Hormone Research in Paediatrics

Research Article

Horm Res Paediatr
DOI: 10.1159/000511873

Received: January 18, 2020
Accepted: September 29, 2020
Published online: December 2, 2020

Role of Body Weight in the Onset and the Progression of Idiopathic Premature Pubarche

Paolo Cavarzere[a] Margherita Mauro[a] Rossella Gaudino[b] Rocco Micciolo[c] Giorgio Piacentini[b] Franco Antoniazzi[d]

[a]Pediatric Division, Department of Pediatrics, University Hospital of Verona, Verona, Italy; [b]Pediatric Clinic, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy; [c]Department of Psychology and Cognitive Sciences, University of Trento, Trento, Italy; [d]Regional Center for the Diagnosis and Treatment of Children and Adolescents Rare Skeletal Disorders, Pediatric Clinic, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy

Keywords
Premature pubarche · Low birth weight · Body mass index · Predictor factors

Abstract
Background: The term premature pubarche (PP) refers to the appearance of pubic hair before age 8 in girls and before age 9 in boys. Although idiopathic PP (often associated with premature adrenarche) is considered an extreme variation from the norm, it may be an initial sign of persistent hyperandrogenism. Factors contributing to PP onset and progression have not been identified to date. ***Aims:*** The objectives of this study are to describe a group of Italian children with PP, to identify potential factors for its onset, and to define its clinical and biochemical progression. ***Methods:*** We retrospectively enrolled all infants born between 2001 and 2014 with PP. Children with advanced bone age (BA) underwent functional tests to determine the cause of PP. Hormonal analysis and BA determination were performed annually during a 4-year follow-up period. ***Results:*** A total of 334 children with PP were identified: idiopathic PP (92.5%, associated with premature adrenarche in some cases); related to precocious puberty (6.6%); late-onset 21-hydroxylase deficiency (0.9%). Low birth weight was associated with premature adrenal activation. Body mass index (BMI) was the only factor that influenced the progression of BA during follow-up. ***Conclusions:*** Low birth weight is a predisposing factor for premature adrenal activation. The increase in BMI in patients with idiopathic PP during the 4-years of follow-up was responsible for BA acceleration. We recommend prevention of excessive weight gain in children with PP and strict adherence to follow-up in order to prevent serious metabolic consequences.

Introduction

Premature pubarche (PP) refers to the appearance of pubic hair, often accompanied by axillary hair, before the age of 8 in girls and before the age of 9 in boys [1]. It occurs more frequently in females, and the cause of the unequal sex ratio is unknown [2–4]. In the majority of cases, PP is idiopathic (due to premature adrenarche) and can be determined only by diagnosis of exclusion [2, 3, 5].

karger@karger.com
www.karger.com/hrp

Paolo Cavarzere
Department of Pediatrics, Child and Mother's Hospital
Piazzale Stefani 1
IT –37126 Verona (Italy)
paolo.cavarzere@aovr.veneto.it

Other disorders, such as milder and nonclassical congenital adrenal hyperplasia (CAH), Cushing's disease, virilizing tumors originating from the adrenals or the gonads, or more rare conditions, may also manifest with PP [3, 6, 7]. A diagnosis of precocious puberty should be considered in patients with progressive signs of pubertal development (e.g., breast development in girls and penile or testicular growth in boys) besides clinical signs of PP [3].

The pathophysiological basis of idiopathic PP and premature adrenarche is unknown [1]. It is secondary to early and isolated maturation of the zona reticularis of the adrenal cortex and is triggered by the activation of androgen production, resulting in a dramatic increase in serum DHEAS levels [8–10]. DHEAS levels ≥40–50 μg/dL are consistent with the onset of adrenarche [3, 11, 12]. DHEAS is converted to active androgens in the gonads and the peripheral target tissues of androgen action, including the skin, leading to the appearance of pubic and axillary hair. Increased androgen production also brings about changes in body odor and oily skin, transient growth spurt, and it contributes to bone maturation [7, 13, 14]. In patients with PP, however, bone age (BA) advancement is linked not only to elevated DHEAS levels but also to obesity, another concurrent factor in these children [12, 13]. Finally, hypersensitivity of hair follicles to steroid hormones has been hypothesized in children with PP and normal androgen levels [5, 15].

Idiopathic PP is considered an extreme variation from the norm; as such, it is a serious source of concern for parents. Furthermore, it may be a risk factor for later dysfunction of the reproductive endocrine system [3, 7, 12]. The main question is whether idiopathic PP (and premature adrenarche) is a form of early adrenal maturation or an initial sign of persistent hyperandrogenism. To answer this question, studies have investigated the potential factors for PP onset; however, none to date has been conclusively identified as a regulator of adrenal androgen secretion. Ethnic origin, elevated body mass index (BMI), and weight gain have all been reported to be factors contributing to adrenarche [3, 8, 12], whereas elevated 17-hydroxyprogesterone (17-OHP) level at newborn screening has been recently excluded as a predictive factor for PP [16]. Furthermore, we do not know which predictor factors are able to identify the clinical and biochemical progression of PP during infancy and puberty. With the abovementioned points in mind, the aims of this study were to describe a group of Italian children with PP, to identify potential factors for its onset, and to define its clinical and biochemical progression.

Patients and Methods

Patients

For this retrospective study, we reviewed the clinical data of Caucasian patients born between 2001 and 2014 referred to the Pediatric Endocrinology Division of Verona Hospital, Italy, for the appearance of pubic hair before the age of 8 in girls and before the age of 9 in boys. Weight, height, and BMI (weight in kg/height in m^2) were recorded. The height, weight, and BMI standard deviation score (SDS) were derived from Italian cross-sectional growth charts [17]. Pubertal development was evaluated according to Tanner and Whitehouse [18]. For boys, testicular volume was measured using a Prader orchidometer.

