Present Knowledge on the Etiology and Treatment of Adrenarche

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Abstract

Premature adrenarche (PA) has been assumed to be a benign variant of normal pubertal development. Yet, current collective information suggests associations between PA and potential risks for development of polycystic ovary syndrome and adult diseases such as the metabolic syndrome. Adrenarche refers to the increased secretion of the adrenal androgen precursors DHEA, DHEAS, and androstenedione, which normally occurs in children at age 6-8 years. PA may be identified clinically by early pubarche, which is defined as the development of pubic or axillary hair before 8 years in girls or 9 years in boys. This paper will consider adrenal steroidogenesis, genetic markers, neurobiological changes, skeletal maturation, and associations with adult disorders. The differential diagnosis will be reviewed because PA remains a diagnosis of exclusion. Finally, synthesis of current knowledge regarding PA, suggestions for evaluation, management, and treatment are offered.

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Abbreviations: ***CYP11A1*** *(Cytochrome P450 Family 11 Subfamily A Member 1 or Cholesterol Side-Chain Cleavage Enzyme);* ***CYP17A1*** *(Cytochrome P450 Family 17 Subfamily A Member 1 or Steroid 17-Alpha-Hydroxylase);* ***CYP11B1*** *(Cytochrome P450 Family 11 Subfamily B Member 1);* ***CYP21A2*** *(Cytochrome P450 Family 21 Subfamily A Member 2);* ***3B-HSD*** *(3B-Hydroxysteroid dehydrogenase);* ***HSD17B5*** *(17B-Hydroxysteroid dehyodrogenase 5);* ***SRD5A*** *(3-oxo-5a-steroid 4-dehydrogenase);* ***11B-HSD2*** *(Corticosteroid 11-B-dehydrogenase isozyme 2);* ***AKR1C3*** *(Aldo-Keto Reductase Family 1 Member C3);* ***SULT2A1*** *(DHEA Sulfotransferase Family 2A Member 1);* ***POR*** *(Cytochrome P450 oxidoreductase)*

Introduction

Adrenarche, beginning between 6-8 years of age, is a process unique to humans and higher primates (1). Pubarche is the physical manifestation of adrenarche. Pubarche is defined as the appearance of pubic or axillary hair, which is often accompanied by adult apocrine odor, increased oiliness of the skin and hair, and acne (2). In the National Health and Nutrition Examination Survey (NHANES), the mean ages for pubic hair development were 9.5 years for non-Hispanic black girls, 10.3 years for Mexican-American girls, and 10.5 years for non-Hispanic white girls (3). For boys, mean ages for pubic hair development were 11.1 years for non-Hispanic blacks, 12.3 years for Mexican-Americans, and 12.0 years for non-Hispanic whites (3). Adrenarche reflects a change in adrenal

steroidogenesis with increased secretion of C19 steroids, predominantly dehydroepiandrosterone sulfate (DHEAS) and DHEA, from the zona reticularis (4). Adrenarche and pubarche can occur in individuals with gonadal dysgenesis and hypothalamic hypogonadism indicating that adrenarche occurs independently of gonadarche (5).

This review will summarize recent developments in the study of premature adrenarche (PA) including adrenal steroidogenesis, differential diagnosis, genetic associations, establishment of the clinical diagnosis, and the potential co-morbidities of polycystic ovary syndrome (PCOS) and the metabolic syndrome. Approaches to diagnosis and management of PA are offered.

Adrenal Steroidogenesis

The adrenal cortex is comprised of three distinct zones. The outer zone, the zona glomerulosa (ZG), synthesizes mineralocorticoids (4). The middle zone, the zona fasciculata (ZF), secretes glucocorticoids (4). The inner zone, the zona reticularis (ZR), secretes C19 steroids especially DHEA and DHEAS (4). The proteins required for DHEAS synthesis include steroidogenic acute regulatory protein (StAR), cytochrome P450 cholesterol side chain cleavage (P450scc), 17α-hydroxylase/17,20 lyase (P450c17), cytochrome P450 oxidoreductase (P450oxo), cytochrome b_5, and DHEA sulfotransferase 2A1 (4) (**figure 1**).

