REVIEW

Premature adrenarche: novel lessons from early onset androgen excess

Jan Idkowiak, Gareth G Lavery, Vivek Dhir, Timothy G Barrett, Paul M Stewart, Nils Krone and Wiebke Arlt
School of Clinical and Experimental Medicine, Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Birmingham B15 2TT, UK
(Correspondence should be addressed to W Arlt; Email: w.arlt@bham.ac.uk)

Abstract

Adrenarche reflects the maturation of the adrenal zona reticularis resulting in increased secretion of the adrenal androgen precursor DHEA and its sulphate ester DHEAS. Premature adrenarche (PA) is defined by increased levels of DHEA and DHEAS before the age of 8 years in girls and 9 years in boys and the concurrent presence of signs of androgen action including adult-type body odour, oily skin and hair and pubic hair growth. PA is distinct from precocious puberty, which manifests with the development of secondary sexual characteristics including testicular growth and breast development. Idiopathic PA (IPA) has long been considered an extreme of normal variation, but emerging evidence links IPA to an increased risk of developing the metabolic syndrome (MS) and thus ultimately cardiovascular morbidity. Areas of controversy include the question whether IPA in girls is associated with a higher rate of progression to the polycystic ovary syndrome (PCOS) and whether low birth weight increases the risk of developing IPA. The recent discoveries of two novel monogenic causes of early onset androgen excess, apparent cortisone reductase deficiency and apparent DHEA sulphotransferase deficiency, support the notion that PA may represent a forerunner condition for PCOS. Future research including carefully designed longitudinal studies is required to address the apparent link between early onset androgen excess and the development of insulin resistance and the MS.

European Journal of Endocrinology (2011) 165 189–207

Introduction

Adrenarche refers to the developmental maturation of the adrenal gland, observed only in the human, chimpanzee and gorilla (1–4). At adrenarche, the innermost layer of the human adrenal cortex, the zona reticularis (ZR), starts to produce increasing amounts of the androgen precursor DHEA and its sulphate ester DHEAS (5). The term ‘adrenarche’ was coined by Fuller Albright and Nathan Talbot in the 1940s when they linked the developmental rise in adrenal androgens to the appearance of pubertal and axillary hair, which they called ‘sexual hair’ (6–8). Soon thereafter, Lawson Wilkins’ group described a group of girls who developed pubic and axillary hair before the age of 8 years (9), a condition they termed ‘premature pubarche’ (PP). They considered PP a benign constitutional variant with no impact on later life if ‘adrenal tumours’ or ‘adrenal hyperplasia’ were excluded as underlying causes (9).

Adrenarche is a physiological mystery as it is not well understood how the development of the ZR is initiated or controlled (see (5) for review) nor why adrenal androgens are significant for human pre-pubertal development. Adrenal androgens contribute to changes in body composition and transient growth acceleration but without having a major impact on final height or subsequent developmental milestones like puberty. From the evolutionary perspective, it has been suggested that adrenarche is a key component of ‘juvenility’, a period that emerges during evolution in the late Hominids and prolongs the transition from childhood to adolescence and adult life; juvenility may serve the adaptation of body composition and metabolic status to environmental conditions (10, 11). Another interesting hypothesis refers to the neuromodulatory effects of DHEAS that may help to protect more metabolically active regions of the cerebral cortex to support brain maturation in the developing pre-pubertal child (12).

Premature adrenarche (PA), the precocious appearance of adrenarche, is a phenomenon increasingly receiving attention, as more evidence emerges for an intriguing link between early onset androgen excess and metabolic disease. This review aims to provide an overview of the current understanding of PA and its clinical implications. We specifically highlight novel insights into this multi-faceted condition provided by the recent discovery of two novel monogenic conditions that manifest with PA.
Adrenarche, pubarche and puberty

Circulating DHEAS is high in the immediate neonatal period, but quickly drops below the limit of detection during the first few months of life (13, 14), subsequent to the involution of the foetal zone of the adrenal cortex. The re-appearance and accelerating increase in circulating DHEAS, i.e. adrenarche, have previously been perceived as a relatively sudden surge, physiologically occurring between 6 and 8 years of age (15, 16). However, previous studies employing immunoassays for determination of serum DHEAS obviously only picked up increasing levels once they reached above the lower limit of detection. However, a recent study applied a highly sensitive method for the analysis of 24 h urinary androgen metabolite excretion, gas chromatography/mass spectrometry (GC/MS); results clearly indicate that adrenarche is a continuous developmental process, starting with a detectable increase in the excretion of DHEA and related androgenic steroids at least as early as 3 years of age (17). In addition, there was no sex difference in androgen excretion within the pre-pubertal and early pubertal age groups, and consequently, these results may challenge the sex differences in the well-accepted age cut-offs for PA, i.e. 8 years in girls and 9 years in boys. However, these are derived from Marshall and Tanner’s clinical observations that the appearance of pubic hair occurs about 1 year earlier in girls than in boys (18, 19).

In normal development, the first appearance of pubic hair, i.e. pubarche, from the age of 8 years onwards is the direct result of the physiological rise in adrenal androgen production during adrenarche. DHEA is converted to active androgens in the gonads and peripheral target tissues of androgen action including the skin, resulting in the development of pubic and also axillary hair. Women with adrenal insufficiency without physiological DHEA production suffer from lack of axillary and pubic hair, which reappears after initiation of DHEA replacement therapy (20). A recent study in adolescent girls with secondary adrenal insufficiency demonstrated onset and progression of pubic and axillary hair following DHEA replacement (21). Physiologically, increasing androgen production during adrenarche manifests with distinct changes in body odour and oily skin and hair, followed by the first appearance of pubic and axillary hair. In addition, the rise in adrenal androgens can result in transient growth acceleration and contributes to bone maturation (22–24).

Several studies have demonstrated that adrenarche and pubarche are a causally related sequence (25, 26) and dissociation of the two events is rarely observed. One of these exceptions is Turner syndrome in which an early onset of adrenarche with increased DHEA and DHEAS levels has been documented, but concurrently delayed pubarche in those girls who developed premature ovarian failure (27). Increased levels of DHEA and DHEAS despite low circulating levels of active androgens have also been described in premature ovarian failure of autoimmune origin (28, 29). The ovary not only synthesises DHEA but also takes up DHEA produced in the adrenals and converts it to active androgens (30). Possible disruption of this capacity in premature ovarian failure will result in increased levels of the androgen precursor DHEA but decreased active androgens, which would explain the apparent dissociation of adrenarche and pubarche in this condition.