Gestational age (GA), birth weight (BW), and birth length (BL) were evaluated, and familiar genetic target was calculated according to the parents' height. Target height was determined by calculating the midparental height as follows: ([father's height cm − 13 cm] + mother's height cm)/2 for girls; ([mother's height cm + 13 cm] + father's height cm)/2 for boys [19]. Children born small for gestational age (SGA) were defined according to Bertino Neonatal Anthropometric Charts [20]. We defined SGA as a newborn with a birth weight and/or length of <−2 SD according to the Consensus Statement of the International Societies of Pediatric Endocrinology and of the Growth Hormone Research Society [21]. Figure 1 presents the study flowchart showing the number of patients and type of tests and radiological exams performed.

Radiography was performed in all children to determine BA, which was evaluated by the same pediatric endocrinologist using the Greulich and Pyle method [22]. Children with advanced BA (ratio of BA to chronological age >1) underwent the adrenocorticotropic hormone (ACTH) stimulation test (intravenous administration of soluble Synacthen 250 mg). Serum 17-OHP and cortisol levels were measured at baseline and after 60 min. Data were analyzed using Maria New nomogram [23]. Levels of testosterone, ACTH, DHEAS, and Δ4-androstenedione were also measured.

Children with clinical signs of precocious puberty (Tanner stage ≥ B2 in girls and testicular volume ≥4 mL in boys) were submitted to GnRH-analogue (GnRH-a) stimulation testing (subcutaneous administration of 0.1 mg of GnRH-a (Triptorelin) after overnight fasting). Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol in females, and testosterone in males were measured at baseline and 4 h afterward. A LH peak of ≥15 U/L was indicative of activation of the hypothalamic-pituitary-gonadal (HPG) axis in both sexes.

Abdominal, pelvic, and/or testicular ultrasound studies were performed in patients with elevated androgen levels and advanced BA to exclude organic causes for PP, such as ovarian, testicular, or adrenal tumors. Pelvic ultrasound was performed to measure uterine and ovarian size in females with pubertal signs.

Children with idiopathic PP and advanced BA, born between 2001 and 2012, were followed up for an average period of 4 years. Children born after 2012 were excluded from the present analysis because the follow-up period was not yet complete. Exams at follow-up assessment included repeated BA and hormonal analysis (DHEAS, Δ4-androstenedione, ACTH, and cortisol). Two groups were formed based on DHEAS level at the time of diagnosis.

The present study was conducted in compliance with the terms of the Helsinki II Declaration. The Institutional Ethics Committee of the provinces of Verona and Rovigo, Italy, took note of the retrospective conduct of the study and approved it for publication of

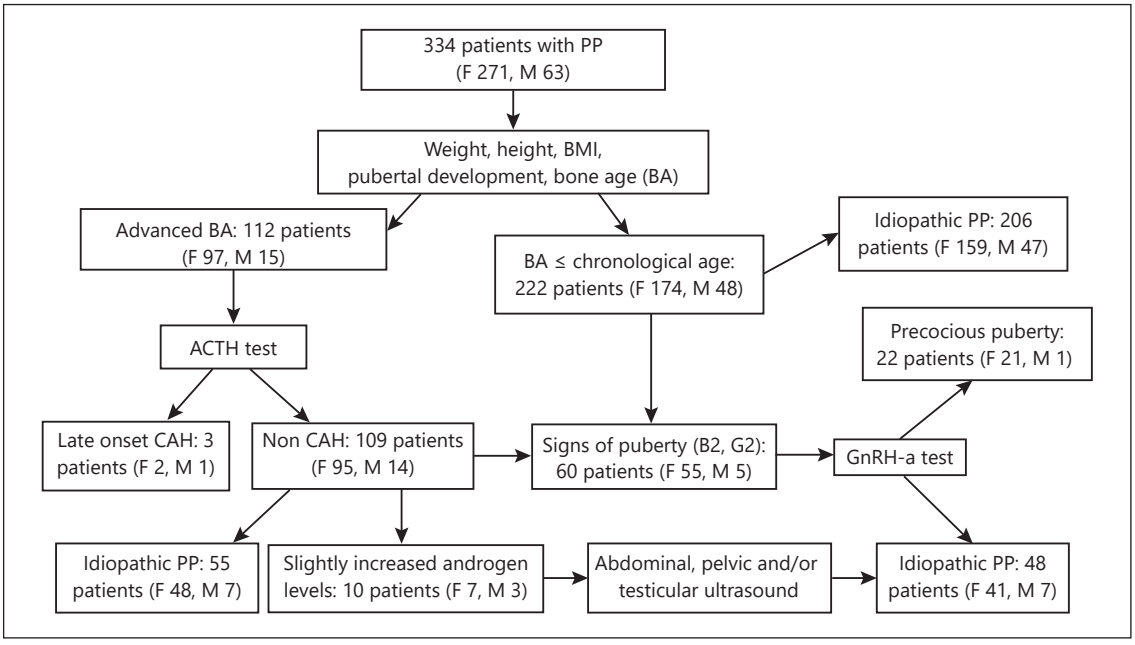

Fig. 1. Study flowchart. PP, premature pubarche; BA, bone age; ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia.

the results. Written, informed consent was obtained from the child's parents or legal guardian.

Assay

Serum total testosterone, ACTH, cortisol, Δ4-androstenedione, DHEAS, estradiol, FSH, and LH were measured using a solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000; Siemens Healthcare Diagnostic, USA). The analytical sensitivity was 14.4 ng/dL for total testosterone, 5 pg/mL for ACTH, 0.2 μg/dL for cortisol, 0.3 ng/mL for Δ4-androstenedione, 0.3 μg/dL for DHEAS, 0.1 U/L for FSH, 0.05 U/L for LH, and 15 pg/mL for estradiol.

Intraassay and interassay coefficients of variation were 11.7 and 13.0%, respectively, for testosterone; 9.5 and 10.0%, respectively, for ACTH; 7.4 and 9.4%, respectively, for cortisol; 9.3 and 12%, respectively, for Δ4-androstenedione; 4.1 and 6.3%, respectively, for DHEAS; 2.9 and 4.1%, respectively, for FSH; 3.6 and 6.7%, respectively, for LH; 11.7 and 13%, respectively, for estradiol. Serum 17-OHP was assayed using a radioimmunoassay (DSL-5000 Active 17α-OH Progesterone Coated-Tube Radioimmunoassay, Diasorin, Saluggia, Italy). The assay sensitivity was 0.01 ng/dL, and intra- and interassay coefficients of variation were both 9.0%.