Cholesterol serves as the substrate for adrenal steroidogenesis (4,6). The enzyme, 17α-hydroxylase/17,20-lyase (P450c17), encoded by the 17α-hydroxylase/17,20 lyase (CYP17A1) gene, serves as the "gatekeeper" of adrenal steroidogenesis. This microsomal enzyme, which is expressed in the adrenal cortex and the gonads, has two distinct activities: **1.** 17α-hydroxylase and **2.** 17,20-lyase (7). This enzyme is not expressed in the zona glomerulosa resulting in the conversion of pregnenolone to mineralocorticoids (4). In the zona fasciculata, the 17α-hydroxylase activity predominates resulting in glucocorticoid synthesis (4). In the zona reticularis, allosteric interactions with cytochrome b_5 favor the 17,20-lyase activity and production of C19 steroids (8-10).

DHEA sulfotransferase 2A1 (SULT2A1) is highly expressed in the zona reticularis, where it can sulfate pregnenolone, 17α-hydroxypregnenolone, and DHEA to their respective sulfated products (4). Following sulfation, pregnenolone-sulfate, 17α-hydroxypregnenolone-sulfate, and DHEAS cannot serve as substrates for P450c17 or 3-beta hydroxysteroid dehydrogenase type 2 (3βHSD type 2). In addition, they cannot act as agonists at steroid hormone receptors (4). It is assumed that this metabolic pathway optimizes the flux of the Δ5 pathway from pregnenolone to DHEAS (11).

Investigations using liquid chromatography-tandem mass spectroscopy (LC-MS/MS) and gas chromatography-mass spectroscopy (GC-MS) have revealed that the steroid

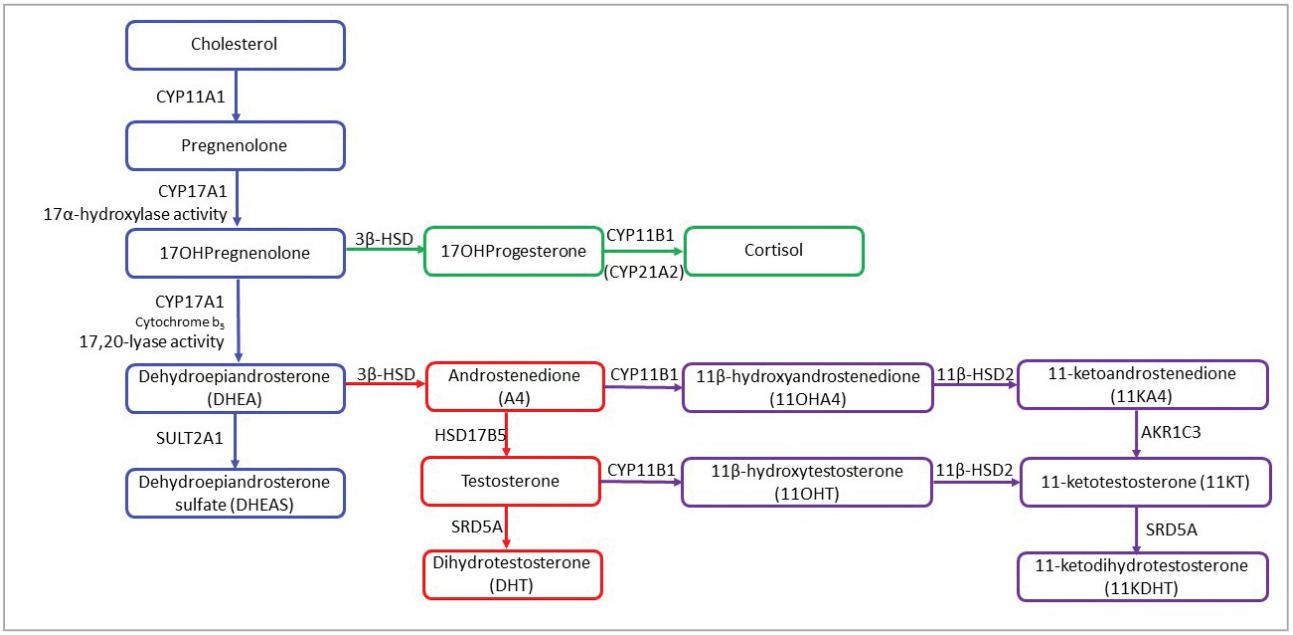

Figure 1. Pathway of adrenal steroidogenesis
Blue boxes and arrows show DHEAS pathway, green show cortisol pathway, red show active adrenal androgen pathway, and purple show 11-oxC19 pathway.