Importantly, adrenarche generally appears to represent a developmental process independent of the maturation of the gonads (25, 26). Gonadarche, i.e. the onset of sex steroid production by the gonads, manifests with testicular enlargement and penile growth in boys and breast development and menarche in girls. Children with precocious puberty have been shown to have no corresponding advance in the timing of adrenarche: their basal and ACTH-stimulated adrenal androgens are lower than in children matched for pubertal stage and only slightly higher than in age-matched children (31, 32). Conversely, children with isolated hypogonadotrophic hypogonadism and subsequent lack of spontaneous puberty were found to have no corresponding delay in adrenarche (25, 26).

Although pubertal onset crucially relies on the emerging activity of the GnRH pulse generator in the hypothalamus and subsequent LH/FSH release from the anterior pituitary, no centrally derived factor regulating adrenarche has been identified yet. An N-terminal proopiomelanocortin fragment termed cortical androgen stimulating hormone (CASH) has been proposed as crucial to the regulation of adrenarche (33), but no convincing in vitro data for its action have been presented yet (34). A lack of adrenarche has been observed in patients with familial glucocorticoid deficiency due to disruption of ACTH signalling (35). However, in patients with combined pituitary hormone deficiency due to Pit1 (POU1F1) mutations, who are characterised by normal ACTH and cortisol secretion and spontaneous onset and progression of puberty, the absence or delay of adrenarche and pubarche has been documented (36). Thus, ACTH has a permissive effect on the initiation of adrenal androgen production, but its presence alone does not suffice. In addition, an ACTH receptor polymorphism has been found to be associated with the severity of PA also indicating a modulatory effect of the hypothalamic–pituitary–adrenal (HPA) axis in this condition (37). In the same cohort, Lappalainen et al. (38) could also show that mean CAG repeat length of the androgen receptor (AR) gene is shorter in PA girls and that a polymorphic allele of the transcription factor TCF7L2, involved in the Wnt signalling pathway, was more frequent in PA subjects (39). However, genome-wide association studies in appropriately powered cohorts of children with early androgen excess are currently lacking. Elucidating genetic variability in large-scale cohorts by applying next generation sequencing technologies will certainly be subject of future
studies aiming to identify novel regulators and predictors of PA.

Finally, there is some evidence that adrenarche and gonadarche are interdependent in the physiological situation. A prospective cohort study in 109 healthy children showed that adrenal androgens do influence pubertal timing and importantly indicate that adrenarche triggers the pattern of subsequent pubertal development: higher pre-pubertal urinary androgen excretion correlated with an earlier onset of pubertal growth and penile growth respectively, and a shorter duration of pubertal growth spurt (40). Furthermore, adrenal androgens are positively correlated with diaphyseal bone strength during adrenarche and in late puberty (22, 41). These data suggest that adrenal androgens may either directly or after peripheral conversion (e.g. to oestrogens) modulate the GnRH pulse generator, thereby fine-tuning pubertal development. Nutritional status has been suggested as linked to adrenal androgen production (40) and obese children have significantly increased serum DHEAS levels (42), with evidence of advanced bone maturation and less but significantly decreased final height (43). As consistently shown in a number of different study populations, final height is not significantly affected in children with PA (23, 44–47) but they have earlier transient pre-pubertal growth acceleration, i.e. they are taller than their peers upon entering puberty. Also, compared with controls matched for chronological age, bone age in PA is significantly advanced (23, 45, 48), whereas height-adjusted bone mineral density is similar to age-matched controls, with evidence for a higher body fat mass in PA (49).

PA: definitions and differential diagnosis

It is important to note that PA is not equivalent to PP. Indeed, there is some inconsistency in the literature where PP is often used synonymously for PA. First, some of these studies only scored the onset of pubic hair growth but lack biochemical confirmation of increased adrenal androgen production. Second, equating the two terms would limit the attention to the development of pubic hair only, but ignore other signs of increased androgen action including adult-type body odour and oily hair and skin (23, 46, 47, 50, 51). Conversely, some investigators have defined PA very strictly as the biochemical detection of a premature increase in circulating adrenal androgens irrespective of the clinical presentation (52). The additional use of the term ‘exaggerated adrenarche’ has created further confusion, as it has been used to describe adrenal androgen levels above the pubertal range in children of pre-pubertal age (53, 54) but also as a definition for the presence of exaggerated clinical features of androgen action associated with physiological, normal-timed adrenarche (55).

A recently proposed definition of PA is the concurrent presence of adrenal androgen levels increased above the age- and sex-specific reference range and clinical signs of an increase in androgen action, such as adult-type body odour, oily hair and skin and/or PP occurring before the age of 8 years in girls and 9 years in boys (56). We consider this a very useful definition for clinical purposes (Table 1). The definition of the exact age limits should take influences of ethnicity into account. In Caucasian populations, two studies found pubic hair Tanner stage 2 or above before the age of 8 years in girls in 0.6 and 0.8% of US American and Lithuanian girls respectively (57, 58). By contrast, a fivefold higher incidence of PP was reported in girls of Afro-American descent (59). All these studies focussed on the premature appearance of pubic hair only and did not report on the incidence of other signs of increased androgen action such as adult-type body odour or oily skin. Thus the overall incidence of PA may well be higher. Generally, the reported prevalence of PA is about tenfold higher in girls than in boys (60), which may at least in part be explained by a sex-specific detection and reporting bias.

Constitutional or idiopathic PA (IPA) is most often observed, and is a diagnosis of exclusion. Distinct conditions manifesting PA include milder and non-classic variants of congenital adrenal hyperplasia (CAH) that have been diagnosed in 0–40% of children with PP (51, 61–65), depending on the pre-selection bias applied to the studied cohorts. Baseline blood sampling for measurement of DHEAS, androstenedione, 17α-hydroxyprogesterone (17OHP), testosterone, and sex hormone binding globulin (SHBG) will be generally sufficient to confirm increased adrenal androgens and to differentiate between IPA, CAH, and virilising tumours (55, 61). Other causes potentially underlying a presentation with PA are summarised in Table 1.

