Mini Review

HORMONE RESEARCH IN PÆDIATRICS

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Premature Adrenarche – A Common Condition with Variable Presentation

Pauliina Utriainen Saila Laakso Jani Liimatta Jarmo Jääskeläinen
Raimo Voutilainen

Department of Pediatrics, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland

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Adrenarche · Adrenal androgens · Adrenal hyperandrogenism · Birth weight · Growth · Ovarian hyperandrogenism · Prepubertal children · Pubarche · Metabolic syndrome

Abstract
Adrenarche refers to a maturational increase in the secretion of adrenal androgen precursors, mainly dehydroepiandrosterone (DHEA) and its sulfate (DHEAS). In premature adrenarche (PA), clinical signs of androgen action appear before the age of 8/9 years in girls/boys, concurrently with the circulating DHEA(S) concentrations above the usually low prepubertal level. The most pronounced sign of PA is the appearance of pubic/axillary hair, but also other signs of androgen effect (adult type body odor, acne/comedones, greasy hair, accelerated statural growth) are important to recognize. PA children are often overweight and taller than their peers, and the higher prevalence of PA in girls than in boys is probably explained by higher female adiposity and peripheral DHEA(S) conversion to active androgens. PA diagnosis requires exclusion of other causes of androgen excess: congenital adrenal hyperplasia, androgen-producing tumors, precocious puberty, and exogenous source of androgens. PA has been linked with unfavorable metabolic features including hyperinsulinism, dyslipidemia, and later-appearing ovarian hyperandrogenism. Although this common condition is usually benign, PA children with additional risk factors including obesity should be followed up, with the focus on weight and lifestyle. Long-term follow-up studies are warranted to clarify if the metabolic changes detected in PA children persist until adulthood.

Introduction

Adrenarche refers to a maturational increase in the secretion of adrenal androgen precursors (AAPs) in mid-childhood, occurring typically at around 5–8 years of age. The main AAPs are dehydroepiandrosterone (DHEA) and its sulfate (DHEAS). The clinical signs of adrenal androgen action are normally seen after the age of 8 and 9 years in girls and boys, respectively. Premature adrenarche (PA) refers to the presentation of androgenic signs – appearance of pubic and axillary hair, adult type body odor, oily hair, acne or comedones – before the age of 8 years in girls or 9 years in boys in the absence of central puberty, steroidogenic enzyme defects, androgen-producing tumors, or exogenous source of androgens, concurrently with circulating AAP concentrations above the usual low prepubertal level [1–5]. The first descriptions of the phenomenon were published in early 1950s, when early development of pubic hair (premature pubarche, PP) in otherwise healthy prepubertal girls was reported [6]. These historical reasons probably explain why PP is still often erroneously used as a synonym for

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E-Mail karger@karger.com
www.karger.com/hrp

Pauliina Utriainen
Department of Pediatrics
Kuopio University Hospital and University of Eastern Finland
PO Box 100, FI–70029 Kuopio (Finland)
E-Mail pauliina.utriainen@hus.fi

PA although only about half of the children with PA have pubic or axillary hair at the time of PA diagnosis, at least in the Northern European Caucasian population [2, 3, 5].

Until late 1990s, PA was regarded as a benign variant of pubertal development with no need for special follow-up or treatment. Thereafter, several studies have connected PA with components of the metabolic syndrome (MBS) [7–13] and some with various other disturbances including functional ovarian hyperandrogenism (FOH) [14–16]. The extended Barker hypothesis of intrauterine programming of metabolism has been suggested also in PA [16]. While a growing body of evidence suggests a connection of PA with metabolic disturbances at the prepubertal age, solid evidence for the persistence of the observed metabolic changes through pubertal development until adulthood is lacking.

The mechanisms of PA remain unclear, but the adipose tissue seems to play a role in the presumably multifactorial etiology. No genome-wide association studies on timing of adrenarche exist, but several candidate genes have been studied with only weak associations found [reviewed in 4, 5]. In this mini review, we discuss the definitions, mechanisms and clinical presentation of PA, and the connection between PA and various metabolic disturbances. The recommendations for management and follow-up of children with PA are also discussed.