hormone repertoire of the adrenal cortex is broader than traditionally recognized. Additional C19 steroids include 11-ketoandrostendione (11ketoA4), 11ß-hydroxyandrostenedione (11OHA4), 11ß-hydroxytestosterone (11OHT), and 11-ketotestosterone (11ketoT) (8,9). The enzyme cytochrome P450 11-ß hydroxylase (P450 11B type 1) encoded by *CYP11B1* participates in the synthesis of these 11oxC19 steroids (8). Studies of adrenal vein samples have demonstrated that 11ß-hydroxyandrostenedione is the most abundant unconjugated C19 adrenal steroid product; ACTH stimulation can enhance its production (12). Although the adrenal cortex can synthesize 11-ketoandrostenedione and 11-ketotestosterone, peripheral enzymes such as 11ß-hydroxysteroid dehydrogenase type 2 (HSD11B2) and aldo-keto reductase 1C3 (AKR1C3/17 ß-hydroxysteroid dehydrogenase type 5) are responsible for the conversion of 11ß-hydroxyandrostenedione to these other steroids (4). Subsequently, 11-ketotestosterone can be converted to 11-ketodihydrotestosterone (11KDHT) by peripheral 5α-reductase activity (8,9) (**figure 1**).

Androstenedione, DHEA, and DHEAS do not display significant agonist activity at the human androgen receptor (4). These steroids require additional conversion for biologic activity at the androgen or estrogen receptor. In contrast, 11-ketotestosterone and 11-ketodihydrotesterone are potent agonists of the androgen receptor (12,13). The other 11oxC19 steroids, 11ß-hydroxytestosterone, 11-ketoandrostenedione, and 11ß -hydroxyandrostenedione are less potent androgens than 11KT and 11KDHT, but all have demonstrated androgen activity in *in vitro* studies (13-15). Preliminary data suggest that the 11oxC19 steroids may play a biologically significant role in the clinical signs associated with adrenarche (8,16,17). The relative abundance of 11OHA4 in the adrenal gland and the potency of its derivatives, 11KT and 11KDHT, suggest that 11OHA4 is a significantly more important adrenal androgen than previously thought (18).

HPA Axis

The hypothalamic-pituitary-adrenal (HPA) axis primarily regulates glucocorticoid secretion by negative feedback inhibition limiting the secretion of ACTH (4). ACTH is an agonist of the ACTH receptor (MC2R) and has both chronic and acute actions (4). Its chronic actions are to maintain the transcription and translation of adrenal steroidogenic enzymes (4). Acutely, ACTH promotes cortisol secretion. While ACTH facilitates the function of the zona glomerulosa, aldosterone secretion is primarily regulated by the renin-angiotensin system and serum potassium concentrations (19).

Whereas the feedback loops are well characterized for glucocorticoid and mineralocorticoid secretion, the existence and specific elements of a feedback loop involved in the regulation of adrenal androgen secretion remain to be elucidated. The absence of adrenarche in patients with ACTH receptor mutations and ACTH deficiency imply at least a partial regulatory role for ACTH in adrenarche (20). Yet, the increasing DHEAS concentrations at adrenarche appear to be independent of circulating cortisol and ACTH concentrations (21). Despite attempts to identify an adrenal androgen stimulating factor, none of the proposed factors have withstood rigorous assessment (22).

In a cell culture system utilizing the NCI-H295R human adrenal cell line, cortisol was shown to increase DHEA production in association with competitive inhibition of 3ß-hydroxysteroid dehydrogenase type 2 activity (11). In a different experimental paradigm using solubilized and liposome-bound preparations of purified human 3ßHSD2, androstenedione was found to inhibit purified 3ß-hydroxysteroid dehydrogenase type 2 activity (23). Whether these findings are applicable to the normal regulation of the human zona reticularis remains to be determined.

Adrenarche

During fetal life, the fetal adrenal cortex produces DHEAS and DHEA, which provide the substrates for placental estrogen biosynthesis (4). Following birth, the involution of the fetal adrenal cortex is accompanied by a decline in DHEA and DHEAS concentrations (4,24). Adrenarche is characterized by increased DHEA and DHEAS secretion without significant changes in ACTH and cortisol secretion (4,24). Adrenarche accompanied by increased DHEA and DHEAS secretion is associated with morphological changes in the zona reticularis (24-26). These changes include increased expression of cytochrome b_5 and DHEA sulfotransferase 2A1 whereas the expression of 3ß-hydroxysteroid dehydrogenase type 2 decreases (27,28). Although adrenarche has traditionally been considered to begin only in late childhood, urinary steroid excretion indicates increased urinary androgen metabolites reflecting adrenal C19 steroid synthesis begins much earlier than 6 years of age (29). Indeed, adrenarche may represent a gradual process originating in early childhood (30).