If in addition to the clinical signs and symptoms associated with PA, progressive signs of pubertal development are also present, such as breast development or menarche in girls and penile or testicular growth in boys, a diagnosis of precocious puberty or precocious pseudo-puberty has to be considered (Table 1). The clinical picture of these two distinct conditions is relatively similar. However, they can be distinguished by analysing the gonadotrophin response to GnRH stimulation. Centrally driven true precocious puberty results from premature activation of the hypothalamic GnRH pulse generator, resulting in upregulated gonadotrophins that increase further after exogenous GnRH stimulation. Constitutional or idiopathic precocious puberty is the most frequent underlying cause, in particular, in girls aged 6 years or older while more than half of affected boys have an identifiable cause of precocious puberty. A lesion of the central nervous system affecting the hypothalamic–pituitary region has to be excluded and is a frequent cause of the condition in particular in children presenting at age 6 years or
<table>
<thead>
<tr>
<th>Definition</th>
<th>Causes</th>
<th>Laboratory investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premature adrenarche</strong></td>
<td>Increased adrenal androgen secretion above the age- and sex-specific normal reference range before the age of 8 years in girls and 9 years in boys (precocious biochemical adrenarche)</td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td>Clinical signs of androgen action before the age of 8 years in girls and 9 years in boys including</td>
<td></td>
</tr>
<tr>
<td>Pubic hair (premature pubarche), axillary hair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AND</td>
<td>No signs of pubertal development (i.e. no development of secondary sexual characteristics including breast development in girls or penile growth in boys)</td>
<td></td>
</tr>
<tr>
<td><strong>Precocious pseudo-puberty</strong></td>
<td>Development of secondary sexual characteristics (penile growth, breast development and menarche) before the age of 8 years in girls or 9 years in boys AND Low gonadotrophins before and after GNRH stimulation</td>
<td></td>
</tr>
<tr>
<td>GNRH independent; usually non-harmonic chronology of sexual characteristics, e.g. lack of bilateral testicular enlargement in boys (exceptions: gonadal and familial testotoxicosis)</td>
<td></td>
<td>Gonadotrophins remain low after GNRH stimulation</td>
</tr>
<tr>
<td>Also termed peripheral precocious puberty</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Precocious puberty</strong></td>
<td>Development of secondary sexual characteristics (testicular/penile growth, breast development and menarche) before the age of 8 years in girls or 9 years in boys AND Increase of gonadotrophins after GNRH stimulation</td>
<td></td>
</tr>
<tr>
<td>GNRH dependent; usually harmonic chronology of sexual characteristics, e.g. bilaterally enlarged testicular volume in boys</td>
<td></td>
<td>Gonadotrophins increase after GNRH stimulation</td>
</tr>
</tbody>
</table>
younger. Precocious pseudo-puberty is defined by the occurrence of sexual characteristics driven by GNRH-independent peripheral sex steroid production, most frequently without concurrent signs of gonadal maturation, i.e. no testicular enlargement in boys (Table 1). Accordingly, in precocious pseudo-puberty, the gonadotrophins are low and remain low after GNRH stimulation. The condition is rare and most of the identified cases in boys are due to simple virilising and non-classic CAH variants. In CAH, transition from precocious pseudo-puberty to secondary central precocious puberty has been observed and is thought to be due to the induction of the GNRH pulse generator by persistently increased sex steroids (66). Pubertal progression in central precocious puberty is efficiently halted by GNRH analogues blocking GNRH action (67, 68).

Metabolic implications of PA

Traditionally, IPA has been considered to be an extreme variation of the normal (9, 23, 45). However, a number of studies in children with early onset androgen excess provide increasing evidence for the notion that IPA in girls may precede the development of polycystic ovary syndrome (PCOS). PCOS manifesting during adolescence or early adulthood carries a significantly increased risk for developing the metabolic syndrome (MS) (52, 69–71) and represents the leading cause of female infertility (72–74). IPA and adolescent PCOS are linked by two similarities, early onset androgen excess and an increased prevalence of insulin resistance. The following section reviews the available evidence associating IPA with insulin resistance, MS and PCOS.

Metabolic risk factors in PA

The first evidence for a link between premature androgen excess and MS emerged in 1995 from a study in American–Hispanic girls who presented with PP and evidence of insulin resistance (75) (Table 2). Later on, Ibanez et al. (76) published a number of case–control studies in lean Spanish (Catalonian) girls with a history of PP that showed evidence of insulin resistance based on both fasting insulin levels and the insulin response to a standard oral glucose tolerance test (OGTT) (76–80). Interestingly, these observations could not be confirmed in boys from the same population (81) but similar findings were obtained in pre-pubertal boys with PA from North America (82). In PP girls from North America, an inverse correlation between insulin sensitivity and ACTH-stimulated Δ5-androgen precursors (17-hydroxypregnenolone, DHEA) has been found; however, the study population was not body mass index (BMI) matched (83). Overall, impaired insulin sensitivity is a consistent finding in the majority of studies (Table 2).

Ibanez et al. (78) could show that Catalan PP girls develop significant dyslipidaemia, a finding indicative of an increased cardiovascular risk profile and consistently found in PCOS (84). Moreover, Catalan PP girls had increased waist circumference, waist-to-hip-ratio and total fat mass in comparison to their BMI-matched peers (85). Dyslipidaemia and elevated blood pressure were also found in smaller cohorts of Turkish (86) and Brazilian (87) PP girls. However, the validity of these latter studies was also hampered by a lack of BMI-matched controls and insulin resistance was only observed in obese PP girls. In a recent case–control study from Turkey, PP girls had elevated lipoprotein(a) levels, another risk factor for cardiovascular morbidity (88). By contrast, in Finnish girls with IPA, evidence of insulin resistance was identified using the OGTT, but no alterations in lipid metabolism or blood pressure were found (56). Similarly, in recent studies from Greece, Andalusia and Scotland girls with IPA had normal lipid profiles (55, 89, 90).