Definitions

Adrenarche refers to a maturational increase in the adrenal production of androgen precursors in mid-childhood. In the adrenal cortex, two main changes are needed for adrenarche: the cortical zone specialized for producing androgens (zona reticularis, ZR) has to be formed, and the expression of the steroidogenic enzymes and cofactors favoring AAP production has to be appropriate [17–19]. The mid-childhood increase in AAP production can be called 'biochemical adrenarche', whereas the appearance of androgenic signs due to increasing adrenal androgen secretion stands for 'clinical adrenarche'. A serum DHEAS level exceeding 1 μmol/l (≈40 μg/dl) has often been regarded as a biochemical hallmark of adrenarche [3, 5]. The androgenic signs of adrenarche include adult-type body odor, greasy hair, acne and/or comedones, and axillary and/or pubic hair. The appearance of pubic hair is called pubarche. PA refers to an earlier than normal appearance of clinical signs of adrenarche [1–5]. As the appearance of pubic hair is often considered the most striking of these clinical signs, PP has often been used as a synonym for clinical PA. Analogically with the phrase 'biochemical adrenarche', PA could also be understood as premature *biochemical* adrenarche, defined by increased circulating AAP levels or urinary adrenal androgen metabolites. As the increase in adrenal androgen production in childhood is gradual and usually relatively slow, it would be difficult to define valid serum or urinary AAP (metabolite) threshold levels for biochemical adrenarche.

The term 'exaggerated adrenarche' has also been used in connection with PA [20–22]. This term usually refers to PA with androgen levels higher than expected for the Tanner stage of pubic hair, but some authors have used it as a synonym for PA [22]. According to Likitmaskul et al. [20], circulating DHEAS concentrations exceeding the late-pubertal reference values or 6 μmol/l (≈222 μg/dl) would indicate exaggerated adrenarche. Other terms that have been used in connection with PA include amplified [23] and pronounced adrenarche [16]. Due to the variable and confusing use of the terms exaggerated, pronounced and amplified adrenarche, we preferably use just the term PA for this condition [5].

Adrenal and Peripheral Androgen Metabolism

Development of the Adrenal Cortex, Adrenal Androgen Metabolism, and Factors Modulating Androgenic Effects

During prenatal life, the fetal zone (FZ) of the adrenal cortex secretes androgen precursors, mainly DHEA and DHEAS, for the placental estrogen production [reviewed in 24]. During the first months after birth, the FZ regresses by apoptosis, and the secretion of AAPs decreases remaining low until adrenarche [25]. Thereafter, the androgen-producing ZR begins to develop from small focal islets. Adrenarche is a gradual process, and in some children AAPs are produced from early years [26, 27]. By mid-childhood, a continuous ZR has usually been formed producing increasing but individually highly variable amounts of AAPs [reviewed in 5].

The steroidogenic pathways in the ZR are presented in figure 1. All adrenal steroid hormones are synthesized from cholesterol which is converted to pregnenolone in the mitochondria by the cholesterol side-chain cleavage enzyme (P450scc, CYP11A1). The steroidogenic acute regulatory protein governs the acute response to adrenocorticotropic hormone (ACTH) by facilitating the movement of cholesterol from the outer to the inner mitochondrial membrane. The remaining enzymes needed for