During adrenarche, DHEAS concentrations rise to reach their peak during the second decade of life followed by a gradual decline (31). DHEAS has the highest concentration of all circulating steroid hormones (12), has a longer half-life, and shows minimal diurnal variation (32). Yet, the function(s) of DHEA and DHEAS remain unclear. These substances do not bind to the androgen receptor, but may serve as precursors for other sex steroids including estrogen, testosterone, 11ß-hydroxyandrostenedione, and 11ß-hydroxytestosterone (8,9).

Using normal adrenal glands obtained from subjects of different chronologic ages, double immunofluorescence analysis showed that HSD3B2 expression was largely limited

to the ZG and ZF and did not change with increasing age (33). The expression of P450c17 increased in the ZF and ZR around 5 years of age while CYB5A expression markedly rose in the ZR with increasing age (33). *CYB5A* is the gene that codes for cytochrome b_5, a strong modulator of 17,20-lyase activity. These data verify that increasing CYB5A expression in the zona reticularis is associated with increased 17,20-lyase activity and the onset of adrenarche (34).

The ascending DHEAS concentrations during adrenarche are paralleled by rising 5-androstenediol-3-sulfate (Adiol-S) concentrations (34). When desulfated, Adiol-S can supply precursors for production of more potent androgens such as testosterone in skin and liver (28,32). In addition to signifying the onset of adrenarche, Adiol-S may serve as a precursor for additional sex steroids through peripheral tissue conversion (34).

Differential Diagnosis of Premature Pubarche

Based on the mean ages of pubarche in girls and boys, premature pubarche is defined as appearance of pubic or axillary hair earlier than 8 years of age in girls and 9 years in boys (3). The differential diagnosis for premature pubarche includes PA, mild or non-classical congenital adrenal hyperplasia, androgen secreting tumors, rare genetic disorders, and exogenous androgen exposure. Gonadotropin-dependent precocious puberty rarely presents with pubic hair; breast development and testicular enlargement are typically the initial manifestations. In the absence of a validated diagnostic test, PA is a diagnosis of exclusion.

The most common differential diagnosis is congenital adrenal hyperplasia (35,36). The virilizing congenital adrenal hyperplasias are a group of autosomal recessive disorders characterized by defective glucocorticoid biosynthesis leading to loss of negative feedback inhibition, increased ACTH secretion, and subsequent increased adrenal androgen secretion (37,38). The most common form is 21-hydroxylase deficiency due to mutations in the 21-hydroxylase (*CYP21A2*) gene (38). The other virilizing CAHs are 3-beta-hydroxysteroid dehydrogenase deficiency due to *HSD3B2* mutations and 11-beta hydroxylase deficiency due to *CYP11B1* mutations (39,40). All forms manifest a phenotypic spectrum reflecting the consequences of the specific mutations. The mildest phenotype is called non-classical or late onset. The prevalence of non-classical 21-hydroxylase deficiency has been estimated to be approximately 1:1000/2000 among European Caucasians and 1:100 among Ashkenazi Jews and other middle Eastern populations, with lowest rates of 21-hydroxylase deficiency among Black patients (41). In contrast, reported cases of non-classic CAH due to *CYP11B1* and *HSD3B2* mutations are extremely rare (42). Whereas random elevated 17-hydroxyprogesterone concentrations may confirm the diagnosis of non-classical 21-hydroxylase deficiency, obtaining an elevated ACTH stimulated 17-OHP value may be necessary to confirm the diagnosis of 21-hydroxylase deficiency in some patients (35,42).