Accumulation of visceral fat has been related to an increased risk of cardiovascular disease evolving through distinct metabolic and inflammatory perturbations (91) and adipose tissue is increasingly recognised as an active endocrine organ secreting adipokines that act as immunoendocrine signals linking obesity to the development of atherosclerosis. A pro-inflammatory shift in the adipokine profile including increased secretion of interleukin 6 (IL6), plasminogen activator inhibitor 1 (PAI1) and leptin has been shown to positively correlate with measures of insulin resistance (92, 93) and is a feature frequently found in the context of PCOS (94). Several studies in IPA girls from different ethnic backgrounds studied in comparison to BMI-matched controls have shown a pro-inflammatory shift of their adipokine profile comprising higher levels of TNFα, IL8, C-reactive protein (CRP), PAI1 and a decrease in tissue plasminogen activator (t-PA) (79, 89, 95).

To date, only a single study has assessed the presence of the diagnostic consensus criteria for the childhood MS in IPA girls, demonstrating an increased frequency of childhood MS in comparison to BMI-matched controls, both according to modified United States (US) National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III (ATPIII) criteria (24 vs 10%) and modified World Health Organization (WHO) criteria (16 vs 5%) (56).

PA and the PCOS

Ibanez et al. (72) published a number of studies investigating 35 adolescent Catalan girls with a history of PP and found that 16 (45%) went on to develop PCOS with hirsutism, menstrual disturbances and elevated androgen levels (Table 3). Ovarian stimulation with the GNRH analogue leuprolide acetate in this cohort resulted in exaggerated levels of 17OHP and androstenedione and correlated with baseline
<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Controls</th>
<th>Population</th>
<th>Evidence of IR?</th>
<th>Measures and outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppenheimer et al. (75)</td>
<td>Pre-pubertal PP girls with (n=5) and without (n=7) acanthosis nigricans</td>
<td>None</td>
<td>American–Hispanic</td>
<td>Yes</td>
<td>Increased insulin resistance (HOMA-IR) in PP girls with acanthosis nigricans</td>
</tr>
<tr>
<td>Ibanez et al. (76)</td>
<td>Adolescent girls with a history of PP (n=24)</td>
<td>n=21 matched for age, sex and BMI</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Higher serum insulin levels during OGTT in all PP girls, insulin sensitivity inversely correlated with the increase in 17OHP and androstenedione following GNRH analogue</td>
</tr>
<tr>
<td>Ibanez et al. (77)</td>
<td>PP girls (n=98; divided in five subgroups from pre- to post-pubertal)</td>
<td>n=86 matched for Tanner stage and bone age</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>All PP subgroups showed an increased fasting insulin resistance index, increased mean blood glucose and serum insulin, increased early insulin response to glucose (OGTT), elevated free androgen index, decreased SHBG and IGFBP1 levels</td>
</tr>
<tr>
<td>Ibanez et al. (78)</td>
<td>PP girls (n=81; divided into five subgroups from pre- to post-pubertal)</td>
<td>n=55 matched for Tanner stage and bone age</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>In all PP subgroups higher mean serum insulin after OGTT, increased triglycerides (TG), VLD-TG, VLD-cholesterol, LDL/HDL-ratio and decreased SHBG</td>
</tr>
<tr>
<td>Potau et al. (81)</td>
<td>Boys with a history of PP (n=29)</td>
<td>n=29 matched for age and sex</td>
<td>Spanish (Catalan)</td>
<td>No</td>
<td>No difference in serum insulin and plasma glucose during OGTT</td>
</tr>
<tr>
<td>Vuguin et al. (83)</td>
<td>Pre-pubertal PP girls (n=35); n=25 with history of T2DM and acanthosis nigricans</td>
<td>None</td>
<td>American–Black/ Hispanic</td>
<td>Yes</td>
<td>PP girls with decreased insulin sensitivity and higher BMI had higher ACTH-stimulated androgens and higher IGF1 levels compared with PP girls with normal insulin sensitivity</td>
</tr>
<tr>
<td>Silfen et al. (103)</td>
<td>Pre-pubertal obese PP girls (n=17)</td>
<td>n=9 matched for age, sex and BMI</td>
<td>American–Hispanic</td>
<td>No</td>
<td>IGF1 levels in PP girls were elevated and positively correlated to androgen levels. No differences in fasting insulin and insulin response after OGTT</td>
</tr>
<tr>
<td>Denburg et al. (82)</td>
<td>Pre-pubertal PP boys (n=11)</td>
<td>n=8 matched for age and sex</td>
<td>American</td>
<td>Yes</td>
<td>PP boys had higher IGF1 levels, higher fasting insulin and a higher AUC insulin during the OGTT</td>
</tr>
<tr>
<td>Meas et al. (116)</td>
<td>Post-menarcheal PP girls (n=27)</td>
<td>n=25 matched for age and sex</td>
<td>French</td>
<td>No</td>
<td>No significant difference in fasting serum insulin, insulin and glucose levels (AUC) during OGTT and fasting lipids</td>
</tr>
<tr>
<td>Ibanez et al. (79)</td>
<td>Pre-pubertal PP girls (n=33)</td>
<td>n=13 matched for age, sex, and Tanner stage</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Higher levels of plasminogen activator inhibitor 1 (PAI1-act) in PP girls. In small follow-up sub-cohort (n=10; 3 years), PAI1-act positively correlates with insulin and androgen levels</td>
</tr>
<tr>
<td>Ibanez et al. (85)</td>
<td>Pre- to post-pubertal PP girls (n=67)</td>
<td>n=65 matched for sex, pubertal stage and BMI</td>
<td>Spanish (Catalan)</td>
<td>NM</td>
<td>Increased waist circumference, waist-to-hip ratio and total fat mass in PP girls</td>
</tr>
<tr>
<td>Reference</td>
<td>Subjects</td>
<td>Controls</td>
<td>Population</td>
<td>Evidence of IR?</td>
<td>Measures and outcomes</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Potau et al. and Ibanez et al. (80, 85)</td>
<td>Pre- to post-pubertal PP girls (n=51)</td>
<td>n= 68 matched for sex, pubertal stage and BMI</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Increased fasting insulin, decreased fasting insulin sensitivity (HOMA-IR) and higher insulin levels during OGTT in PP girls are most closely related to cardiovascular risk factors (total/LDL cholesterol, TG, abdominal fat (DXA)). Fasting insulin levels were correlated with higher central fat mass (DXA) in PP girls</td>
</tr>
<tr>
<td>Teixeira et al. (87)</td>
<td>PP girls (obese and non-obese) (n=25)</td>
<td>n= 14 matched for age and sex</td>
<td>Brazilian</td>
<td>Yes</td>
<td>Higher fasting serum insulin, glucose, leptin and cholesterol levels only in obese PP girls</td>
</tr>
<tr>
<td>Güven et al. (86)</td>
<td>Pre-pubertal PP girls (n=24)</td>
<td>n= 13 matched for age</td>
<td>Turkish</td>
<td>NM</td>
<td>Unfavourable lipid profile and higher blood pressure in PP girls</td>
</tr>
<tr>
<td>Utriainen et al. (56)</td>
<td>Pre-pubertal PA girls (PP + PA (n=32), PA only (n=31)</td>
<td>n= 80 matched for age, sex and BMI</td>
<td>Finnish</td>
<td>Yes</td>
<td>Increased mean insulin during OGTT in all PA girls; increased fasting insulin, decreased SHBG and diagnostic criteria for childhood MS only in PA-PP group. No difference in lipid profile, glucose after OGTT and blood pressure</td>
</tr>
<tr>
<td>Andiran &amp; Yordam (88)</td>
<td>Pre- to post-pubertal PP girls (n=25)</td>
<td>n= 20 matched for age and sex</td>
<td>Turkish</td>
<td>No</td>
<td>No significant differences between fasting insulin and fasting insulin/glucose ratio between PP and controls. Lp(a) levels were higher in pubertal PP girls</td>
</tr>
<tr>
<td>Mathew et al. (95)</td>
<td>Pre-pubertal PP children (n=10)</td>
<td>n= 10 matched for age, sex and BMI</td>
<td>American</td>
<td>NM</td>
<td>Android fat distribution (DXA), higher TC/HDL-ratio and higher inflammation markers (TNFα, IL8) in PP group</td>
</tr>
<tr>
<td>Livadas et al. (89)</td>
<td>Adolescent girls with history of PP (n=45)</td>
<td>n= 19 matched for age, sex and BMI</td>
<td>Greek</td>
<td>Yes</td>
<td>Increased insulin resistance (HOMA-IR), higher baseline glucose and insulin levels, inflammation markers (CRP, PAI1) and androgen levels, decreased SHBG in PP girls. No differences in lipid profile</td>
</tr>
<tr>
<td>Paterson et al. (55)</td>
<td>Pre-pubertal PP girls (n=42) and boys (n=8)</td>
<td>None</td>
<td>Scottish</td>
<td>Yes</td>
<td>Higher fasting insulin levels in PP boys compared with age- and sex-related reference ranges</td>
</tr>
<tr>
<td>Larque et al. (90)</td>
<td>Pre-pubertal PP girls (n=22)</td>
<td>n= 20 matched for age and sex only</td>
<td>Spanish (Andalusia)</td>
<td>Yes</td>
<td>No difference in lipid metabolism, increased mean insulin levels in the OGTT and decreased postprandial adiponectin levels in PP girls</td>
</tr>
</tbody>
</table>