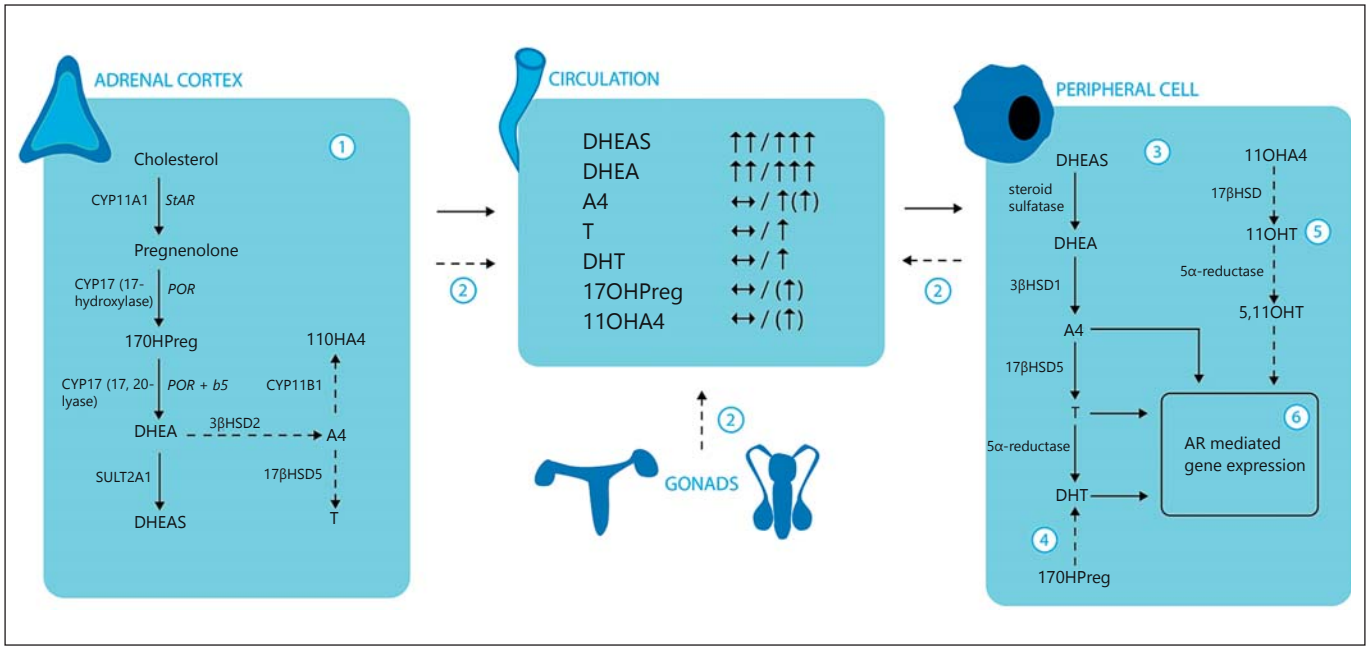

Fig. 1. Steroidogenesis in the ZR of the human adrenal cortex (left panel) and peripheral conversion of AAPs DHEA and DHEAS prior to the final AR-mediated action in peripheral cells (right panel). The middle panel depicts the variably altered steroid pattern in the circulation of children with PA compared to that of age-matched control children [2, 5]. (1) The expression and activity of the steroidogenic enzymes and their cofactors in ZR influence the adrenal androgen (precursor) secretion; high 17,20-lyase activity of the 17-hydroxylase/17,20-lyase enzyme (CYP17) and expression of POR and cytochrome b5 (b5) are essential [18]. (2) Possible minor T secretion from ZR [19], gonads or peripheral tissues may contribute to circulating T levels. (3) The expression and activity of the steroid-converting enzymes in peripheral tissues determine the formation of biologically active androgens from AAPs. (4) An alternative backdoor pathway to DHT formation [30]. (5) An alternative pathway from 11β-hydroxyandrostenedione (11OHA4) via 11β-hydroxytestosterone (11OHT) to a bioactive androgen 5α,11β-hydroxytestosterone (5,11OHT) [19]. (6) The activity of AR is influenced by *AR* gene polymorphisms, epigenetic modulations, and expression of its cofactors/comodulators [70–72]. A4 = Androstenedione; StAR = steroidogenic acute regulatory protein; 17OHPreg = 17OH-pregnenolone; 3βHSD = 3β-hydroxysteroid dehydrogenase (HSD3B); 17βHSD = 17β-hydroxysteroid dehydrogenase (HSD17B); ↑ = increased steroid concentration; ↔ = no reported change in the circulation of children with PA.

AAP synthesis in the ZR are 17-hydroxylase/17,20-lyase (P450c17, CYP17A1), 3β-hydroxysteroid dehydrogenase 2 (3βHSD2, HSD3B2), and sulfotransferase (SULT2A1). P450 oxidoreductase (POR) serves as an obligatory electron donor for P450c17, and cytochrome b5 acts as an allosteric factor promoting the 17,20-lyase reaction [reviewed in 18].

The AAPs DHEA and DHEAS are very weak androgen receptor (AR) agonists [18, 19], and their concentrations do not straightforwardly correlate with the clinical androgenic signs [3]. In the light of current data, peripheral metabolism of AAPs is needed for the efficient AR activation and clinical androgenic action. This view is supported by our recent studies demonstrating low androgen bioactivity in serum samples of children with PA [28] and higher prevalence of clinical signs of androgen action in prepubertal girls than in boys with equal serum DHEAS concentrations [29]. The enzymes involved in the peripheral AAP metabolism include 3βHSD1 (HSD3B1), 17β-hydroxysteroid dehydrogenase 5 (17βHSD5, HSD17B5), and 5α-reductase (SRD5A). Dihydrotestosterone (DHT) can also be formed via the so-called alternative backdoor pathway which bypasses both androstenedione and testosterone (T) as intermediates [30] (fig. 1).

Regulation of AAP Secretion in Normal-Timed and Premature Adrenarche

Biochemical adrenarche, the reactivation of AAP production, is a gradual process [26, 27]. The regulators of this physiologic process remain at least partly obscure. Pituitary ACTH is needed for adrenocortical androgen production, as evidenced e.g. by the lack of adrenarche in familial glucocorticoid deficiency due to ACTH receptor defects [31] and in children with hypopituitarism [32].

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However, ACTH is probably not the trigger for adrenarche, and no other initiator has been identified [reviewed in 4, 5, 18, 19]. While the initiating mechanisms of normal adrenarche remain unknown, several factors have been suggested to participate in the regulation of increased androgen production in PA, and this process may sometimes be a consequence of prenatal programming. The causes of (clinical) PA can basically act at two levels: (1) by activating the maturation of ZR and increasing AAP production, or (2) by enhancing peripheral conversion of AAPs to T and DHT, and/or by activating the AR.

