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/m²-d (~0.035 and 0.070 mg/kgd, 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 study, we assessed whether 1 yr of GH treatment with 1 and 2 mg/m²/d (~0.035 and 0.070 mg/kgd, respectively) had an effect on serum DHEAS levels of prepubertal short SGA children.

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/ m²d) 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 (with the exception of the Silver Russell syndrome), and previous or mosomal disorders, growth failure caused by other disorders (emotional

9 yr. Exclusion criteria were: endocrine or metabolic disorders, chro-

mosomal disorders, catch-up growth (15, 16); 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 pubertal stage II or III, 7) absence of emotional deprivation, serious chronic illness, and metabolic or endocrine disorders, 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/m²d) 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 height velocity SDS for 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 pubertal stage II or III, 7) absence of emotional deprivation, serious chronic illness, and metabolic or endocrine disorders, 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.

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

<table>
<thead>
<tr>
<th>Age group</th>
<th>SGA children</th>
<th>AGA controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Age (yr)</td>
<td>DHEAS (µmol/liter)</td>
</tr>
<tr>
<td>Boys</td>
<td>I</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>36</td>
</tr>
<tr>
<td>Girls</td>
<td>I</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>30</td>
</tr>
</tbody>
</table>

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.

* 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.

Data expressed as mean ± SD. For the three 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/m2 compared with the groups without GH treatment and the group receiving 1 mg GH/m2.

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/m2 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/m2 compared with the groups without GH treatment and the group receiving 1 mg GH/m2.

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...
Age, serum DHEAS levels, and pubertal 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

<table>
<thead>
<tr>
<th>Age group</th>
<th>0 mg/m² (n = 280)</th>
<th>2 mg/m² (n = 111)</th>
<th>1 mg/m² (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>DHEAS (μmol/liter)</td>
<td>ΔBAAGA</td>
<td>Age (yr)</td>
</tr>
<tr>
<td>I</td>
<td>4.9 (4.1–5.5)</td>
<td>2.0 (0.1–0.7)</td>
<td>0.2 (0.0–0.7)</td>
</tr>
<tr>
<td>II</td>
<td>7.0 (6.3–7.4)</td>
<td>0.6 (0.4–1.4)</td>
<td>0.8 (0.3–1.1)</td>
</tr>
<tr>
<td>III</td>
<td>8.2 (8.1–8.7)</td>
<td>0.4 (0.3–0.7)</td>
<td>1.0 (0.7–1.2)</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range).
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 effect on serum DHEAS levels in SGA children regardless of the GH dose of 1 or 2 mg GH/m²·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/m²·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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