

Association between Body Mass Index and Serum Dehydroepiandrosterone Sulfate Level in 8-Year-Old Girls

Ji-Hyun Na, Young-Hwan Kim, Suk-Jin Hong, Jin-Kyung Kim*

Department of Pediatrics, Daegu Catholic University School of Medicine, Daegu, Korea

Background: Adiposity may play a role as a potential trigger for adrenarche. The purpose of this study was to evaluate the association between body mass index (BMI) and serum dehydroepiandrosterone sulfate (DHEAS) level.

Methods: The medical records of 8-year-old girls who presented to our clinic between 2014 and 2016 with concerns regarding pubertal changes were retrospectively reviewed. The 192 girls were divided into two groups depending on activation of the hypothalamic-pituitary-gonadal (HPG) axis. Group I included 77 subjects with a breast Tanner stage 1 with unknown HPG axis or thelarche without activated HPG axis. Group II included 115 subjects with activated HPG axis. Serum DHEAS level ≥ 1.1 $\mu\text{mol/L}$ was regarded as biochemical adrenarche.


Results: Based on correlation analyses, BMI standard deviation score (SDS) was positively correlated with height SDS, bone age divided by chronological age (BA/CA), and DHEAS level in all subjects ($r=0.269$, $r=0.270$, $r=0.298$; all $P<0.001$, respectively). BMI SDS was negatively correlated with peak luteinizing hormone level in group II ($r=-0.236$, $P=0.011$). Based on multiple linear regression analyses, BMI SDS was associated with serum DHEAS level in all subjects ($\beta=0.280$, $P<0.001$), group I ($\beta=0.415$, $P=0.001$), and group II ($\beta=0.206$, $P=0.030$). DHEAS level was also associated with BA/CA in all subjects ($\beta=0.402$, $P<0.001$), group I ($\beta=0.494$, $P<0.001$), and group II ($\beta=0.347$, $P<0.001$).

Conclusion: BMI SDS was associated with DHEAS level, which was associated with BA/CA. Childhood obesity may influence the development of adrenarche, which may contribute to advanced skeletal maturation.

Key words: Biochemical adrenarche, Dehydroepiandrosterone sulfate, Body mass index

Received January 23, 2018
Reviewed February 20, 2018
Accepted April 23, 2018

*Corresponding author
Jin-Kyung Kim

 <https://orcid.org/0000-0003-0018-851X>

Department of Pediatrics, Daegu
Catholic University School of Medicine,
33 Duryugongwon-ro 17-gil, Nam-gu,
Daegu 42472, Korea
Tel: +82-53-650-4597
Fax: +82-53-650-4243
E-mail: kimjk@cu.ac.kr

INTRODUCTION

Pubertal maturation consists of two processes, gonadarche and adrenarche. Gonadarche is the secretion of gonadal sex steroids by pubertal activation of the hypothalamic-pituitary-gonadal (HPG) axis. The age of onset in girls is typically between 8 and 13 years.¹ Adrenarche refers to a maturational increase in adrenal androgen production.^{2,3} Adrenarche is characterized by expansion of the adrenal zona reticularis, unique expression of steroidogenic enzymes and cofactors^{4,6}, and changes in the pattern of adrenal biosynthetic

and secretory response to adrenocorticotrophic hormone (ACTH). In adrenarche, 17-ketosteroid responsiveness to ACTH increases, while cortisol responsiveness to ACTH remains unchanged.⁷ Therefore, adrenarche leads to increased production of adrenal androgens, dehydroepiandrosterone (DHEA), and its sulfate ester (dehydroepiandrosterone sulfate [DHEAS]), but no increase in cortisol level.^{2,4} While the clinical signs of adrenal androgen action are normally observed after the age of 8 years, the increase in adrenal androgen production associated with adrenarche generally begins at approximately 6–8 years of age.³ DHEAS has a much lower