Statistical Analysis

Statistical analyses were performed using software R version 3.5.1 (R Core Team [2018] R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Since the majority of the variables were not normally distributed, nonparametric statistics were employed. The Mann-Whitney *U* test was used to compare differences between 2 independent groups, and Friedman's nonparametric ANOVA was employed to compare differences between time points. Multiple linear regression analysis was also performed in order to explore the relationship between DHEAS levels and selected independent variables (BW SDS, GA, BMI SDS, age, and sex) at the time of DHEAS measurement. Furthermore, multiple regression analysis was performed at the last follow-up visit using BA acceleration (ΔBA) as the dependent variable and BMI SDS, sex, age, GA, Tanner genital/breast stage, and serum DHEAS as independent variables.

Correlations were evaluated using either the Spearman or the Pearson correlation test, when appropriate. Fisher's exact test was used to compare 2 proportions. Data are expressed as numbers with frequency, median plus range, or mean ± SD, as appropriate. Statistical significance was set at $p \leq 0.05$.

Results

Between 2001 and 2014, we identified 334 patients with PP (271 females and 63 males). Table 1 presents the clinical data and the neonatal characteristics of the patients. Forty children (12%) in the cohort were born premature and 8 (2.4%) were SGA; 43.7% of the children were overweight.

Of the total of 334 patients, 112 (97 females and 15 males) had a BA to chronological age ratio of >1 (Fig. 1). The difference between BA and chronological age was 1.3 ± 1.0 years for the females and 1.4 ± 1.0 years for the

Table 1. Clinical characteristics of all patients at diagnosis and at birth

	Females (n = 271)	Males (n = 63)
Age, years	7.2±1.7 (0.5 to 10.3)	7.8±2.1 (0.4 to 9.9)
Weight SDS	3.1±2.1 (−1.3 to 11.4)	3.0±2.4 (−1.6 to 7.9)
Height SDS	2.0±1.2 (−1.7 to 5.4)	1.8±1.2 (−1.3 to 5.3)
BMI SDS	2.0±1.2 (−2.2 to 9.9)	2.5±2.7 (−2.2 to 8.6)
Target height SDS	0.2±0.9 (−2.4 to 2.9)	0.4±0.9 (−1.5 to 2.4)
Pubic hair, n (%)		
Tanner Ph 2	247 (91.1)	57 (90.5)
Tanner Ph 3	24 (8.9)	6 (9.5)
Tanner Ph 4	0	0
Tanner Ph 5	0	0
Axillary hair, n (%)		
Tanner A1	249 (91.9)	60 (95.2)
Tanner A2	20 (7.4)	2 (3.2)
Tanner A3	2 (0.7)	1 (1.6)
Breast, n (%)		
Tanner B1	216 (79.7)	–
Tanner B2	43 (15.9)	
Tanner B3	12 (4.4)	
Tanner B4	0	
Tanner B5	0	
Genitalia, n (%)		
Tanner G1	–	58 (92)
Tanner G2		5 (8)
Tanner G3		0
Tanner G4		0
Tanner G5		0
GA, weeks	38.6±2.5 (25.0 to 42.1)	38.1±2.7 (29.0 to 41.0)
BW, g	3,045.9±638.0 (787.0 to 5,000.0)	3,081.0±746.9 (950.0 to 4,260.0)
BL, cm	49.3±2.8 (25.0 to 54.5)	49.9±3.5 (35.0 to 55.0)

Data are expressed as mean ± SD and range in the brackets. SDS, standard deviation score; GA, gestational age; BW, birth weight; BL, birth length.

males. The mean age was 7.3 ± 1.8 years for the females and 8.6 ± 1.3 years for the males. Table 2 presents the results of blood analysis to identify the etiology of PP and the results of the GnRH-a test to determine activation of the HPG axis in the 60 children presenting clinical signs of puberty.

PP was defined as idiopathic in 92.5% (248 females and 61 males), related to precocious puberty in 6.6% (21 females and 1 male) and a manifestation of late-onset CAH due to 21-hydroxylase deficiency (21-OHD) in 0.9% (2 females and 1 male). In 25 children (24 females and 1 male), the 17-OHP level measured at the ACTH test was compatible with being heterozygous for 21-OHD based on Maria New nomogram [22].

Comparison between the females with precocious puberty and those with idiopathic PP and advanced BA showed that those with precocious puberty were older (8.0 ± 0.9 vs. 7.2 ± 1. 2 years, p = 0.043) and had higher FSH and LH basal levels (FSH 4.2 ± 2.5 vs. 1.8 ± 1.6 U/L; LH 1.3 ± 1.5 vs. 0.2 ± 0.9 U/L; $p < 0.001$ for all comparisons). Basal LH >2.2 U/L and basal FSH >8.7 U/L levels were predictive of precocious puberty (sensitivity 99.3%). Owing to the small number of males, these data were analyzed only for the females.

Clinical and biochemical evaluation was performed annually for 4 years in all patients with idiopathic PP and advanced BA (87 females and 13 males). Ten children in the cohort (10%) were born preterm, and one (1%) was SGA. Three children (2 females and 1 male) were excluded from this analysis because they were born after 2012. At each assessment, hormonal levels, auxological data, and BA were recorded with a particular focus on 2 parameters: growth rate and ΔBA (difference between bone and chronological age). A growth rate of >5.5 cm/year and an