Several rare genetic disorders are associated with premature pubarche. As noted above DHEA is converted to DHEAS by the enzyme, SULT2A1 (4). This enzyme requires a sulfate donor, PAPS (43). Loss of function mutations in the *PAPSS2* gene have been associated with premature pubarche, elevated DHEA concentrations, elevated androgens, and low DHEAS concentrations (43,44). Apparent cortisone reductase deficiency, due to loss of function mutations in the hexose-6-phosphate dehydrogenase (*H6PD*) gene, can also be associated with premature pubarche and increased DHEAS, androstenedione, and testosterone concentrations (45). The *H6PD* loss of function mutations prevent local conversion of cortisone to cortisol resulting in accelerated peripheral clearance of cortisol, decreased negative feedback inhibition of the HPA axis, and increased ACTH secretion (45).

Virilizing adrenal or gonadal tumors are rare, but can present with premature pubarche and virilization (46,47). Adrenal tumors include adrenocortical adenomas, adrenocortical carcinomas, bilateral macronodular hyperplasia, and adrenal oncocytomas (48). Expression of steroidogenic enzymes may be altered in the neoplastic tissue (49). Curiously, an androgen and desoxycorticosterone (DOC)-secreting right adrenal tumor was identified in a non-Cushingoid 14-year-old girl who presented with secondary amenorrhea, hypertension and virilization; her hormone concentrations recapitulated the findings associated with 11ß-hydroxylase deficiency (50). Removal of the tumor normalized her clinical and hormone findings suggesting that the pattern of steroidogenesis provoked by the tumor mimicked a secondary inhibition of 11ß-hydroxylase (50). The tempo of pubertal progression is often rapid in patients with androgen secreting tumors (47-50). Growth velocity and skeletal maturation may be accelerated (48). Tumors in the testis, brain, or liver may secrete serum ß-human chorionic gonadotropin (hCG) that can stimulate testicular LH receptors to produce testosterone (51,52). Hence, boys with hCG secreting tumors may have testicular enlargement (51,52). Girls generally do not present with PA or precocious puberty due to hCG secreting tumors because in the absence of FSH estrogens are not synthesized. Ovarian sclerosing cell tumors and ovarian sex cord stromal tumors can secrete androgens and present with premature pubarche or virilization (47,53,54).

Exogenous androgen exposure from creams or gels containing testosterone, DHT or A4 can result in premature pubarche, and/or other androgenic signs (55,56). Exogenous steroids can be transferred to a patient by direct application, or via skin-

to-skin contact (55,56). In general, a thorough medical history can exclude the possibility of exogenous androgen exposure.

Central precocious puberty (CPP), also known as GnRH-dependent precocious puberty, is caused by early reactivation of the hypothalamic-pituitary-gonadal axis (57). CPP may present with pubic or axillary hair, but is clinically differentiated from PA by the presence of breast or testicular development (57). As in PA, androgens are elevated for age. Bone age and linear growth velocity are usually accelerated (58). In some instances, secondary CPP occurs associated with advanced skeletal maturation caused by virilizing tumors or untreated congenital adrenal hyperplasia (59-61).

PA is a diagnosis of exclusion. In other words, other potential etiologies need to be excluded based on medical history, clinical findings, or laboratory results (2,35,47). Typically, patients present with premature development of pubic hair, axillary hair, apocrine body odor, or acne (2,4). Characteristically, features of gonadarche are absent (2,62). Patients with PA tend to be heavier and taller than their peers (2). In a retrospective cohort, girls with PA demonstrated greater linear growth and weight gain beginning in early childhood (4,63). The age at menarche was found to be slightly earlier than expected in Finnish and Catalan girls who had presented with PA (64,65).

Laboratory data typically reveal DHEAS and DHEA concentrations consistent with the stage of pubic hair development. Decreased IGFBP1 and increased IGF-1 concentrations have been described in girls with PA (66). However, it has been documented that clinical signs of adrenarche and pubarche do not always correlate well with circulating levels of DHEA, DHEAS, or androstenedione (63,67). In these cases, prepubertal intracrine metabolism within target tissues is speculated to modulate the clinical features (68). Armengaud *et al*. proposed that an early morning basal 17-OHP concentration greater than 200 ng/dL is 100% sensitive and 99% specific for non-classical 21-hydroxylase deficiency; these data suggest that early morning 17-OHP concentrations less than 200 ng/dl would distinguish patients with PA from those with non-classical CAH (35).

Advanced Bone Age and Height Predictions

PA may be accompanied by advanced skeletal maturation as assessed by bone age X-rays. If the bone age is significantly advanced, the likelihood of identifying a child with non-classical CAH is increased (69).