Intrauterine growth retardation, being born small for gestational age, or even lower birth weight within the normal range are associated with increased serum DHEAS levels before puberty, especially if accompanied with rapid weight gain in early childhood [33, 34]. A linkage between a history of low birth weight (LBW) and clinical PA has been shown in some [16, 35, 36] but not all studies [22, 33, 37, 38]. Moreover, obesity (increased fat mass) has been associated with higher prepubertal AAP production also in children with normal birth weight [39, 40]. Factors that have been suggested to mediate the effect of obesity on AAP production include insulin, IGF-1, and leptin [reviewed in 4, 5]. Moreover, the conversion of AAPs to active androgens in peripheral adipose tissue may be enhanced by obesity [29].

Differential Diagnosis of PA

Before the diagnosis of PA can be accepted, other causes of androgen excess should be ruled out. Differential diagnosis of PA should include defects of cortisol synthesis, most importantly late-onset congenital adrenal hyperplasia (LO-CAH) and even simple virilizing CAH especially in boys, adrenal or gonadal androgen-producing tumors, precocious puberty, and exposure to exogenous androgens [reviewed in 4, 5].

Of the pathologic causes of prepubertal adrenal hyperandrogenism, LO-CAH due to 21-hydroxylase deficiency is the most common. Other enzymatic defects causing LO-CAH with hyperandrogenism include mutations in the genes encoding for 3βHSD2 (HSD3B2) [41] and 11β-hydroxylase (P450c11, CYP11B1) [42]. 'True' cortisone reductase deficiency, inactivating mutations in the 11β-hydroxysteroid dehydrogenase 1 *(11βHSD1, HSD11B1)* gene, and apparent cortisone reductase deficiency due to inactivating mutations in the hexose-6-phosphate dehydrogenase *(H6PDH)* gene, cause ACTH-driven adrenal hyperandrogenism by reduced peripheral conversion of cortisone to cortisol [43]. A rare genetic reason in adrenal androgen metabolism leading to PP with high DHEA and biologically active androgens but low DHEAS, was recently explained by an inactivating mutation in the *PAPSS2* gene encoding for a cofactor (PAPS synthase 2) needed in SULT2A1 enzymatic action [44].

The prevalence of CAH among PP patients varies substantially in different study populations (0–43% for all types of CAH) [3, 41, 45–47]. Some investigators suggest that LO-CAH can be excluded in PP subjects by the measurement of basal serum 17-OH-progesterone [48], while others suggest performing the ACTH test if CAH is suspected clinically [46, 49, 50]. A useful and accurate method for the differential diagnosis of steroidogenic enzyme defects is the analysis of urinary steroid metabolome in experienced hands [42, 43].

Differential diagnosis between PA and LO-CAH (and the other mentioned genetic reasons for adrenal hyperandrogenism) is not always obvious based on clinical examination, but rapidly accelerating growth in height, remarkable androgenic signs and bone age advancement, and a positive family history are clues to a genetic disorder. Androgen-producing tumors are rare in children, but they should be considered if androgenic signs are severe (for example clitoromegaly in a girl or penile enlargement in a boy with a prepubertal testicle size) and/or growth velocity is markedly accelerated. Precocious central puberty can usually be diagnosed clinically: the Tanner stage for breast development ≥B2 in girls and testicular volume >3 ml in boys indicate ongoing puberty. However, in obese PA girls, budding breast development can sometimes occur owing to peripheral estrogen synthesis from AAPs without central puberty.

Clinical Presentation of PA

The prevalence of PA varies considerably depending on which criteria are used and which population is studied, with higher incidence in children of African-American ethnicity [51]. In a recent Finnish population-based study, the prevalence of PA (defined by serum DHEAS exceeding 1 μmol/l and any androgenic sign before the age of 8 years in girls and 9 years in boys) was 8.6% in girls and 1.8% in boys [29]. Several previous studies have also shown that PA is more common in girls than in boys [1–3, 22, 36].

The clinical signs of PA include oily hair and skin, adult-type body odor and the appearance of pubic and

axillary hair [1–5]. The androgenic signs in PA often manifest in a typical order but with varying circulating androgen levels between patients. In our Finnish-Caucasian PA cohort, the first clinical sign of adrenarche was most often adult-type body odor, while pubarche and axillary hair were typically the last androgenic signs and present in only about half of the subjects at diagnosis. Serum DHEAS concentrations were higher in the PA subjects with pubic or axillary hair than in those with other signs only, forming a logic continuum [3]. DHEAS is considered the best marker of adrenal androgen secretion. Also other adrenal androgens (DHEA and androstenedione) may be increased for age. On the other hand, it is not uncommon that a child with signs typical for PA has a normal prepubertal serum DHEAS concentration [<1 μmol/l (≈40 μg/dl)] [3, 5]. In follow-up studies of PA girls, the increase in serum AAP concentrations has been slow, their levels have usually remained appropriate for the pubic hair stage, and they have in most cases normalized for age by the end of puberty [1, 37, 52]. However, studies on Catalan PP girls have suggested that ovarian and adrenal hyperandrogenism may persist until postpuberty [15, 53].