Table 2. Blood exams (ACTH test and GnRH-analogue test) at the time of diagnosis

	Females (n = 112)	Males (n = 16)
Δ4-androstenedione, ng/mL	0.6±0.5 (0.3–3.0)	0.7±0.4 (0.3–1.9)
DHEAS, μg/dL	66.6±42.5 (0.4–248.0)	117.8±58.3 (15.0–291.0)
ACTH, pg/mL	29.1±44.8 (6.2–373.0)	27.2±26.3 (8.7–135.0)
ACTH test		
Cortisol basal, μg/dL	11.8±8.6 (1.6–6.0)	9.5±4.5 (6.1–29.6)
Cortisol peak, μg/dL	26.8±5.4 (1.0–42.9)	24.4±5.8 (4.7–33.3)
17 OHP basal, ng/dL	1.2±2 (0.1–15.7)	1.7±3.7 (0.3–18.0)
17 OHP peak, ng/dL	4.7±8.9 (1.1–76.0)	7.5±20.7 (1.5–110.0)
GnRH-analogue test		
FSH basal, U/L	2.2±1.9 (0.1–9.7)	1.2±1.1 (0.3–4.3)
FSH peak, U/L	22.9±13.1 (1.7–83.6)	9.5±4.6 (3.7–19.4)
LH basal, U/L	0.4±1.1 (0.1–10.0)	0.3±0.4 (0.1–1.8)
LH peak, U/L	8.1±16.3 (0.1–111.0)	6.5±6.8 (0.9–27.3)
Estradiol basal, pg/mL	38.2±28.1 (80.2–195.0)	–
Estradiol peak, pg/mL	40.1±35.2 (19.8–264.0)	–
Testosterone basal, ng/dL	–	20.3±6.8 (0.3–39.6)
Testosterone peak, ng/dL	–	22.3±14.7 (2.1–72.8)

Data are expressed as mean ± SD and range in the brackets. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

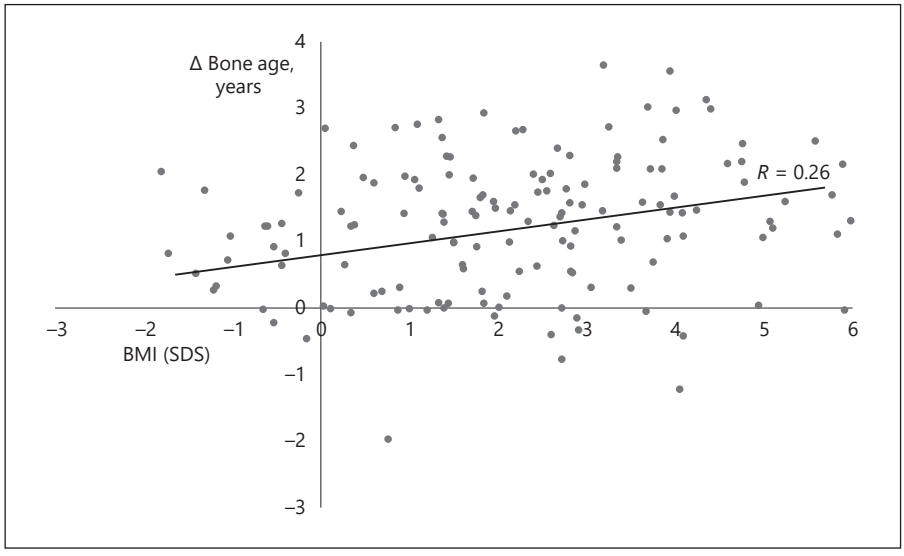

Fig. 2. Relationship between BMI SDS and the difference between bone age and chronological age (ΔBA) (R = 0.26; p = 0.011). The bone age used for the ΔBA was determined during the last follow-up visit, and the BMI shown in the figure was determined at the same visit. BMI, body mass index; SDS, standard deviation score.

advanced BA of >1.5 years were considered a marker of progression of the condition. No predictive factor for growth rate was identified; the only factor that was positively and significantly (p = 0.011) associated with Δ BA was BMI (Fig. 2). This association remained significant (p = 0.007) even after having adjusted for the effects of sex, age, GA, Tanner genital/breast stage, and serum DHEAS.

The cohort was divided into 2 groups according to serum DHEAS level: one group with PP and elevated DHEAS (≥40 μg/dL) and the other with PP and normal DHEAS (<40 μg/dL). Table 3 presents the characteristics of the 2 groups. The group with elevated DHEAS was noted to have had a lower weight at birth (p < 0.05), suggesting an association between lower BW and higher adrenal androgen secretion (Fig. 3). Multiple linear regression analysis confirmed this observation; serum levels of

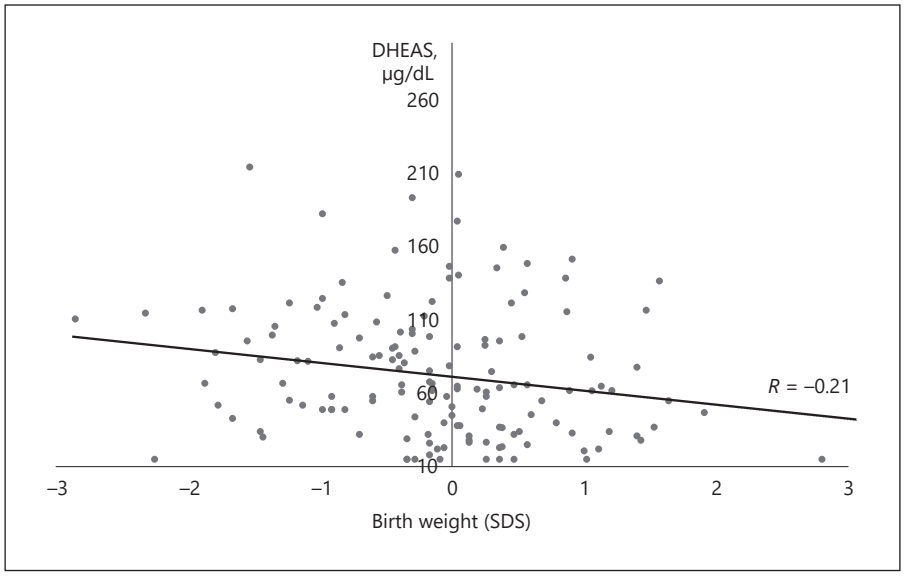

Fig. 3. Inverse relationship between DHEAS level at the time of diagnosis and birth weight (BW SDS): patients with lower BW had higher serum DHEAS levels ($R = -0.21$; $p < 0.01$). SDS, standard deviation score.