IR, insulin resistance; OGTT, oral glucose tolerance test; VDL, very low density; IGF1, insulin-like growth factor 1; IGFBP1, insulin-like growth factor binding protein 1; SHBG, sex hormone binding globulin; DXA, dual-energy X-ray absorptiometry; HOMA-IR, homeostasis model assessment-insulin resistance; PAI1, plasminogen activator inhibitor type 1; NM, not measured.
DHEAS and androstenedione levels at the time of presentation with PP (72, 96). The pattern of ovarian hyper-responsiveness was more pronounced during mid and late puberty (96) and associated with a degree of hyperinsulinaemia (76). Importantly, the same study sample also showed adrenal hyper-responsiveness following ACTH stimulation in pre- and post-puberty (97). By contrast, both ACTH and GnRH stimulation in a smaller sample of American PP adolescents revealed exclusively adrenal hyper-responsiveness (98). Based on the chronological pattern of adrenal hyper-responsiveness at presentation with PP followed by ovarian hyper-responsiveness after menarche, Ibáñez et al. (69) suggested that the underlying mechanism may be abnormal regulation or increased expression of the crucial androgen synthesising enzyme CYP17A1 in adrenals and ovaries resulting in androgen excess during adrenarche and puberty. Recently, two studies on pre-pubertal PP girls measured anti-Müllerian hormone (AMH), a marker of ovarian function that is increased in PCOS (99). In a cross-sectional study in Scottish PP girls (mean age 5.5–8.8 years), AMH levels were increased above the sex- and age-specific reference ranges (55), whereas a case–control study found normal AMH levels in Finnish PA girls (100).

Hyperinsulinaemia has been suggested as the common origin of both IPA and PCOS (69, 71). From a mechanistic point of view, this hypothesis seems to be plausible as insulin and insulin-like growth factors (IGF1 and IGF2) are able to stimulate steroidogenesis in human foetal and adult adrenal cells in vitro (101, 102). Low levels of IGF binding protein 1 (IGFBP1) would increase the amount of active unbound IGF1, and several studies in children with PP have described disturbances in the IGF system (77, 83, 103, 104). However, a recent meta-analysis examining the available evidence for a decrease in IGFBP1 in PCOS patients concluded that IGFBP1 levels inversely correlate with BMI and thus are primarily associated with obesity rather than androgen excess (105).

**Low birth weight and early onset androgen excess**

About 20 years ago, Barker et al. (106–108) introduced the hypothesis that malnutrition in prenatal life leads to metabolic programming of the foetal organs with subsequent development of insulin resistance and MS, if nutrients are available in abundance later in life. This hypothesis, also known as ‘thrifty phenotype hypothesis’ (109), was based on epidemiological associations between poor infant and foetal growth and the subsequent development of the MS and cardiovascular mortality in adult life. These findings are paralleled by a number of cross-sectional case–control studies in Catalan girls that consistently found premature androgen excess, hyperinsulinemia, dyslipidaemia and ovarian hyper-responsiveness associated with low birth weight (110–112) (Table 4). In a longitudinal follow-up study in Catalan babies born small for gestational age (SGA, i.e. birth weight <10th percentile), hyperinsulinaemic visceral adiposity without weight gain, low adiponectin and higher IGF1 levels started to develop at around 2–4 years of age (113–115). These metabolic changes were observed after sufficient weight gain of the SGA babies, usually occurring before 2 years of age. In addition, DHEAS was higher and SHBG was lower in SGA children between 6 and 8 years (115).