In some studies, patients with PA have been reported to have decreased predicted adult heights (70,71). Yet, other studies suggest that advanced bone age has minimal effect on predicted adult heights in this patient population (64,72,73). A larger cross-sectional study showed that although advanced bone age was common in PA, the impact on predicted adult height appeared to be minor (74). One limitation is that all aforementioned cross-sectional studies lack final height data. A retrospective review of medical records indicated that 85 girls with PA achieved adult heights within their mid-parental range (75).

Though the exact etiology of the advanced bone age observed in some patients with PA remains unclear, many factors including insulin, DHEAS, IGF-1, and leptin concentrations as well as the rate of weight gain influence the tempo of bone maturation. Advanced bone ages are found in approximately 25% of obese children (76). Obesity appears to have a potentiating effect on bone age advancement in children with PA (71,77). In a cross-sectional study involving Korean children, bone age advancement was positively correlated with androstenedione and testosterone concentrations independent of BMI (78).

Genetics

In a 1994 twin study, adrenal androgen excretion showed a heritability of 58% in prepubertal and pubertal subjects (79). Occasionally, premature pubarche can occur without a rise in adrenal androgens (80). In these cases, the bone age is not advanced, the growth velocity is not accelerated for age, and DHEAS concentrations are not elevated (80). It has been suggested that these individuals have increased androgen receptor sensitivity to low circulating androgen concentrations (80). Among a small number of girls (n=25), the length of the polyglutamine tract, which is composed of a variable number of CAG repeats in the androgen receptor (*AR*/*NR3C4*) gene, was decreased and methylation of the *AR* gene was decreased (80). These characteristics may be associated with increased androgen receptor sensitivity to androgens (80). However, no differences in CAG repeat number were found among Korean girls with premature pubarche, but the mean DHEAS concentration was higher in the premature pubarche group compared to the control group indicating that some girls likely had PA and not just premature pubarche (81).

The diallelic melanocortin-2 receptor promoter polymorphism for the ACTH receptor (*MC2R*-2 T>C) has been associated with PA (82). Children with the *MC2R* -2 T>C polymorphism had higher baseline ACTH, DHEA, and androstenedione levels than controls (82). Though the mechanism by which the *MC2R*-2 T>C affects adrenarche remains unclear, this result points toward the potential role of ACTH and its receptor in the etiology of PA.

In both Catalan and Caucasian Oxford populations, variation at aromatase SNP_50 has been associated with premature

pubarche and PCOS (83). Since aromatase catalyzes the conversion of androgens to estrogens, this finding may be relevant to the etiology of PA and PCOS in girls (83). Genetic variations in the aromatase gene have been suggested to contribute to androgen excess through impaired conversion of androgens to estrogens (83).

Heterozygosity for *CYP21A2* mutations has also been associated with PA in some populations (84-86). The A→G single nucleotide polymorphism in the IGF-1 receptor (*IGF1R*) gene has been associated with higher IGF-1 concentrations (87). The frequency of this SNP was increased in a small cohort of American children with PA (87). In a Finnish cohort, common polymorphisms in the *POR*, *SULT2A1*, and *HSD11B1* genes were not associated with PA (88).

Risk for PCOS

Though previously considered a benign variant of normal pubertal development, PA may be associated with an increased risk to develop polycystic ovary syndrome (89-99). Studies of Catalan girls have shown a 45% incidence of PCOS in women who had previously been diagnosed with premature pubarche (89). Low birth weight followed by excessive weight gain during early childhood has been associated with PA, hyperinsulinemia, and central adiposity in some studies (93).

Several studies investigating the relationships between PA and hyperinsulinemic androgen excess have involved a cohort of Catalan girls with PA (65,72,73,83,89,93-99). Findings in this cohort have included dyslipidemia, increased visceral fat, and altered concentrations of inflammatory markers (94). In addition, first-degree relatives of these girls have a higher risk for impaired glucose tolerance, type 2 diabetes, hyperandrogenism, and gestational diabetes mellitus (95). In this cohort, hyperinsulinemia was correlated with the degree of ovarian hyperandrogenism among the girls who developed hyperinsulinemic androgen excess (96). Prenatal growth restraint such as intrauterine growth restriction followed by rapid postnatal weight gain appear to be associated with hyperinsulinemic androgen excess and risk for progression to PCOS (97). A recent paper showed that children born large for gestational age had lower DHEAS concentrations and speculated that early genetic and/or epigenetic factors modulated adrenal androgen secretion and onset of adrenarche (100).