Table 3. Main characteristics of the 2 groups based on DHEAS levels at the time of diagnosis

	DHEAS <40 μg/dL ($n = 38$)	DHEAS ≥40 μg/dL ($n = 62$)	p value
GA, weeks	38.8±2.6 (26.0–41.0)	38.3±2.6 (25.0–41.0)	0.261
BW, g	3,248.6±564.2 (1,000.0–5,000.0)	2,956.5±666.4 (787.0–4,660.0)	**0.003**
BL, cm	49.9±2.9 (51.0–54.0)	49.4±2.4 (41.0–55.0)	0.368
BMI, kg/m^2	18.8±2.5 (14.8–26.2)	16.9±6.6 (13.3–28.3)	0.810
Δ4-androstenedione, ng/mL	0.4±0.2 (0.3–1.1)	0.6±0.4 (0.3–3.0)	**0.007**
ACTH, pg/mL	32.7±53.7 (9.0–373.0)	27.6±38.3 (6.2–344.0)	0.494
Testosterone, ng/dL	6.5±9.4 (0.2–20.0)	7.1±10.9 (0.2–20.0)	0.748
Cortisol, μg/dL	11.3±5.5 (3.6–26.3)	10.5±6.0 (1.6–36.4)	0.420

Data are expressed as mean ± SD and range in the brackets. Bold values represent statistical significance. GA, gestational age; BW, birth weight; BL, birth length; ACTH, adrenocorticotropic hormone.

DHEAS (dependent variable) were significantly ($p < 0.001$) associated with BW SDS even after having adjusted for the effects of sex, age, GA, and BMI SDS. In group with DHEAS ≥40 μg/dL, 16% had a BW of <2,500 g, whereas in the other group (DHEAS <40 μg/dL), only 2.6% had a BW of <2500 g ($p < 0.05$). The serum Δ4-androstenedione levels were higher in the group with elevated DHEAS, with a positive correlation between the serum DHEAS and Δ4-androstenedione levels measured during the follow-up ($p < 0.05$). The serum ACTH and cortisol levels remained stable during the follow-up period. We found a significant difference between DHEAS levels in the 2 groups at each assessment during the 4 years of follow-up ($p < 0.05$) (Fig. 4). The growth rate in both groups was regular without a significance difference during the follow-up; there was a slight increase in the percentage of overweight children (from 50.5% at year 1 to 51.8% at year 4), without significance differences between the 2 groups. Pubertal development began at age 8.9 ± 0.7 years in the females and at age 10.8 ± 1.2 years in the males. These data did not differ between the children born preterm and those born at term.

Discussion

For this retrospective study, we analyzed a cohort of patients of Caucasian origin with PP followed up for a minimum of 4 years at a single center in northeast Italy. Idiopathic PP was diagnosed in the majority of patients, and body weight played a role in the onset and the clinical progression of PP: low BW was associated with prema-

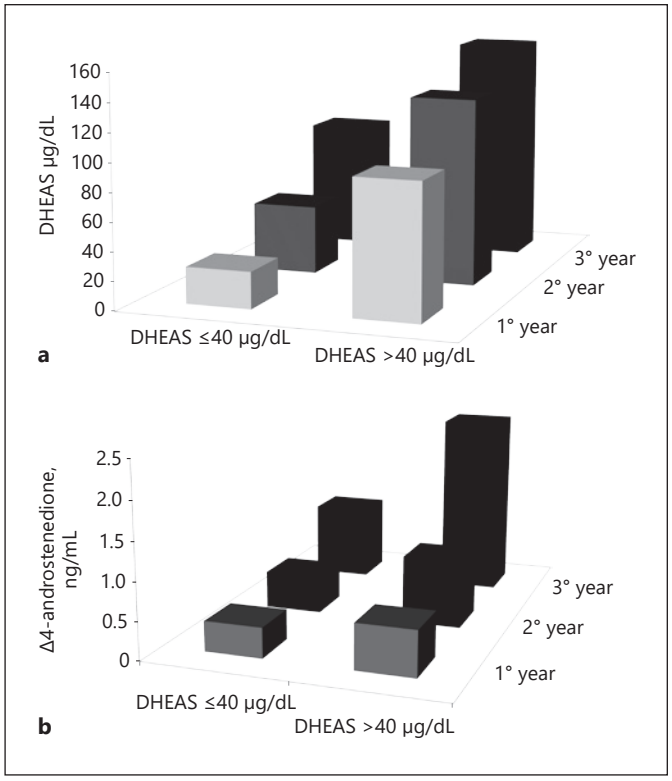

Fig. 4. Mean serum DHEAS (panel **a**) and 4-androstenedione (panel **b**) levels during 3 years of follow-up in the 2 groups (DHEAS >40 or <40 µg/dL at the time of diagnosis). We found a significant difference between DHEAS levels during the follow-up in the 2 groups at each evaluation ($p < 0.05$). There was a significant difference in Δ4-androstenedione levels between the 2 groups only at the third year of follow-up.

ture adrenal activation and increased BMI was the only factor that influenced BA acceleration during the follow-up period.

Only 3 patients in the cohort presented late-onset CAH, consistent with a prevalence estimated between 0 and 40% [7, 24–27]. Furthermore, 7.5% presented 17-OHP levels at the ACTH test indicative of heterozygosity for 21-OHD. Although genetic analysis was not performed, we hypothesized an association between heterozygosity for 21-OHD and the presence of PP. This association has been variously studied [16, 28–30] with some studies reporting a similar risk for mutation carriers and normal subjects [31, 32] and others underlining the association, especially in subjects carrying the V281L mutation [33, 34]. The mechanism behind this association remains unknown.

Precocious puberty was noted in 6.6% of the patients with PP. PP may be secondary to or concomitant with precocious puberty. The incidence of precocious puberty was higher in the females, as reported elsewhere [35]. There was a significant difference between basal LH and FSH levels in the girls with precocious puberty compared to those with idiopathic PP. LH >2.2 U/L was associated with activation of the HPG axis (sensitivity 99%). The role of basal LH in the diagnosis of precocious puberty has been discussed in the literature; however, the consensus statement on precocious puberty recommends luteinizing hormone-releasing hormone or GnRH-a testing to identify central precocious puberty [36]. While we doubt that baseline LH is sufficient for a diagnosis of precocious puberty, LH levels >2.2 U/L in girls with PP and thelarche should arouse suspicion. Previous studies showed in fact that elevated basal LH levels were significant predictors of central precocious puberty and suggested a threshold of LH >1.6 U/L [37–39].