Children with PA are typically heavier than their peers [3, 7, 9, 12, 22, 35, 36]. Overweight may be accompanied by acanthosis nigricans [7, 9]. Increased mean prepubertal height has been found in most described PA cohorts [2, 6, 38, 52, 54]. Our Finnish PA girls were 1.2 standard deviations scores taller than their prepubertal controls at the median age of 7.6 years. Most of this difference in height had been gained already by the age of 2 years [38]. An increased circulating IGF-1 level has also been found in several PA cohorts [38, 55, 56]. Bone age is often advanced in PA, usually appropriately for the enhancement of growth in height [2, 56]. In a multi-ethnic study with prepubertal PA and control children, bone age advancement was most strongly associated with obesity, and to a smaller extent with estradiol and DHEAS levels [56]. It seems that children with PA use a greater part of their genetic growth potential before puberty compared with controls [52], while normal expected adult height is usually reached [23, 52, 54]. Menarche occurred about 0.5 years earlier in Finnish [52] and slightly less than 1 year earlier than expected in Spanish-Catalan PA girls [23].

Three studies have analyzed bone mineral density (BMD) in PA. In Catalan PP girls, BMD measures were higher than the respective population reference values [57]. An American study showed higher total body BMD in the PA than control girls at prepubertal age [58]. In our study including both girls and boys, BMD did not differ between the PA and control subjects when the size of the child was accounted for [59].

There are only few studies investigating psychological, social or cognitive effects of PA. One American study found lower scores on intelligence tests and more self-reported depression in PA girls compared with peers [60]. Another study found that girls with PA performed worse than controls on verbal, working memory, and visuospatial tasks [61].

Associations of PA with Ovarian and Cardiometabolic Disturbances

An association between PA and increased prevalence of FOH was reported in 1993 in postpubertal Spanish-Catalan girls with a history of PP due to PA [14]. Soon thereafter, a group of girls with PP (due to PA) and acanthosis nigricans was shown to have decreased insulin sensitivity in a small multi-ethnic American cohort [7]. These two studies aroused interest in possible later harmful metabolic consequences of PA which had until then been considered a benign variant of pubertal development. Thereafter, several studies have found unfavorable metabolic features in PA subjects at the time of diagnosis or later during follow-up (table 1). Not all studies, however, have found a connection between PA and hyperinsulinism or other features of MBS.

The most consistently reported component of MBS (insulin resistance/hyperinsulinism, central obesity, hypertension, dyslipidemia) in PA seems to be hyperinsulinism (table 1). However, in Brazilian girls with a history of PP (due to PA), no evidence of hyperinsulinism or insulin resistance was detected at the mean age of 12.1 years [62]. In most PA cohorts, PA has also been connected with overweight [7, 9, 12, 22, 35, 36, 56]. Interestingly, in the most extensively studied Catalan PA population, the girls with a history of PP were nonobese. However, they had an increased mean waist-to-hip ratio, total and abdominal fat mass and fat percentage compared to the control girls (n = 65) matched for age and pubertal breast stage. As the authors recognized, the interpretation of these findings needs some caution due to the height/weight differences of the study groups especially at the prepubertal and early pubertal stages [11]. In our Finnish population-based study, 'childhood MBS' (defined using child-adjusted MBS criteria) was more common in the PA than control children (child-adjusted WHO criteria 16 vs. 5% and ATP III criteria 24 vs. 10%), mainly due to the higher prevalence of overweight in the PA group [12].

Table 1. Main studies investigating components and markers of the metabolic syndrome in PA subjects