rate of clearance from the circulation than DHEA. DHEAS has neither a diurnal rhythm nor day-to-day variation. Serum DHEAS level is the best marker of adrenal androgen secretion.^{2,3} DHEAS levels above 1.1 $\mu\text{mol/L}$ are regarded as a biochemical hallmark of adrenarche.^{2,3} Guran et al.⁸ reported the cut-off age for an increase in DHEAS above 1.1 $\mu\text{mol/L}$ is 8 years for girls and 7 years for boys. High prepubertal DHEAS level is associated with premature adrenarche (PA), defined as the appearance of clinical signs of adrenarche before the age of 8 years in girls, along with elevated DHEAS level for that age. Although PA is usually considered benign, in some girls, PA has been associated with several metabolic disturbances including hyperinsulinemia, dyslipidemia, or polycystic ovary syndrome.^{2,3} The initiation mechanisms of adrenarche remain mostly unclear although adiposity may play a role as a potential trigger.^{2,3} Previous studies have shown that low birth weight and small size for gestational age are associated with higher prepubertal adrenal androgen production, mainly in girls, especially if accompanied by rapid weight gain in early childhood.⁹⁻¹³ Higher prepubertal adrenal androgen production has also been reported in obese children with normal birth weight.¹³⁻¹⁵ Therefore, we retrospectively evaluated the medical records of 8-year-old girls to investigate the associations between body mass index (BMI) and serum DHEAS level.

METHODS

Subjects

We retrospectively reviewed the medical records of 8-year-old girls who visited Daegu Catholic University Medical Center between January 2014 and December 2016 with concerns regarding pubertal changes. In the present study, 192 healthy girls who underwent medical and physical examinations were evaluated. All subjects were born at term with a birth weight $\geq 2,500$ g. Girls with chronic diseases, organic brain lesions, or receiving any drug treatment or exogenous hormone therapy were excluded. Pubertal status (breast development and pubic hair) was also recorded. Gonadotropin-releasing hormone (GnRH) stimulation test was conducted in 178 girls. The subjects were divided into two groups depending on activation of the HPG axis. Group I included 77 subjects with a breast Tanner stage 1 with unknown HPG axis or the-

larche without activation of the HPG axis, and group II included 115 subjects with activated HPG axis. This study was approved by the Institutional Review Board of the Daegu Catholic University Medical Center, Daegu, Korea (IRB No. CR-17-060). The need for informed consent was waived by the board.

Measurement and laboratory evaluation

The height and weight of each patient were measured, and BMI was calculated by dividing weight (kg) by squared height (m^2). Height, weight, and BMI were expressed as a standard deviation score (SDS) according to age- and sex-matched growth charts of Korean children and adolescents published in 2007 by the Korea Centers for Disease Control and Prevention and the Korea National Institute of Health.¹⁶ Normal weight was defined as a BMI < 85 th percentile for age and sex, and overweight/obese was defined as a BMI ≥ 85 th percentile for age and sex. Sexual maturity ratings were determined according to the Marshall and Tanner staging method.¹⁷ Bone age (BA) was assessed using radiographs of the left hand according to the method of Greulich and Pyle.¹⁸ Bone age divided by chronological age (BA/CA) was used as an index of BA advancement. In subjects with thelarche, the GnRH stimulation test was performed by intravenous administration of 100 μg of gonadorelin (Relefact; Sanofi-Aventis, Frankfurt am Main, Germany) for the diagnosis of gonadarche. Activation of the HPG axis was defined by peak luteinizing hormone (LH) level ≥ 5 IU/L using the GnRH stimulation test.¹⁹ Serum LH level was measured using an electrochemiluminescence immunoassay on a Cobas 8000 modular analyzer (Roche Diagnostics, Mannheim, Germany). Serum DHEAS concentration was measured using chemiluminescence immunoassay on an Immulite 2000 XPi System (Siemens Healthcare Diagnostics, Flanders, NJ, USA). Biochemical adrenarche was defined as an increase in circulating adrenal androgen concentration with a serum DHEAS level ≥ 1.1 $\mu\text{mol/L}$.^{2,3}

Statistical analysis

All statistical analyses were performed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Values are presented as mean \pm standard deviation for continuous variables. Student *t*-test and Mann-Whitney *U*-test were applied for comparison between two groups. The chi-square test was used to compare proportions.

Correlations were evaluated using Spearman correlation coefficient. Multivariate linear regression analyses were performed to investigate the influence of clinical and biochemical variables on the changes in serum DHEAS level and the degree of advanced skeletal maturation (BA/CA). A P -value < 0.05 was considered statistically significant.

