DHEAS levels at varying prepubertal ages. In the Dutch GH trials, pubic hair development at a stage greater than stage I was not an exclusion criterion (17). Because serum DHEAS levels in our SGA group were normal, it is not surprising that only 2.2% of the girls and none of the boys had a premature pubarche. This is comparable with the incidence of premature pubarche in the normal population, in which the incidence in white girls younger than 8 yr is 2.8% (25). One of the two SGA girls with a premature pubarche had DHEAS levels above the normal range.

Some studies reported a positive correlation between weight and serum DHEAS levels. Particularly marked weight gain and obesity were associated with high serum DHEAS levels (26). In contrast, we did not find a correlation between BMI SDS and serum DHEAS levels in our prepubertal SGA group. One of the explanations might be that our SGA children were lean with a mean BMI SDS significantly lower than zero. Only one boy had a BMI SDS above 2. In addition, there was only a narrow variation in the BMI SDS of our prepubertal SGA children.

The SGA children had a 1-yr delay in BA that was

similar for all three age groups. Mean bone maturation was not advanced, at least not until a mean (SD) age of 7.9 (0.6) yr, which does not exclude that acceleration of bone maturation might occur at a later age as has previously been reported. Tanner *et al.* (27) found an acceleration of BA from the age of 8 yr in short children with Silver Russell syndrome born SGA. Before the age of 7 yr, we did not find a correlation between serum DHEAS levels and BA delay. But, after the age of 7 yr, we found a weak but significant negative correlation between serum DHEAS levels and BA delay, suggesting that DHEAS might be one of the factors responsible for the acceleration of bone maturation in SGA children after the age of 7 yr. In addition, the two SGA girls who had a premature pubarche showed high serum DHEAS levels and an advanced BA.

In several studies, short SGA children are being treated with biosynthetic GH. It is known that GH increases IGF-I levels, and IGF-I plays an important role in the biosynthesis of adrenal steroids (6, 18). For this reason, we investigated whether GH treatment might have an influence on the adrenarche of SGA children; however, we showed that 1 yr of GH treatment has no influence on serum DHEAS levels in SGA children regardless of the GH dose of 1 or 2 mg GH/m^2·d. The age in age group III was significantly different between the three GH treatment groups. For this reason, the DHEAS levels were different after 1 yr of GH treatment, but, after correction for age, there was no significant difference between serum DHEAS levels in the three groups. It has also been reported that the administration of GH in children with idiopathic GH deficiency did not modify the adrenal androgen plasma levels (28). These data support our data indicating that GH treatment does not induce higher serum DHEAS levels. After 1 yr, the progression of bone maturation was only significantly higher in age group II patients who received 2 mg GH/m^2·d. However, Van Pareren *et al.* (29) showed in the same group that there was no GH dose effect on bone maturation after 5 yr of GH treatment.

In conclusion, this study shows that small size at birth, which might be a feature of fetal growth restriction, has no effect on serum DHEAS levels before the age of 9 yr. The incidence of premature pubarche is comparable with the normal population. In addition, 1 yr of GH treatment has no effect on serum DHEAS levels.

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