Metabolic feature	Ethnic origin	PA subjects	Control subjects	Parameter	Findings in PA/PP subjects	Reference
Adiposity	Spanish (Catalan)	67 girls, PP (PA) history; different pubertal stages	65; matched for Tanner breast stage and BMI	Fat distribution	Increased WC, WH ratio, total and central fat mass	11
	American (mixed)	10 (7 girls), PP (PA); prepubertal	10; matched for age, sex and BMI	Fat distribution (DXA body scan)	Android fat distribution; no difference in height-adjusted fat distribution or trunk fat %	13
	Caucasian (Finnish)	64 PA (54 girls); prepubertal	62 (52 girls); matched for age, sex and pubertal stage	Body composition (bio-impedance)	Higher total fat mass and fat %	59
Glucose metabolism	Hispanic/ African-American	12 PP (PA) girls; prepubertal	No controls	Insulin sensitivity (modified minimal model)	Decreased insulin sensitivity in PP with acanthosis nigricans	7
	Spanish (Catalan)	81 girls with PP (PA) history; age range 5.9–18 years	53; Tanner breast stage and bone age-matched	Serum insulin oncentrations after OGTT	Higher mean serum insulin after OGTT (all Tanner breast stages)	8
	Caribbean Hispanic/ African-American	35 PP (PA) girls; prepubertal	No controls	Insulin sensitivity (FSIVGTT with tolbutamide)	Decreased insulin sensitivity in 43% of the PA girls	9
	American (mixed)	11; prepubertal PP (PA) boys	8; prepubertal boys	Insulin sensitivity	Increased AUC insulin and decreased composite insulin sensitivity index in OGTT	10
	Caucasian (French)	27 girls with PP (PA) history; age 17.4±1.3 years	25 girls; age-matched	Glucose metabolism	No signs of reduced glucose tolerance, hyperinsulinemia or reduced insulin sensitivity in OGTT	37
	Caucasian (Finnish)	63 PA girls (32 with PP); prepubertal	80 girls; prepubertal age-matched	Glucose metabolism	Higher weight-for-height -adjusted mean insulin levels during OGTT, also higher fasting insulin in the PP subgroup	12
Lipid profile	Spanish (Catalan)	81 girls with PP (PA) history; age range 5.9–18 years	53; Tanner breast stage- and bone age-matched	Serum lipid and lipoprotein concentrations	Higher TG, VLDL-TG, VLDL cholesterol and LDL/HDL cholesterol ratio throughout puberty (no BMI adjustment)	8
	Caucasian (Finnish)	63 PA girls (32 with PP); prepubertal	80 girls; prepubertal, age-matched	Serum lipid concentrations	No difference in weight-for-height-adjusted TG, total, LDL or HDL cholesterol	12
	American (mixed)	10 (7 girls), PP (PA); prepubertal	10; matched for age, sex and BMI	Serum lipid concentrations	Higher total/HDL cholesterol ratio, but significance disappeared when corrected for height	13
	Caucasian (French)	27 girls with PP (PA) history; age 17.4±1.3 years	25 girls; age-matched	Serum lipid concentrations	No difference in fasting TG, total or HDL cholesterol	37
BP	American (mixed)	10 (7 girls), PP (PA); prepubertal	10; matched for age, sex and BMI	Systolic and diastolic BP	Higher BP values, but the difference disappeared when adjusted for height	13
	Caucasian (Finnish)	63 PA girls (32 with PP); prepubertal	80 girls; prepubertal, age-matched	Systolic and diastolic BP	No difference in weight-for-height-adjusted diastolic or systolic BP	12

WC = Waist circumference; WH ratio = waist to hip ratio; OGTT = oral glucose tolerance test; FSIVGTT = frequently sampled intravenous glucose tolerance test; TG = triglycerides; VLDL = very low-density lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein; BP = blood pressure.

Table 2. Candidate gene polymorphism studies showing association between the variants and premature adrenarche

Gene	Polymorphism	PA subjects (girls/boys)	Controls (girls/boys or total)	Heterozygote frequency (PA vs. control)	p	Association with minor variant	Reference
MC2R	–2T→C	64/10	79/18	28, 11 vs. 10%[1]	0.04	ACTH, DHEA, A4	67
CYP19	SNP50	186/0[2]	71/0	44 vs. 26%[3]	0.001	T, DHEAS, IS	68
AR	CAG_n	181/0[2]	124/0	0.7 shorter CAG_n	0.003	FOH	70
	CAG_n	25/0[2]	33	0.9 shorter CAG_n	<0.05		71
	$mwCAG_n$	63/10	79/18	0.8 shorter $mwCAG_n$	0.017	BMI SDS	72
IGF-1R	E1013E (A→G)	63/6	31/61	60.9 vs. 48.9%	0.04		73

MC2R = Melanocortin type 2 receptor; A4 = androstenedione; IS = insulin sensitivity; AR = androgen receptor; CAG_n = number of CAG repeats; $mwCAG_n$ = methylation weighted biallelic mean of CAG repeats; SDS = standard deviation score; IGF-1R = IGF-1 receptor. [1] Combined T/C and C/C frequency (PP, PA with other clinical signs vs. controls). [2] PP subjects. [3] Major allele homozygote frequency.

Also the circulating levels of some adipokines and inflammatory markers, including leptin, plasminogen activator inhibitor-1 and TNF-α, have been reported to be increased in PA subjects [13, 57, 63, 64].