French, Finnish and Scottish girls presenting with PP did not have significantly lower birth weight than controls (55, 56, 116) (Table 4). Moreover, data from Finnish and British birth cohort studies indicate no correlation between the occurrence of PCOS and low birth weight (117, 118). In contrast, an association between low birth weight and PP in girls has been found in three different study samples from France, Italy and Australia (119–121). In a large birth cohort study from the UK investigating 770 boys and girls at 8 years of age, low birth weight was associated with higher adrenal androgen levels (122). Interestingly, children with a more rapid postnatal catch-up weight gain had higher adrenal androgen levels (122). In a cross-sectional study in 190 healthy children from the UK, urinary steroid excretion was measured at the age of 9 years (123). Androgen excretion was higher in children with low birth weight, showing up to 40% increase in excretion by a 1 kg decrease in birth weight. However, cortisol metabolite excretion was also higher in children with low birth weight, possibly indicating an altered function of the hypothalamo–pituitary–adrenal axis (123).

These observations suggest that the origins of premature androgen excess and associated disorders such as childhood MS and PCOS may in some cases already be defined by the pre-natal environment. However, most of this evidence derives from investigations in the Catalonian population and other studies performed in children from diverse ethnic backgrounds are contradictory. Thus more research and in particular well-controlled longitudinal studies are required for a proper assessment of metabolic risk. However, low birth weight followed by excessive catch-up weight gain may initiate a pattern of events leading to the clustering of metabolic complications, with the successive manifestation of PA, PCOS and the MS (Fig. 1).

**Adrenal steroidogenesis during adrenarche**

A basic understanding of adrenal steroidogenesis in the developmental context is important to approach disorders presenting with precocious androgen excess. The adrenal cortex comprises three distinct zones, the outer zona glomerulosa responsible for mineralocorticoid production, the middle zona fasciculata...
synthesising glucocorticoids and the inner ZR that produces the crucial androgen precursor DHEA (124–129). Importantly, recent studies based on cell morphology and analysis of steroidogenic enzyme expression support the results of earlier, histology-based studies from the 1970s suggesting that maturation of the adrenal ZR starts at least 4–5 years before the physiological manifestation of pubarche (17, 127).

Adrenal steroidogenesis is facilitated by the import of cholesterol esters into adrenocortical cells via scavenger receptor B1 and their cleavage by hormone-sensitive lipase to yield free cholesterol, which is subsequently imported into the mitochondrion by action of the STAR protein. For de novo synthesis of DHEA from cholesterol, only two steroidogenic cytochrome P450 (CYP) enzymes are required, CYP11A1 (or P450scc) and CYP17A1 (Fig. 2). CYP11A1 is located in the mitochondrion and cleaves the cholesterol side chain, yielding pregnenolone. CYP11A1 is equally expressed in all three zones of the adrenal cortex throughout childhood (127).

The microsomal enzyme CYP17A1 is the qualitative regulator of adrenal steroid synthesis and exerts two distinct catalytic activities. Its 17α-hydroxylase activity catalyses the production of the glucocorticoid precursors 17OHP and 17α-hydroxyprogrenenolone (17Preg: Fig. 2). The 17,20 lyase activity of CYP17A1 catalyses their subsequent conversion to the adrenal androgen precursors androstenedione and DHEA respectively (Fig. 2). Of note, 17,20 lyase has an about 100-fold increased substrate preference for 17Preg over 17OHP (130). Consequently, in the physiological situation, almost all androgen synthesis proceeds through DHEA, which, therefore, is considered the principal human androgen precursor. An early study employing human adrenal microsomes from individuals of different ages found lower CYP17A1 activities in individuals aged 2 months to 9 years than in adults (131) and subsequently has been cited as evidence for a characteristic increase in 17,20 lyase activity at the time of adrenarche. However, current in vivo evidence points towards a much earlier onset of adrenal androgen secretion at around age 3 years (17).

Recent immunohistochemistry data are consistent with this latter suggestion, demonstrating a significant increase in CYP17A1 expression in ZR from 5 years of age onwards. This is paralleled by reticularis-specific increase in P450 oxidoreductase (POR) that transfers electrons from NADPH to microsomal CYP enzymes including CYP17A1 (127). In addition, reticularis-specific expression of cytochrome b5 is observed (127), which is thought to enhance the allosteric interaction of the CYP17A1 and POR proteins, thereby specifically enhancing 17,20 lyase activity (130).

While CYP11A1 and CYP17A1 are essential and theoretically sufficient to create the biochemical environment observed in adrenarche, other steroidogenic enzymes also affect androgen synthesis.

Table 3 Summary of clinical studies investigating features of PCOS in children with PP or PA. All studies were cross-sectional.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Controls</th>
<th>Population</th>
<th>PCOS risk*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibanez et al. (72)</td>
<td>35 adolescent PP girls</td>
<td>12, age- and sex-matched</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>16 of 35 PP girls had hirsutism, elevated baseline androstenedione and/or testosterone levels; higher 17OHP and androstenedione response to GnRH analogue in oligomenorrheic PP girls compared with PP girls with regular menstruation</td>
</tr>
<tr>
<td>Ibáñez et al. (96)</td>
<td>76 adolescent PP girls</td>
<td>49, sex- and age-matched</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Higher increases in 17Preg and DHEA throughout puberty and in 17OHP and androstenedione at Tanner stage B4 in PP girls after GnRH analogue</td>
</tr>
<tr>
<td>Ibanez et al. (73)</td>
<td>36 adolescent PP girls</td>
<td>49, age- and sex-matched</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Higher frequency of anovulatory cycles only in PP girls in late post-menarche (more than 3 years after menarche)</td>
</tr>
<tr>
<td>Ibanez et al. (97)</td>
<td>47 PP girls at pre- and post-puberty</td>
<td>None</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Increased baseline DHEAS and androstenedione; increased 17OHP response to ACTH at time of diagnosis, increased DHEA and androstenedione response to ACTH during adolescence</td>
</tr>
<tr>
<td>Mathew et al. (98)</td>
<td>13 pre-pubertal PP girls</td>
<td>8, age- and sex-matched</td>
<td>American–Black and American–White</td>
<td>Yes</td>
<td>Increased 17Preg, DHEA and androstenedione response to ACTH in PP girls; by contrast, 17OHP, androstenedione and oestradiol response to GnRH analogue in PP girls similar to controls</td>
</tr>
<tr>
<td>Paterson et al. (55)</td>
<td>42 pre-pubertal PP girls</td>
<td>None</td>
<td>Scottish</td>
<td>Yes</td>
<td>Increased AMH levels in PP girls</td>
</tr>
<tr>
<td>Utriainen et al. (100)</td>
<td>52 pre-pubertal PA girls</td>
<td>48, age-matched</td>
<td>Finnish</td>
<td>No</td>
<td>No abnormalities in AMH concentrations in PP girls</td>
</tr>
</tbody>
</table>