Although PP is a relatively common, usually nonprogressive, clinical sign, its natural history is not well known [8]; it may be correlated with metabolic disorders including obesity, hyperinsulinism, hyperandrogenism, and polycystic ovary syndrome in females [1, 3, 7]. No factors contributing to PP onset and progression have been identified to date. Numerous studies found a relationship between low BW and androgen excess [3, 8, 12, 40]. Weight gain during infancy seems to trigger adrenarche [1]. Some studies have hypothesized that malnutrition in prenatal life could lead to metabolic programming of fetal organs and result in metabolic alterations, such as hyperinsulinemia and premature androgen excess [8, 41]. While French, Portuguese, Finnish, and Scottish studies reported no association with low BW in children with premature adrenarche [42–45], other studies from Spain, Italy, France, and Australia found a correlation between low BW and adrenarche [46–49], which our data confirm. A role for low BW in the onset of adrenarche in relation to country of origin has not been established, but genetic diversity might be responsible for the difference [9]. The relationship that we found between premature adrenarche and BW was adjusted for sex, age, GA, and BMI. Consequently, it is possible to exclude a role of preterm delivery in the onset of premature adrenarche. Although SGA patients may also experience premature adrenarche [12, 49], only 1 patient in the cohort was born SGA, precluding definitive conclusions about its role.

PP has been associated with obesity, hyperinsulinemia, and hyperandrogenism; however, it is not clear whether the primum movens is overweight or hyperandrogenism. A higher prevalence of overweight among children with PP has been recently documented [47, 50–52], and body

weight is thought to be involved in the onset of pubarche [1, 3]. Some studies have shown that overweight girls tend to experience an earlier onset and a more rapid evolution of puberty and pubarche [53–55]. Other studies have described PP as an early clinical feature of metabolic syndrome [50, 56]. Our data suggest that hyperandrogenism is a primary factor and overweight a secondary factor. Although overweight was predominant in this cohort, both at diagnosis and during follow-up, we found no association between PP and overweight. On the contrary, during the follow-up, when adrenal androgen secretion was already active, the rise in BMI played an important role in the advancement of BA. Obese children are noted to present advanced BA secondary to increased adipose tissue aromatization of androgens into estrogens, which are the sex hormones critically involved in skeletal maturation [12, 50]. In addition, hyperinsulinemia and high leptin levels, both consequences of obesity, can contribute to bone maturation. Hyperinsulinemia can act on the IGF-1 receptor and stimulate growth, while leptin appears to act as a skeletal growth factor [57, 58]. Furthermore, androgen action, which potentiates the effect of obesity on advancement of BA, has been described in children with obesity and/or pubarche [13, 59, 60] but not confirmed by the data for our cohort.

The role of androgens in PP is debated. DHEA and DHEAS are the best serum markers of adrenal androgen secretion [3]. The variable peripheral conversion of these circulating adrenal androgen precursors to the biologically more active androgens, testosterone and dihydrotestosterone, is essential for androgen action. Normal ACTH secretion and action are needed for adrenarche [3, 8, 12]. The data for our cohort show normal testosterone, ACTH, and cortisol concentrations. Moreover, we observed a linear rise in DHEAS and Δ4-androstenedione levels, which gradually increased over the 4-year follow-up period. We believe that in addition to DHEAS, the elevated Δ4-adrostenedione levels were also a marker of adrenarche in our cohort; however, this hypothesis needs to be confirmed in larger patient populations in prospective clinical trials. Furthermore, since Δ4-adrostenedione can be formed peripherally from DHEAS, as well as directly from the gonads, circulating Δ4-adrostenedione levels do not necessarily reflect the adrenal production rate [3]. Finally, we found no direct relationship between androgen concentrations and obesity, advancement of BA, and increased growth rate.

During the 4-year follow-up, the children in the cohort presented a regular and linear growth rate, confirming previous data which described only a transient acceleration in growth in children with PP. Moreover, pubertal development began at normal age in both sexes, in line with previous studies [3, 12, 14, 61, 62].

The limitations of this study are its retrospective design, the lack of a control group, the absence of metabolic data, the absence of final height and weight, and a population sample consisting only of patients of Caucasian origin. Nevertheless, the objective was to describe a cohort of Italian children with PP and to identify potential predictive factors for its onset and progression. Evaluation of metabolic disorders or final height and weight was beyond the scope of the present study but will be an area of focus in a future study. Ethnicity seems to play a role in the onset of PP, with a higher prevalence reported among Hispanic and African-American girls [1, 8]. Data for other ethnic groups would have been interesting to evaluate, but given the lack of ethnic diversity in our area, we could not have drawn any meaningful conclusions.

In conclusion, the mechanism underlying PP remains unclear and is probably of multifactorial etiology. Low BW is a predisposing factor for premature adrenarche among children born in northeast Italy; the clinical and biochemical progression of PP depends on diverse factors, including increased BMI, which is responsible for BA acceleration. We recommend prevention of excessive weight gain in children with PP and strict adherence to follow-up in order to prevent serious metabolic consequences.

Statement of Ethics

The study was conducted in compliance with the terms of the Helsinki II Declaration. The Institutional Ethics Committee of the provinces of Verona and Rovigo, Italy, took note of the retrospective conduct of the study and approved it in order to publish the results. Written informed consent was obtained from the parents of each patient.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the affirmation reported.

Funding Sources

This manuscript did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author Contributions

All the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Moreover, all authors read and approved the final manuscript. P.C. and M.M.: study conception and acquisition, analysis, and interpretation of data; P.C., M.M., and R.G.: drafting the manuscript; R.M.: statistical analysis; P.C., F.A., R.G., R.M., and G.P.: critical revision of the manuscript; P.C. and F.A.: coordination of study.