In Catalan girls with a history of PP due to PA, the prevalence of FOH was increased during and after puberty [14, 15]. Especially the combination of LBW and hyperinsulinism was connected with subsequent development of FOH in postpubertal PP girls [16], thereby suggesting an extension to the hypothesis of the developmental origin of health and disease. On the other hand, a small American study on prepubertal PP (PA) girls did not show evidence of FOH [65]. In French-Caucasian postpubertal girls with a history of PP due to PA, the frequency of oligomenorrhea and insulin resistance parameters in oral glucose tolerance tests were similar to controls, and no connection between body weight and serum androgen levels was found [37]. On the basis of the observed inconsistencies in the frequency of FOH and polycystic ovarian morphology in subjects with a history of PA, additional follow-up studies on ovarian function from the diagnosis of PA until adulthood will be needed.

Genetic Background of PA

It is apparent that genetic factors contribute to adrenal androgen secretion and action, and thus also to the timing and strength of adrenarche. In a twin study, adrenal androgen excretion rate showed a heritability of 58% in prepubertal and pubertal subjects. Environmental factors accounted for 17% of the variation, and their role might be more important in girls than in boys [66]. Several studies have searched for susceptibility variants in genes involved in steroidogenesis, androgen action, insulin-IGF signaling, body weight regulation, and Wnt signaling. Already one of the first reports showed the presence of polymorphisms/mutations at several candidate loci, especially steroidogenic enzyme genes, in American children with PP and adolescent girls with hyperandrogenism [41]. Studies revealing statistically significant associations between genetic variation and PA are listed in table 2. Many of the studies had insufficient power to exclude the negative findings, and genome-wide association studies on adrenarche or adrenal androgen secretion during childhood and adolescence are missing.

Melanocortin type 2 receptor mediates the effects of ACTH on ZR, and a single nucleotide polymorphism (SNP) near the transcription initiation site of the gene encoding for this receptor has been associated with PA severity [67]. The genes encoding steroidogenic enzymes have been tempting candidates for the genetic regulation of PA. *P450-aromatase (CYP19)* encodes the aromatase enzyme that catalyzes the conversion of androgens to estrogens. The genotype distribution of SNP50 at the coding region of *CYP19* is different in Catalan PP girls, in whom the major allele homozygosity is associated with higher serum T and DHEAS levels and decreased insulin sensitivity [68]. On the other hand, common polymorphisms at *POR*, *SULT2A1* or *11βHSD1 (HSD11B1)* were not associated with PA in a Finnish Caucasian population, suggesting that they do not significantly contribute to PA [69]. Increased sensitivity of hair follicles to androgens has been postulated as a possible pathogenic mechanism for PA. The *AR* gene contains a polymorphic region with a variable number of CAG repeats (CAG_n) encoding