*Evidence of increased PCOS risk. 17Preg, 17-hydroxyprogrenenolone; 17OHP, 17α-hydroxyprogesterone; AMH, anti-Müllerian hormone.
Table 4 Summary of clinical studies investigating the relationship between low birth weight (LBW) and disorders of androgen excess.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Controls</th>
<th>Population</th>
<th>LBW*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cresswell et al.</td>
<td>235 women at 40–42 years</td>
<td>None</td>
<td>UK</td>
<td>No</td>
<td>49 women (21%) had polycystic ovaries on ultrasound, a higher frequency of hirsutism and acne and higher LH and androgens; overweight mothers and a high birth weight slightly increased the risk of development of PCOS in later life</td>
</tr>
<tr>
<td>Clark et al.</td>
<td>190 healthy children (89 boys and 101 girls)</td>
<td>None</td>
<td>UK</td>
<td>Yes</td>
<td>Higher urinary androgen excretion in children with low birth weight</td>
</tr>
<tr>
<td>Ibanez et al.</td>
<td>102 pre- to post-pubertal PP girls</td>
<td>83, matched for pubertal stage and bone age</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Lowest birth weight in PP girls with most severe phenotype (PP + increased 17OHP + androstenedione response to GNRH analogue + insulin resistance)</td>
</tr>
<tr>
<td>Ibanez et al.</td>
<td>83 pre- to post-pubertal girls with PP</td>
<td>104, matched age and BMI</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>PP girls with dyslipidaemia and low IGFBP1 levels had lower birth weight</td>
</tr>
<tr>
<td>Ibanez et al.</td>
<td>23 healthy girls born SGA, investigated at 14 years</td>
<td>40 healthy girls born AGA, investigated at 14 years</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Higher DHEAS, androstenedione and baseline insulin levels in SGA group</td>
</tr>
<tr>
<td>Ghirri et al.</td>
<td>31 SGA girls (12 pre-pubertal, 19 post-</td>
<td>31, age-matched</td>
<td>Italian</td>
<td>Yes</td>
<td>DHEAS levels higher in SGA group. No difference in final height and sexual maturation/menarche age</td>
</tr>
<tr>
<td>Meas et al.</td>
<td>27 post-menarcheal PP girls</td>
<td>25, age- and sex- matched</td>
<td>French</td>
<td>No</td>
<td>No correlation between PP and birth weight</td>
</tr>
<tr>
<td>Laitinen et al.</td>
<td>2007 adult women</td>
<td>None</td>
<td>Finnish</td>
<td>No</td>
<td>Data from longitudinal, population-based cohort. No correlation between birth weight and presence of PCOS</td>
</tr>
<tr>
<td>Charkaluk et al.</td>
<td>216 pre-pubertal PP children (189 girls)</td>
<td>None</td>
<td>French</td>
<td>Yes</td>
<td>18.5% of PP girls had birth weight &lt; 10th percentile (expected rate: 10%)</td>
</tr>
<tr>
<td>Ong et al.</td>
<td>770 children at 8 years from birth cohort</td>
<td>None</td>
<td>UK</td>
<td>Yes</td>
<td>Data from birth cohort study. Inverse correlation between birth weight and adrenal androgen levels. Children with rapid postnatal catch-up growth had higher DHEAS levels</td>
</tr>
<tr>
<td>Neville &amp; Walker</td>
<td>89 children with PP (79 girls)</td>
<td>None</td>
<td>Australia</td>
<td>Yes</td>
<td>Retrospective analysis. 35% were SGA, 24% premature birth</td>
</tr>
<tr>
<td>Ibanez et al.</td>
<td>29 children born SGA</td>
<td>22 children born AGA; no difference in weight, height and BMI</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Follow-up at 2, 3 and 4 years. After catch-up, weight gain between birth and 2-year SGA children develop central adiposity (DXA) and insulin resistance (HOMA-IR) between 2 and 4 years</td>
</tr>
<tr>
<td>Ibanez et al.</td>
<td>32 children born SGA</td>
<td>32 children born AGA, matched for sex, height and weight</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Follow-up at 6 years. SGA children have more visceral fat (DXA), are hyperinsulinaemic and had lower adiponectin levels than AGA controls</td>
</tr>
<tr>
<td>Ibanez et al.</td>
<td>32 children born SGA</td>
<td>32 children born AGA, matched for sex, height and weight</td>
<td>Spanish (Catalan)</td>
<td>Yes</td>
<td>Follow-up at 8 years. Visceral obesity (DXA), hyperinsulinaemia and hypo-adiponectinemia stabilises in SGA children; moreover, DHEAS levels were higher and SHBG levels were lower</td>
</tr>
<tr>
<td>Utriainen et al.</td>
<td>54 pre-pubertal PA girls</td>
<td>52, age-matched</td>
<td>Finnish</td>
<td>No</td>
<td>Retrospective analysis. No correlation between LBW and PA, PA girls were taller at diagnosis and had enhanced early childhood growth</td>
</tr>
<tr>
<td>Paterson et al.</td>
<td>52 pre-pubertal PP (42 girls, 8 boys)</td>
<td>No</td>
<td>Scottish</td>
<td>No</td>
<td>No evidence of reduced foetal growth in PP children</td>
</tr>
</tbody>
</table>