References

1 Diaz A, Bhandari S, Sison C, Vogiatzi M. Characteristics of children with premature pubarche in the New York metropolitan area. Horm Res. 2008;70(3):150–4.
2 Silverman SH, Migeon C, Rosemberg E, Wilkins L. Precocious growth of sexual hair without other secondary sexual development; premature pubarche, a constitutional variation of adolescence. Pediatrics. 1952;10(4):426–32.
3 Ibáñez L, Dimartino-Nardi J, Potau N, Saenger P. Premature adrenarche: normal variant or forerunner of adult disease? Endocr Rev. 2000;21(6):671–96.
4 Oberfield SE, Sopher AB, Gerken AT. Approach to the girl with early onset of pubic hair. J Clin Endocrinol Metab. 2011;96(6):1610–22.
5 Ghizzoni L, Gasco V. Premature pubarche. Horm Res Paediatr. 2010;73(5):420–2.
6 Saenger P, Reiter EO. Premature adrenarche: a normal variant of puberty? J Clin Endocrinol Metab. 1992;74(2):236–8.
7 Voutilainen R, Jääskeläinen J. Premature adrenarche: etiology, clinical findings, and consequences. J Steroid Biochem Mol Biol. 2015;145:226–36.
8 Idkowiak J, Lavery GG, Dhir V, Barrett TG, Stewart PM, Krone N, et al. Premature adrenarche: novel lessons from early onset androgen excess. Eur J Endocrinol. 2011;165(2):189–207.
9 Williams RM, Ward CE, Hughes IA. Premature adrenarche. Arch Dis Child. 2012;97(3):250–4.
10 Baulieu EE, Corpechot C, Dray F, Emiliozzi R, Lebeau MC, Mauvais Jarvis P, et al. An adrenal-secreted "Androgen": dehydroisoandrosterone sulfate. Its metabolism and a tentative generalization on the metabolism of other steroid conjugates in man. Recent Progr Horm Res. 1965;21:411–500.
11 Kelnar CJ, Brook CG. A mixed longitudinal study of adrenal steroid excretion in childhood and the mechanism of adrenarche. Clin Endocrinol. 1983;19(1):117–29.
12 Utriainen P, Laakso S, Liimatta J, Jääskeläinen J, Voutilainen R. Premature adrenarche: a common condition with variable presentation. Horm Res Paediatr. 2015;83(4):221–31.
13 Sopher AB, Jean AM, Zwany SK, Winston DM, Pomeranz CB, Bell JJ, et al. Bone age advancement in prepubertal children with obesity and premature adrenarche: possible potentiating factors. Obesity. 2011;19(6):1259–64.
14 Remer T, Manz F, Hartmann MF, Schoenau E, Wudy SA. Prepubertal healthy children's urinary androstenediol predicts diaphyseal bone strength in late puberty. J Clin Endocrinol Metab. 2009;94(2):575–8.
15 Rosenfield RL. Normal and almost normal precocious variations in pubertal development premature pubarche and premature thelarche revisited. Horm Res. 1994;41(Suppl 2):7–13.
16 Cavarzere P, Mauro M, Vincenzi M, Lauriola S, Teofoli F, Gaudino R, et al. Children with premature pubarche: is an alterated neonatal 17-OHP screening test a predictive factor? Ital J Pediatr. 2018;44(1):10.
17 Cacciari E, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, et al. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). J Endocrinol Invest. 2006;29(7):581–93.
18 Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child. 1976;51(3):170–9.
19 Tanner JM, Goldstein H, Whitehouse RH. Standards for children's height at ages 2-9 years allowing for heights of parents. Arch Dis Child. 1970;45(244):755–62.
20 Bertino E, Spada E, Occhi L, Coscia A, Giuliani F, Gagliardi L, et al. Neonatal anthropometric charts: the Italian neonatal study compared with other European studies. J Pediatr Gastroenterol Nutr. 2010;51(3):353–61.
21 Clayton PE, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, Rogol A. Management of the child born small for gestational age through to adulthood: a consensus statement of the International societies of pediatric endocrinology and the growth hormone research society. J Clin Endocrinol Metab. 2007;92(3):804–10.
22 Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford: Stanford University Press; 1959.
23 New MI, Lorenzen F, Lerner AJ, Kohn B, Oberfield SE, Pollack MS, et al. Genotyping steroid 21-hydroxylase deficiency: hormonal reference data. J Clin Endocrinol Metab. 1983;57(2):320–6.
24 Armengaud JB, Charkaluk ML, Trivin C, Tardy V, Bréart G, Brauner R, et al. Precocious pubarche: distinguishing late-onset congenital adrenal hyperplasia from premature adrenarche. J Clin Endocrinol Metab. 2009;94(8):2835–40.
25 Ghanny BA, Malhotra S, Kumta S, Kazachkova I, Homel P, Jacobson-Dickman E, et al. Should children with isolated premature adrenarche be routinely evaluated for non-classical congenital adrenal hyperplasia? J Pediatr Endocrinol Metab. 2016;29(3):351–6.
26 Ibáñez L, Bonnin MR, Zampolli M, Prat N, Alia PJ, Navarro MA. Usefulness of an ACTH test in the diagnosis of nonclassical 21-hydroxylase deficiency among children presenting with premature pubarche. Horm Res. 1995;44(2):51–6.
27 Leite MV, Mendonça BB, Arnhold IJ, Estefan V, Nunes C, Nicolau W, et al. Identification of nonclassical 21-hydroxylase deficiency in girls with precocious pubarche. J Endocrinol Invest. 1991;14(1):11–5.
28 Speiser PW, Dupont B, Rubinstein P, Piazza A, Kastelan A, New MI. High frequency of nonclassical steroid 21-hydroxylase deficiency. Am J Hum Genet. 1985;37(4):650–67.
29 Skordis N, Shammas C, Phedonos AA, Kyriakou A, Toumba M, Neocleous V, et al. Genetic defects of the CYP21A2 gene in girls with premature adrenarche. J Endocrinol Invest. 2015;38(5):535–9.
30 Neocleous V, Shammas C, Phedonos AP, Karaoli E, Kyriakou A, Toumba M, et al. Genetic defects in the cyp21a2 gene in heterozygous girls with premature adrenarche and adolescent females with hyperandrogenemia. Georgian Med News. 2012;210(210):40–7.
31 Knochenhauer ES, Cortet-Rudelli C, Cunnigham RD, Conway-Myers BA, Dewailly D, Azziz R. Carriers of 21-hydroxylase deficiency are not at increased risk for hyperandrogenism. J Clin Endocrinol Metab. 1997;82(2):479–85.
32 Escobar-Morreale HF, San Millán JL, Smith RR, Sancho J, Witchel SF. The presence of the 21-hydroxylase deficiency carrier status in hirsute women: phenotype-genotype correlations. Fertil Steril. 1999;72(4):629–38.
33 Admoni O, Israel S, Lavi I, Gur M, Tenenbaum-Rakover Y. Hyperandrogenism in carriers of CYP21 mutations: the role of genotype. Clin Endocrinol. 2006;64(6):645–51.
34 Witchel SF, Lee PA, Suda-Hartman M, Hoffman EP. Hyperandrogenism and manifesting heterozygotes for 21-hydroxylase deficiency. Biochem Mol Med. 1997;62(2):151–8.
35 Carel JC, Léger J. Clinical practice. Precocious puberty. N Engl J Med. 2008;358(22):2366–77.