RESULTS

Anthropometric characteristics and hormonal status of the study population

Medical records of 192 girls aged 8 years were evaluated. Group I included 77 girls and group II included 115 girls. The mean BA/CA was 1.09 ± 0.11 in group I and 1.13 ± 0.09 in group II ($P = 0.009$). The mean BMI SDS was 0.8 ± 1.1 in group I and 0.3 ± 1.2 in group II ($P = 0.003$). The mean DHEAS level was 1.3 ± 0.9 $\mu\text{mol/L}$ in group I and 1.2 ± 0.8 $\mu\text{mol/L}$ in group II. Biochemical adrenarche was observed in 34 girls (44.2%) in group I and 49 girls (42.6%) in

group II. The number of overweight/obese girls was higher in group I (42.9%) than in group II (22.6%, $P = 0.004$) (Table 1).

Correlations and multiple linear regression analysis

Based on Spearman correlation analyses, BMI SDS was significantly and positively correlated with height SDS, BA/CA, and DHEAS level in all subjects ($r = 0.269$, $r = 0.270$, $r = 0.298$; all $P < 0.001$, respectively); group I subjects ($r = 0.292$, $P = 0.010$; $r = 0.276$, $P = 0.015$; $r = 0.398$, $P < 0.001$, respectively), and group II subjects ($r = 0.251$, $P = 0.007$; $r = 0.366$, $P < 0.001$; $r = 0.252$, $P = 0.007$, respectively). BMI SDS was significantly and negatively correlated with peak LH level in all subjects ($r = -0.353$, $P < 0.001$) and in group II subjects ($r = -0.236$, $P = 0.011$) (Table 2).

Based on multiple linear regression analyses, BMI SDS was associated with serum DHEAS level in all subjects ($\beta = 0.280$, $P < 0.001$), group I ($\beta = 0.415$, $P = 0.001$), and group II ($\beta = 0.206$, $P = 0.030$) (Table 3). DHEAS level was associated with BA/CA in all subjects ($\beta = 0.402$, $P < 0.001$), group I ($\beta = 0.494$, $P < 0.001$), and group II ($\beta = 0.347$, $P < 0.001$) (Table 4).

Table 1. Anthropometric characteristics and hormonal status of the subjects

Variable	Group I (n=77)	Group II (n=115)	P
CA (yr)	8.6±0.3	8.6±0.3	0.106
BA (yr)	9.3±0.9	9.7±0.8	0.001
BA/CA	1.09±0.11	1.13±0.09	0.009
Height (cm)	132.6±4.7	132.7±5.3	0.907
Height SDS	0.8±0.9	0.8±1.0	0.919
BMI (kg/m ²)	18.8±2.7	17.7±2.8	0.006
BMI SDS	0.8±1.1	0.3±1.2	0.003
LH peak	3.2±1.1*	12.6±10.3	<0.001 [†]
DHEAS (μmol/L) [‡]	1.3±0.9	1.2±0.8	0.694 [†]
Biochemical adrenarche	34 (44.2)	49 (42.6)	0.832 [§]
Overweight/obese	33 (42.9)	26 (22.6)	0.004 [§]
Tanner stage, breast, I/II/III/IV/V	14/59/4/0/0	0/81/31/3/0	-
Tanner stage, pubic hair, I/II/III/IV/V	0/4/0/0/0	0/2/0/0/0	-

Values are presented as mean ± standard deviation or number (%). Student t -test was applied for comparison between the two groups. Group I included subjects with a breast Tanner stage 1 with unknown HPG axis or thelarche without activation of the HPG axis, and group II included subjects with activated HPG axis.

*Gonadotropin-releasing hormone stimulation test was conducted in 63 of 77 girls in group I and all girls in group II; [†]Mann-Whitney U -test was applied for comparison between the two groups; [‡]DHEAS level < 0.4 $\mu\text{mol/L}$ was calculated as 0.38 $\mu\text{mol/L}$; [§]Chi-square test was applied to compare proportions.

CA, chronological age; BA, bone age; BA/CA, bone age divided by chronological age; SDS, standard deviation score; BMI, body mass index; LH peak, peak stimulated luteinizing hormone level; DHEAS, dehydroepiandrosterone sulfate; HPG, hypothalamic-pituitary-gonadal.