The estimated incidence of PCOS worldwide is 6-15% (101). Women with PCOS have been found to have higher incidence of cardiovascular risk factors, including insulin resistance, hyperinsulinemia, glucose intolerance, increased abdominal adiposity, dyslipidemia, hypertension, and endothelial dysfunction (99,102). Since an association has been made between PA, adolescent hyperinsulinemic androgen excess, and PCOS, metformin treatment has been utilized to normalize circulating insulin, IGFBP1, lipids, and leptin concentrations (99). However, long term longitudinal studies are essential to confirm these initial promising results and potentially identify which factors predict progression from PA to PCOS (103).

Obesity, Insulin, Metabolic Syndrome and Premature Adrenarche

Hyperinsulinemia and/or insulin resistance are common in children with PA and may influence the relationship between PA and PCOS. Previous studies have demonstrated associations between PA, hyperinsulinemia, insulin resistance, and ovarian hyperandrogenism (66,72,104). *In vitro*, IGF-1 and insulin potentiate LH-stimulated androgen synthesis in theca-interstitial cells, suppress SHBG production in hepatoma cell lines, and induce steroidogenic enzymes in cultured human adrenocortical cells (105-107). PCOS and PA are also both associated with decreased IGFBP1 concentrations, which are inversely correlated with fasting insulin levels and ACTH-stimulated adrenal steroid levels (66). Insulin also decreases SHBG synthesis resulting in elevated circulating free androgen concentrations (108). SHBG concentrations may represent a biomarker associated with insulin resistance and increased risk for development of type 2 diabetes (109).

The molecular basis of the insulin resistance and hyperinsulinemia in PA is likely multi-factorial. Obesity generally decreases insulin sensitivity, resulting in compensatory hyperinsulinemia to maintain euglycemia (110,111). With obesity, one potential mechanism is that adipose tissue lipid storage is saturated leading to impaired insulin-suppressed lipolysis resulting in increased circulating free fatty acid concentrations and ectopic fat storage (110,111). This alteration in lipid storage can provoke a shift to a pro-inflammatory state accompanied by increased peripheral insulin resistance and metabolic dysfunction (110,111). In addition to obesity, other potential mechanisms for insulin resistance include defective post-receptor insulin signaling, increased free fatty acids (FFAs), hyperandrogenemia, and altered cytokine secretion and action (112).

The metabolic syndrome is defined as a cluster of cardio-metabolic risk factors that predict the propensity to develop type 2 diabetes and cardiovascular disease (113). Although several definitions have been delineated for metabolic syndrome in children, the presence of metabolic syndrome in children and adolescents is associated with an increased risk to develop type 2 diabetes in adulthood (114). All available definitions of the metabolic syndrome in children include components representing obesity (BMI or waist circumference), dyslipidemia (high triglycerides and low HDL cholesterol

concentrations), elevated blood pressure, and glucose metabolism (115). Using a metabolic syndrome severity score to account for significant sex- and racial/ethnic differences in these components among children, the longitudinal Princeton Lipid Cohort Study reported that higher childhood metabolic syndrome severity scores were associated with development of cardiovascular disease and type 2 diabetes (116).

Insulin resistance has been described among girls with PA. In a homogenous Catalan population, insulin resistance, dyslipidemia, increased waist circumference, and increased total fat mass were reported in girls with PA (96,99,117). Williams *et al*. also found that androgens were associated with higher triglycerides concentrations, greater waist circumference, and higher lean mass (90). However, these findings have not been uniformly corroborated by other groups (118).

In a cross-sectional study involving 30 children with PA and 28 controls, obesity appeared to be the driver of metabolic risk in children with PA because metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III, was only seen in obese patients, whether or not they had PA (90). This association between obesity and PA informed on the relationship between PA and bone age advancement (77). Sopher *et al*. suggested the possibility of a hormone factor which exaggerates the effect of obesity on bone age maturation in children with obesity and/or PA (119). Despite comparable DHEAS concentrations, increased percent body fat and increased occurrence of clinical signs of adrenarche were more common among Finnish girls compared to Finnish boys leading to the speculation that the sexual dimorphism in the incidence of PA could reflect sex-dependent differences in peripheral androgen metabolism or action as modified by adipose tissue (120). The lack of conclusive data emphasizes the need for further study of the possible mechanism(s) linking PA, insulin sensitivity, insulin secretion, obesity, dyslipidemia, inflammation, PCOS, and the metabolic syndrome.