36 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.
37 Brito VN, Batista MC, Borges MF, Latronico AC, Kohek MB, Thirone AC, et al. Diagnostic value of fluorometric assays in the evaluation of precocious puberty. J Clin Endocrinol Metab. 1999;84(10):3539–44.
38 Ding Y, Li J, Yu Y, Yang P, Li H, Shen Y, et al. Evaluation of basal sex hormone levels for activation of the hypothalamic-pituitary-gonadal axis. J Clin Endocrinol Metab. 2018;31(3):323–9.
39 Pasternak Y, Friger M, Loewenthal N, Haim A, Hershkovitz E. The utility of basal serum LH in prediction of central precocious puberty in girls. Eur J Endocrinol. 2012;166(2):295–9.
40 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(6):2647–51.
41 Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2(8663):577–80.
42 Paterson WF, Ahmed SF, Bath L, Donaldson MD, Fleming R, Greene SA, et al. Exaggerated adrenarche in a cohort of Scottish children: clinical features and biochemistry. Clin Endocrinol. 2010;72(4):496–501.
43 Utriainen P, Jääskeläinen J, Romppanen J, Voutilainen R. Childhood metabolic syndrome and its components in premature adrenarche. J Clin Endocrinol Metab. 2007;92(11):4282–5.
44 Meas T, Chevenne D, Thibaud E, Léger J, Cabrol S, Czernichow P, et al. Endocrine consequences of premature pubarche in post-pubertal Caucasian girls. Clin Endocrinol. 2002;57(1):101–6.
45 Santos-Silva R, Costa C, Castro-Correia C, Fontoura M. Clinical, biochemical and gender characteristics of 97 prepubertal children with premature adrenarche. J Pediatr Endocrinol Metab. 2019;32(11):1247–52.
46 Charkaluk ML, Trivin C, Brauner R. Premature pubarche as an indicator of how body weight influences the onset of adrenarche. Eur J Pediatr. 2004;163(2):89–93.
47 Ghirri P, Bernardini M, Vuerich M, Cuttano AM, Coccoli L, Merusi I, et al. Adrenarche, pubertal development, age at menarche and final height of full-term, born small for gestational age (SGA) girls. Gynecol Endocrinol. 2001;15(2):91–7.
48 Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. Arch Dis Child. 2005;90(3):258–61.
49 Ibáñez L, Potau N, Francois I, De Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. J Clin Endocrinol Metab. 1998;83(10):3558–62.
50 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(6):2037–42.
51 Reinehr T, De Sousa G, Roth CL, Andler W. Androgens before and after weight loss in obese children. J Clin Endocrinol Metab. 2005;90(10):5588–95.
52 Kaya G, Yavas Abali Z, Bas F, Poyrazoglu S, Darendeliler F. Body mass index at the presentation of premature adrenarche is associated with components of metabolic syndrome at puberty. Eur J Pediatr. 2018;177(11):1593–601.
53 Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. Reproduction. 2010;140(3):399–410.
54 Shalitin S, Phillip M. Role of obesity and leptin in the pubertal process and pubertal growth: a review. Int J Obes Relat Metab Disord. 2003;27(8):869–74.
55 Matkovic V, Ilich JZ, Skugor M, Badenhop NE, Goel P, Clairmont A, et al. Leptin is inversely related to age at menarche in human females. J Clin Endocrinol Metab. 1997;82(10):3239–45.
56 Saenger P, Dimartino-Nardi J. Premature adrenarche. J Endocrinol Invest. 2001;24(9):724–33.
57 Shalitin S, Kiess W. Putative effects of obesity on linear growth and puberty. Horm Res Paediatr. 2017;88(1):101–10.
58 Marcovecchio ML, Chiarelli F. Obesity and growth during childhood and puberty. World Rev Nutr Diet. 2013;106:135–41.
59 Grumbach MM. Estrogen, bone, growth and sex: a sea change in conventional wisdom. J Pediatr Endocrinol Metab. 2000;13(Suppl 6):1439–55.
60 De Groot CJ, Van den Berg A, Ballieux BEPB, Kroon HM, Rings EHHM, Wit JM, et al. Determinants of advanced bone age in childhood obesity. Horm Res Paediatr. 2017;87(4):254–63.
61 Liimatta J, Utriainen P, Voutilainen R, Jääskeläinen J. Trajectories of growth and serum DHEAS and IGF-1 concentrations in girls with a history of premature adrenarche: attenuation of the phenotype by adulthood. Front Endocrinol. 2018;9:375.
62 Oron T, Lebenthal Y, de Vries L, Yackobovitch-Gavan M, Phillip M, Lazar L. Interrelationship of extent of precocious adrenarche in appropriate for gestational age girls with clinical outcome. J Pediatr. 2012;160(2):308–13.