Table 2. Spearman correlation coefficients of the subjects

Variable	BMI SDS		BA/CA		DHEAS		LH peak*	
	r	P	r	P	r	P	r	P
Total (n=192)								
Height SDS	0.269	<0.001	0.407	<0.001	0.206	0.004	0.085	0.262
BMI SDS			0.270	<0.001	0.298	<0.001	-0.353	<0.001
BA/CA					0.487	<0.001	0.175	0.019
DHEAS							-0.050	0.512
Group I (n=77)								
Height SDS	0.292	0.010	0.316	0.005	0.291	0.010	0.055	0.670
BMI SDS			0.276	0.015	0.398	<0.001	0.007	0.959
BA/CA					0.578	<0.001	-0.027	0.834
DHEAS							0.069	0.594
Group II (n=115)								
Height SDS	0.251	0.007	0.482	<0.001	0.150	0.110	0.167	0.075
BMI SDS			0.366	<0.001	0.252	0.007	-0.236	0.011
BA/CA					0.453	<0.001	0.123	0.190
DHEAS							-0.090	0.339

Group I included subjects with a breast Tanner stage 1 with unknown HPG axis or thelarche without activation of the HPG axis, and group II included subjects with activated HPG axis.

*Gonadotropin-releasing hormone stimulation test was conducted in 178 girls.

BMI, body mass index; SDS, standard deviation score; BA/CA, bone age divided by chronological age; DHEAS, dehydroepiandrosterone sulfate; LH peak, peak stimulated luteinizing hormone level; HPG, hypothalamic-pituitary-gonadal.

Table 3. Multiple linear regression analysis of factors affecting serum DHEAS level in 8-year-old girls

Variable	All subjects (n= 192)				Group I (n= 77)				Group II (n= 115)			
	B	SE	β	P	B	SE	β	P	B	SE	β	P
CA	-0.682	4.892	-0.010	0.889	-1.795	9.144	-0.023	0.845	-0.618	5.667	-0.010	0.913
BMI SDS	7.461	1.988	0.280	<0.001	14.833	4.236	0.415	0.001	4.932	2.243	0.206	0.030
LH peak	-0.145	0.240	-0.045	0.545	-0.992	3.889	-0.030	0.800	-0.242	0.250	-0.090	0.335
Adjusted R ²	0.071				0.133				0.029			

Group I included subjects with a breast Tanner stage 1 with unknown HPG axis or thelarche without activation of the HPG axis, and group II included subjects with activated HPG axis.

DHEAS, dehydroepiandrosterone sulfate; B, unstandardized coefficients; SE, standard error; β , standardized coefficients; CA, chronological age; BMI, body mass index; SDS, standard deviation score; LH peak, peak stimulated luteinizing hormone; HPG, hypothalamic-pituitary-gonadal.

Table 4. Multiple linear regression analysis of factors affecting BA/CA in 8-year-old girls

Variable	All subjects (n= 192)				Group I (n= 77)				Group II (n= 115)			
	B	SE	β	P	B	SE	β	P	B	SE	β	P
Height SDS	0.036	0.007	0.335	<0.001	0.034	0.014	0.273	0.020	0.037	0.007	0.391	<0.001
BMI SDS	0.007	0.006	0.080	0.231	-0.001	0.014	-0.005	0.971	0.013	0.006	0.166	0.034
DHEAS	0.001	0.000	0.402	<0.001	0.002	0.000	0.494	<0.001	0.001	0.000	0.347	<0.001
LH peak	0.002	0.001	0.196	0.002	-0.005	0.011	-0.052	0.620	0.001	0.001	0.148	0.052
Adjusted R ²	0.381				0.334				0.406			

Group I included subjects with a breast Tanner stage 1 with unknown HPG axis or thelarche without activation of the HPG axis, and group II included subjects with activated HPG axis.

BA/CA, bone age divided by chronological age; B, unstandardized coefficients; SE, standard error; β , standardized coefficients; SDS, standard deviation score; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; LH peak, peak stimulated luteinizing hormone; HPG, hypothalamic-pituitary-gonadal.