Neurobiological Development

Puberty is characterized by changes in physical development, hormone concentrations, social experiences, and neurobiological development. The precise relationship of adrenarche and increasing DHEA and DHEAS concentrations to neurobiological development is unclear. Although adrenarche has been considered to be limited to humans and a few non-human primates, detailed investigations demonstrated increased DHEA and DHEAS secretion accompanied by morphological differentiation of the ZR occur during the first few weeks of life in rhesus monkeys (121,122). These studies suggest that adrenarche defined as increased DHEA/DHEAS secretion and morphological changes in the ZR may occur in some Old World primates, but likely during a different developmental window (121,122). Thus, it has been suggested that this evolution in the timing of adrenarche has led to extended brain development in humans associated with synaptic pruning (123).

The changes in development and hormone concentrations during adrenarche and gonadarche may influence psychosocial development. Alternatively, environmental exposures such as nutrition and stress may modulate neurobiological maturation. A cross-sectional study showed that first generation female migrants from Bangladesh had earlier onset of adrenarche than second generation girls, native British girls, and girls still living in Sylhet, Bangladesh (124). Although attributed to improved nutrition and catch-up, the stress of the novel environment could be a factor.

Girls with both PA and lower executive functioning had higher externalizing and anxiety symptoms (125). Compared to girls with "on-time puberty", some girls with PA have been reported to manifest more oppositional, defiant, anxiety, mood, or disruptive behavior disorders suggesting a greater vulnerability to psychopathology than "on-time" adrenarche girls (126). The existence of a developmental track that starts with prenatal stress associated with maternal depression and leading to elevated childhood cortisol concentrations, PA, and adolescent mental health issues has been postulated (127).

Findings from studies comparing DHEA/DHEAS concentrations with brain and pituitary morphology showed a positive correlation with cortical thickness in prefrontal areas and pituitary volume (128,129). In a longitudinal study involving healthy children, the structural development of specific subcortical brain regions was found to change during puberty (130). Amygdala and hippocampus volume increased across puberty whereas the volumes of other structures including the nucleus accumbens, caudate, putamen and globus pallidus decreased (130). A systemic review concluded that, in general, earlier onset of adrenarche and higher DHEA/DHEAS concentrations were associated with more mental health problems (131). Hence, adrenarche represents a sensitive period for neurobiological development.

Evaluation and Treatment

Again, PA is a diagnosis of exclusion. Following diagnosis, no specific medical treatment is generally necessary. Nevertheless, regular clinical re-evaluations are recommended to assess linear growth velocity, weight gain, skeletal maturation, and progressive androgen excess. To track potential progression of androgen excess, adrenal androgen levels may be measured annually. After menarche, girls with a history of PA may be followed annually. If menstrual regularity has not been established two years post-menarche, re-evaluation for progression to PCOS may be warranted.

Annual fasting measures of insulin resistance, i.e. fasting glucose to insulin ratio (FGIR), HgbA1C, or homeostatic model assessment of insulin resistance (HOMA), and lipid levels may be helpful because of the potential to develop signs and symptoms of comorbidities such as the metabolic syndrome. If there is evidence of insulin resistance, metformin may be recommended. For irregular menses and/or hirsutism, treatment with oral contraceptive pills may be beneficial. In all cases, adherence to a low-fat, low-glycemic index diet and regular exercise is recommended to mitigate risk for comorbidities and to promote healthy skeletal growth and appropriate pubertal development. Given the potential psychological consequences of premature adrenarche and abnormal pubertal timing on children, monitoring the physical and psychological development of children with premature adrenarche will be worthwhile.

Conclusion

The specific physiologic mechanisms instigating the onset of increased DHEA and DHEAS secretion by the zona reticularis remain to be clarified. Available data support the statement that PA is usually a benign maturational phenomenon that is a diagnosis of exclusion. Nevertheless, children with PA have a higher risk for obesity, impaired carbohydrate metabolism, dyslipidemia, advanced skeletal maturation, and psychopathology during childhood. Alterations in steroidogenesis, neuroendocrine function, insulin sensitivity, genetic factors, and environmental exposure likely influence the risk for progression from PA to PCOS.

Disclosure

None of the authors have conflicts of interest to disclose.

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