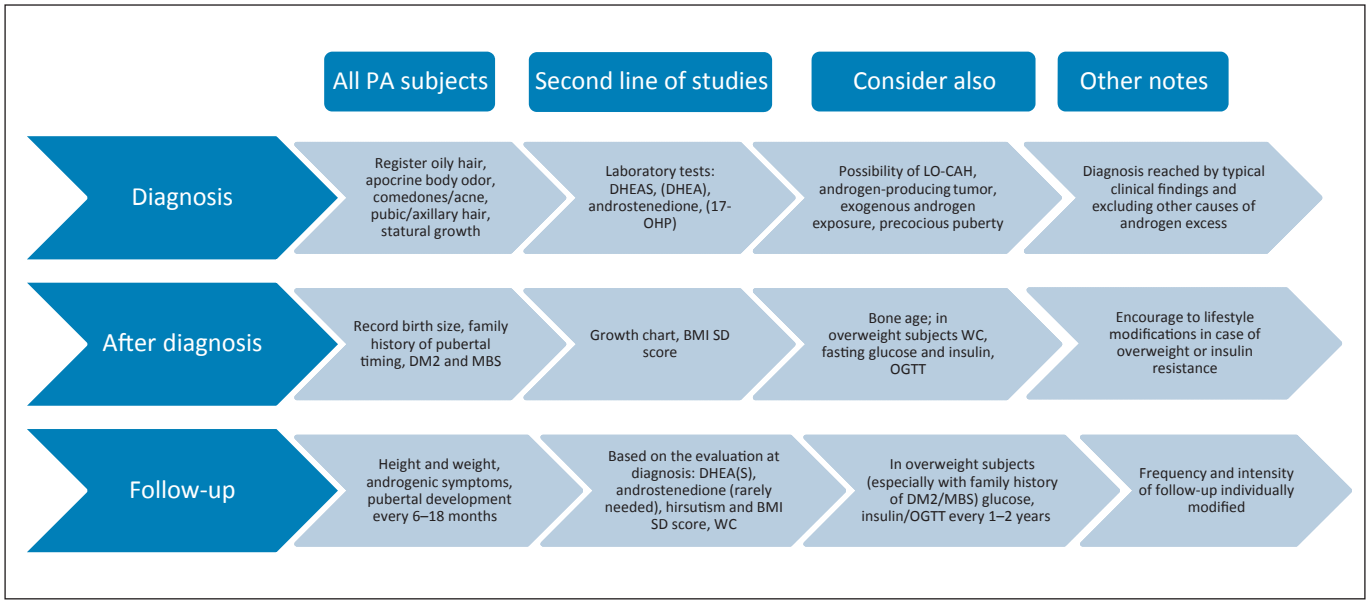

Fig. 2. Management of children with PA. 17OHP = 17-hydroxyprogesterone; DM2 = type 2 diabetes mellitus; SD = standard deviation; OGTT = oral glucose tolerance test; WC = waist circumference.

a polyglutamine tract, the length of which has an inverse relationship with the transcriptional activity of the AR. Mediterranean girls with PP and Finnish PA subjects had the mean CAG_n about one repeat shorter than controls [70–72]. In the Finnish cohort, the lean PA subjects had shorter CAG_n than the PA subjects with higher BMI or the lean control subjects, suggesting that more active AR may play a significant role especially in lean PA subject [72]. The minor variant G at SNP E1013E in *IGF-1R* has been associated with higher circulating IGF-1 levels, and the frequency of this minor variant was increased in American PA children [73].

Physiologic Significance of Adrenarche

The significance of adrenarche in human maturation has remained an enigma. Adrenarche is a separate event from gonadarche, the pubertal activation of the hypothalamo-pituitary-gonadal axis, and it is not needed for the initiation of central puberty. It has been speculated that an increase in the DHEAS level at around 7 years of age enables the prolonged development of the prefrontal cerebral cortex in humans. As a neuroprotective hormone, DHEAS could protect synaptic plasticity in metabolically active parts of the brain [74]. There is some evidence on the anabolic effects of adrenarche. As already mentioned, prepubertal children with PA are often taller than their peers, have advanced bone age and reduced pubertal growth spurt, indicating that they may use a greater part of their growth potential before puberty than those with on-time or late adrenarche [52]. This suggests indirectly that adrenal androgens play a role also in normal pubertal growth spurt. Adrenal androgens may also contribute to the accrual of BMD [57–59] and erythropoiesis [75].

Recommendations for Management of PA

When clinical signs of PA have been noted, a careful physical examination and analysis of the growth chart of the child should be performed. The diagnosis of PA is based on exclusion of other causes of prepubertal hyperandrogenism (fig. 2). After affirming the PA diagnosis, assuring the family of the usually benign nature of the androgenic signs is important.

There are few recommendations for the management of PP or PA, but a Clinical Practice Committee Publication on PP was published in this journal in 2010 [49]. Special treatment is neither available nor required in PA. Usually, intensive follow-up is not needed either, especially when the androgenic signs are mild. Some PA girls may have an increased risk for developing obesity-related

metabolic disturbances, including insulin resistance and FOH or polycystic ovarian syndrome (PCOS). This risk may be higher in girls with LBW. Therefore, glucose and insulin measurements have been suggested for PA children with a history of LBW or acanthosis nigricans [50]. Insulin sensitivity could also be assessed if the child is obese or has a family history of MBS or type 2 diabetes. The PA girls with the triad of LBW, pronounced hyperandrogenism with PP, and hyperinsulinism merit closer follow-up. Emphasis of the follow-up should be in maintaining or reaching normal weight by lifestyle modification including physical exercise and healthy diet (fig. 2). Early metformin treatment has been suggested for PP girls with LBW in order to prevent the development of hirsutism, androgen excess and other PCOS features [76]. In view of the shortage of data on the safety and effectiveness of long-term use of metformin or insulin sensitizers in children and adolescents, the use of these medications in children with PP is not recommended outside of clinical trials [49]. Otherwise, the indications for metformin and insulin-sensitizing treatment should be the same as for other children/adolescents with obesity, insulin resistance and type 2 diabetes.

Conclusions

Adrenarche offers a possibility to study the regulation and physiologic role of AAPs, which remain mostly unclear. As for the PA, the main question is whether it is a form of early adrenal maturation with transient mild metabolic changes, or the first sign of persistent hyperandrogenism. The current evidence for a firm linkage between PA and PCOS is insufficient, although it may be true in some PA girls. Differentiating this subgroup remains a clinical challenge. Pediatricians should be aware that most patients with PA have mild, slowly progressive signs of the androgen effect and uncompromised adult height with no need for special follow-up. The families of the PA children should be informed about the usually benign nature of the condition.

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