DISCUSSION

A distinct interindividual variation was observed not only in the timing of adrenarche, but also in the amount of adrenal androgen precursor production.^{2,3} In this study, serum DHEAS level showed a wide distribution from 0.4 $\mu\text{mol/L}$ to 5.1 $\mu\text{mol/L}$. Serum DHEAS level was below 0.4 $\mu\text{mol/L}$ in 20 of 192 girls. The prevalence of biochemical adrenarche in all subjects with concerns regarding pubertal changes was 43.2% (44.2% of girls without HPG axis activation and 42.6% of girls with HPG axis activation). In most girls without HPG axis activation, thelarche may reflect the peripheral source of sex steroids. However, in several girls, the degree of thelarche progressed during the follow-up period, which might be associated with activation of the HPG axis. Furthermore, some of the overweight/obese girls may have experienced HPG axis activation. Recent studies have shown that obesity affects the LH response to the GnRH stimulation test in girls.^{20,21} During the GnRH stimulation test, peak LH level was significantly lower in obese and overweight subjects than in normal weight subjects, in Tanner stage 2

and 3 girls.²¹ BMI was negatively correlated with peak LH level.²⁰ In this study, BMI SDS was also negatively correlated with peak LH level. Therefore, it is difficult to conclude that the prevalence of biochemical adrenarche in girls with gonadarche (activation of HPG axis) was lower than in girls without activation of the HPG axis.

The present study included 83 girls with biochemical adrenarche. However, only six of these 83 girls presented with pubarche, four of whom presented with pubarche without thelarche. Pubarche in these four girls was due to the development of adrenarche. The clinical presentation of adrenarche did not always correlate with serum DHEAS concentration. DHEA and DHEAS are very weak androgen receptor agonists that undergo extraglandular metabolism to produce active androgen, which activates the androgen receptor. The appearance of clinical signs varies depending on the peripheral metabolism and sensitivity to androgens.^{2,3} In addition, the conversion to active androgens in peripheral adipose tissue may be enhanced by obesity.²²

In several studies, obese children were reported to have BA that

exceeded their CA, which leads to relatively tall stature before puberty and during early puberty, but not to a tall adult height.^{23,24} Kim et al.²⁵ reported that advanced skeletal maturation is associated with elevated DHEAS level in obese children and adolescents. In the present study, serum DHEAS level was significantly associated with BA/CA in all subjects. BMI SDS was significantly correlated with BA/CA, whereas, in the multivariate analysis, a significant association was demonstrated only in subjects with HPG axis activation. BMI SDS was significantly associated with DHEAS level in all subjects, not only in subjects with HPG axis activation.

In several studies, prepubertal adrenal androgen production has been reported to be higher in obese children.^{14,15,26-30} Children with higher DHEAS level were reported to be fatter and tended to be taller and have a higher BA than their counterparts.¹⁴ An increase in BMI in children is associated with an increase in urinary excretion of DHEAS, and BMI gains correlate with DHEAS.²⁷ Obese prepubertal children (8.5 ± 2.1 years) showed significantly increased DHEAS level compared with normal weight children. After 1 year of lifestyle intervention, while levels of other steroids were found to normalize with weight loss, the elevated DHEAS level did not. This finding indicates an irreversible maturation of the zona reticularis of the adrenal gland even after successful weight loss.³⁰

DHEA is synthesized by 17- α -hydroxylase/17,20-lyase and metabolized by 3 β -hydroxysteroid dehydrogenase type 2 (3 β -HSD2) and DHEA-sulfotransferase. Enhancing the 17,20-lyase activity or decreasing the activity of 3 β -HSD2 was shown to play a role in the onset of adrenarche.^{2,3} Insulin, insulin-like growth factor-1 (IGF-1), and leptin have been suggested to mediate the effect of obesity on the initiation of adrenarche.³¹⁻³⁴ However, IGF-1 is likely associated with adrenal growth in early childhood rather than zona reticularis regulation.³⁵ An increase in the intra-adrenal concentration of cortisol during childhood growth may lead to inhibition of 3 β -HSD2 activity.³⁶ Leptin may enhance the 17,20-lyase activity of adrenal cells.³⁷ Reportedly, body fat mass is closely associated with systemic leptin level³⁸ and 17,20-lyase activity in prepubertal girls.³⁹

The present study has several limitations. First, the single clinic-based retrospective design may lead to selection bias. Second, the sample size of overweight/obese girls was relatively small, so the relationship of BMI might have been underestimated. Third, BMI percentiles were used to classify obesity. Although BMI is a good

measure for overweight, it is limited as an indirect measurement of fat mass.

In conclusion, BMI SDS was associated with DHEAS level, which was associated with BA/CA. We postulate that childhood obesity may influence the development of adrenarche, which is associated with advanced skeletal maturation. Future studies including a large sample of Korean children are needed to investigate the influence of obesity on adrenarche.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Bordini B, Rosenfield RL. Normal pubertal development. Part II: clinical aspects of puberty. *Pediatr Rev* 2011;32:281-92.
- Utriainen P, Laakso S, Liimatta J, Jääskeläinen J, Voutilainen R. Premature adrenarche: a common condition with variable presentation. *Horm Res Paediatr* 2015;83:221-31.
- Voutilainen R, Jääskeläinen J. Premature adrenarche: etiology, clinical findings, and consequences. *J Steroid Biochem Mol Biol* 2015;145:226-36.
- Belgorosky A, Baquedano MS, Guercio G, Rivarola MA. Adrenarche: postnatal adrenal zonation and hormonal and metabolic regulation. *Horm Res* 2008;70:257-67.
- Miller WL. Androgen synthesis in adrenarche. *Rev Endocr Metab Disord* 2009;10:3-17.
- Rege J, Rainey WE. The steroid metabolome of adrenarche. *J Endocrinol* 2012;214:133-43.
- Rich BH, Rosenfield RL, Lucky AW, Helke JC, Otto P. Adrenarche: changing adrenal response to adrenocorticotropin. *J Clin Endocrinol Metab* 1981;52:1129-36.
- Guran T, Firat I, Yildiz F, Kaplan Bulut I, Dogru M, Bereket A. Reference values for serum dehydroepiandrosterone-sulphate in healthy children and adolescents with emphasis on the age of adrenarche and pubarche. *Clin Endocrinol (Oxf)* 2015;82:712-8.
- Charkaluk ML, Trivin C, Brauner R. Premature pubarche as an indicator of how body weight influences the onset of adre-

- narche. *Eur J Pediatr* 2004;163:89-93.
10. Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. *Arch Dis Child* 2005;90:258-61.
 11. Ibáñez L, Lopez-Bermejo A, Díaz M, Suárez L, de Zegher F. Low-birth weight children develop lower sex hormone binding globulin and higher dehydroepiandrosterone sulfate levels and aggravate their visceral adiposity and hypoadiponectinemia between six and eight years of age. *J Clin Endocrinol Metab* 2009;94:3696-9.
 12. Ong KK, Potau N, Petry CJ, Jones R, Ness AR, Honour JW, et al. Opposing influences of prenatal and postnatal weight gain on adrenarche in normal boys and girls. *J Clin Endocrinol Metab* 2004;89:2647-51.
 13. Nordman H, Voutilainen R, Antikainen L, Jääskeläinen J. Prepubertal children born large for gestational age have lower serum DHEAS concentrations than those with a lower birth weight. *Pediatr Res* 2017;82:285-9.
 14. Corvalán C, Uauy R, Mericq V. Obesity is positively associated with dehydroepiandrosterone sulfate concentrations at 7 y in Chilean children of normal birth weight. *Am J Clin Nutr* 2013;97:318-25.
 15. Mericq V, Pereira A, Uauy R, Corvalán C. Early BMI gain and later height growth predicts higher DHEAS concentrations in 7-year-old Chilean children. *Horm Res Paediatr* 2017;87:15-22.
 16. Moon JS, Lee SY, Nam CM, Choi JM, Choe BK, Seo JW, et al. 2007 Korean National Growth Charts: review of developmental process and an outlook. *Korean J Pediatr* 2008;51:1-25.
 17. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291-303.
 18. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford (CA): Stanford University Press; 1959.
 19. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR; ESPE-LWPES GnRH Analogs Consensus Conference Group, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009;123:e752-62.
 20. Fu JF, Liang JF, Zhou XL, Prasad HC, Jin JH, Dong GP, et al. Impact of BMI on gonadorelin-stimulated LH peak in premenarcheal girls with idiopathic central precocious puberty. *Obesity (Silver Spring)* 2015;23:637-43.
 21. Lee HS, Yoon JS, Hwang JS. Luteinizing hormone secretion during gonadotropin-releasing hormone stimulation tests in obese girls with central precocious puberty. *J Clin Res Pediatr Endocrinol* 2016;8:392-8.
 22. Mäntyselkä A, Jääskeläinen J, Lindi V, Viitasalo A, Tompuri T, Voutilainen R, et al. The presentation of adrenarche is sexually dimorphic and modified by body adiposity. *J Clin Endocrinol Metab* 2014;99:3889-94.
 23. Kleber M, Schwarz A, Reinehr T. Obesity in children and adolescents: relationship to growth, pubarche, menarche, and voice break. *J Pediatr Endocrinol Metab* 2011;24:125-30.
 24. Johnson W, Stovitz SD, Choh AC, Czerwinski SA, Towne B, Demerath EW. Patterns of linear growth and skeletal maturation from birth to 18 years of age in overweight young adults. *Int J Obes (Lond)* 2012;36:535-41.
 25. Kim SE, Jang JW, Ahn MB, Kim SH, Cho WK, Cho KS, et al. The association between skeletal maturation and adrenal androgen levels in obese children and adolescents. *Ann Pediatr Endocrinol Metab* 2017;22:108-14.
 26. l'Allemand D, Schmidt S, Rousson V, Brabant G, Gasser T, Grüters A. Associations between body mass, leptin, IGF-I and circulating adrenal androgens in children with obesity and premature adrenarche. *Eur J Endocrinol* 2002;146:537-43.
 27. Remer T, Manz F. Role of nutritional status in the regulation of adrenarche. *J Clin Endocrinol Metab* 1999;84:3936-44.
 28. Reinehr T, de Sousa G, Roth CL, Andler W. Androgens before and after weight loss in obese children. *J Clin Endocrinol Metab* 2005;90:5588-95.
 29. Shi L, Wudy SA, Buyken AE, Hartmann MF, Remer T. Body fat and animal protein intakes are associated with adrenal androgen secretion in children. *Am J Clin Nutr* 2009;90:1321-8.
 30. Reinehr T, Kulle A, Wolters B, Lass N, Welzel M, Riepe F, et al. Steroid hormone profiles in prepubertal obese children before and after weight loss. *J Clin Endocrinol Metab* 2013;98:E1022-30.
 31. Vuguin P, Linder B, Rosenfeld RG, Saenger P, DiMartino-Nardi J. The roles of insulin sensitivity, insulin-like growth factor I (IGF-I), and IGF-binding protein-1 and -3 in the hyperandrogenism of African-American and Caribbean Hispanic

- girls with premature adrenarche. *J Clin Endocrinol Metab* 1999;84:2037-42.
32. Cizza G, Dorn LD, Lotsikas A, Sereika S, Rotenstein D, Chrousos GP. Circulating plasma leptin and IGF-1 levels in girls with premature adrenarche: potential implications of a preliminary study. *Horm Metab Res* 2001;33:138-43.
33. Guercio G, Rivarola MA, Chaler E, Maceiras M, Belgorosky A. Relationship between the growth hormone/insulin-like growth factor-I axis, insulin sensitivity, and adrenal androgens in normal prepubertal and pubertal girls. *J Clin Endocrinol Metab* 2003;88:1389-93.
34. Güven A, Cinaz P, Ayvali E. Are growth factors and leptin involved in the pathogenesis of premature adrenarche in girls? *J Pediatr Endocrinol Metab* 2005;18:785-91.
35. Baquedano MS, Berensztein E, Saraco N, Dorn GV, de Davila MT, Rivarola MA, et al. Expression of the IGF system in human adrenal tissues from early infancy to late puberty: implications for the development of adrenarche. *Pediatr Res* 2005;58:451-8.
36. Topor LS, Asai M, Dunn J, Majzoub JA. Cortisol stimulates secretion of dehydroepiandrosterone in human adrenocortical cells through inhibition of 3betaHSD2. *J Clin Endocrinol Metab* 2011;96:E31-9.
37. Biason-Lauber A, Zachmann M, Schoenle EJ. Effect of leptin on CYP17 enzymatic activities in human adrenal cells: new insight in the onset of adrenarche. *Endocrinology* 2000;141:1446-54.
38. Ahmed ML, Ong KK, Morrell DJ, Cox L, Drayer N, Perry L, et al. Longitudinal study of leptin concentrations during puberty: sex differences and relationship to changes in body composition. *J Clin Endocrinol Metab* 1999;84:899-905.
39. Kim SH, Moon JY, Sasano H, Choi MH, Park MJ. Body fat mass is associated with ratio of steroid metabolites reflecting 17,20-lyase activity in prepubertal girls. *J Clin Endocrinol Metab* 2016;101:4653-60.