*Association with LBW. SGA, small for gestational age; AGA, appropriate for gestational age; DXA, dual-energy X-ray absorptiometry; HOMA-IR, homeostasis model assessment-insulin resistance.
ACRD (hexose-6-phosphate deficiency)

The enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is important for amplifying glucocorticoid signals in target tissues such as liver, adipose and muscle by interconverting cortisol and its metabolically inactive metabolite cortisone (137). In principle, 11β-HSD1 is a bidirectional enzyme, interconverting cortisone and cortisol via its oxo-reductase and dehydrogenase activities; however, 11β-HSD1 oxo-reductase activity predominates in vivo, leading to the activation of cortisone to cortisol within the lumen of the endoplasmic reticulum (ER; Fig. 2). Recent in vitro and in vivo studies have identified a further layer of regulation of this crucial glucocorticoid-activating enzyme system. Within the ER, 11β-HSD1 oxo-reductase activity is dependent upon the maintenance of a high NADPH/NADP⁺ ratio and NADPH is supplied by a second ER lumen enzyme, hexose-6-phosphate dehydrogenase (H6PDH). Indeed, 11β-HSD1 oxo-reductase activity is absent in H6PDH KO mice (138–140). However, as the 11β-HSD1 enzyme is not directly affected, the altered ER redox environment subsequent to loss of H6PDH function permits an increase in 11β-HSD1 dehydrogenase activity, resulting in increased inactivation of cortisol to cortisone. In H6PDH KO mice, this leads to insensitivity to feedback suppression of the HPA axis and resultant ACTH-mediated adrenal hyperplasia and elevated circulating glucocorticoid levels (138–140).

In humans, ACRD is characterised by decreased urinary excretion of cortisol metabolites and ACTH-driven adrenal androgen excess manifesting as PA and PCOS (141–143). To date, approximately eight cases have been reported in the literature that have a biochemical and clinical presentation consistent with ACRD. In four of these cases, a complete clinical, biochemical and genetic work-up has been published (135); three adult women presented with a PCOS phenotype and one 6-year-old boy presented with PA (143, 144). In all cases, hyperandrogenaemia was confirmed with markedly elevated serum levels of DHEAs, androstenedione and testosterone.

Genetic analyses determined a normal sequence of the HSD11B1 gene (encoding 11β-HSDD1) in all affected individuals, but revealed inactivating mutations in the H6PDG gene encoding H6PDH, including homozygous and compound heterozygous nonsense, missense and splicing mutations, which were all shown to disrupt enzymatic activity (135). Thus in ACRD, loss of H6PDG activity yields reduced 11β-HSD1 oxo-reductase activity and a concurrent gain in 11β-HSD1 dehydrogenase activity, resulting in enhanced peripheral clearance of cortisol, thereby reducing the negative feedback suppression of the HPA axis, which in turn increases the ACTH drive and an ACTH-mediated increase in adrenal androgen secretion.

Diagnostically, the use of GC/MS to generate steroid profiles from 24 h urine collections has proved invaluable (135). In most cases, serum cortisol levels were within the normal range, as might be expected due to the compensatory increase in HPA axis activity. However, the urinary levels of cortisone metabolites were grossly elevated in all affected individuals, resulting in characteristic decreased ratios of cortisol over cortisone metabolites (5α-tetrahydrocortisol (THF) + THF/tetrahydrocortisone and cortols/cortolones, see Fig. 2). Thus urinary steroid profiling by GC/MS provides a clear-cut diagnostic marker for H6PDG deficiency (135, 145) and reliably helps to distinguish ACRD from other causes of premature androgen excess.

Apparent DHEA sulphotransferase deficiency (PAPS synthase type 2 deficiency)

DHEA serves as the principal human androgen precursor via conversion to the active androgens testosterone and 5α-dihydrotestosterone that bind and activate the AR. Alternatively, DHEA can undergo...
sulphate conjugation yielding DHEAS, a reaction catalysed by the enzyme DHEA sulphotransferase (SULT2A1; Fig. 2). In human adrenals, SULT2A1 is exclusively expressed in the ZR and its immunoreactivity increases from early childhood to adolescence (127). DHEAS represents the most abundant steroid in the human circulation, and it was previously thought that DHEA and its sulphate ester DHEAS would undergo continuous interconversion by action of SULT2A1, converting DHEA to DHEAS, and steroid sulphatase (STS), yielding DHEA after cleavage of the sulphate group from DHEAS. Accordingly, DHEAS was found to serve as a circulating storage pool for the generation of DHEA in peripheral target tissues of sex steroid action. However, while exogenous administration of DHEA in humans yields ample generation of both active sex steroids and DHEAS (20), we have previously shown that the administration of DHEAS does not result in appreciable levels of DHEA or active sex steroids (146, 147). This suggests that DHEA sulphation is a permanent inactivating step and that the reverse reaction, cleavage of DHEAS to DHEA by STS, does not have a major impact on circulating steroid concentrations. This is true with the exception of human foetal development and pregnancy, during which ample cleavage of DHEAS has been demonstrated, driven by abundant placental STS activity. Consequently, we hypothesised that disruption of SULT2A1 activity will result in decreased inactivation of DHEA to DHEAS, thereby fuelling the alternative conversion, i.e. the activation of DHEA to androgens, which will result in androgen excess.

Figure 2 Schematic representation of human adrenal steroidogenesis and androgen synthesis with additional details on the co-factor regulation of DHEA sulphotransferase (SULT2A1) and 11β-hydroxysteroid dehydrogenase (HSD11B1) activities. Disruption of PAPS synthase 2 activity results in apparent DHEA sulphotransferase deficiency, whereas disruption of hexose-6-phosphate dehydrogenase (H6PDH) activity results in apparent cortisol reductase deficiency, two recently described conditions manifesting with early onset androgen excess including premature adrenarche and polycystic ovary syndrome. STAR (transports cholesterol from the outer mitochondrial membrane (OMM) to the inner mitochondrial membrane (IMM)); CYP11A1, cholesterol side chain cleavage enzyme; CYP17A1, 17α-hydroxylase/17,20 lyase; CYB5, cytochrome b5; POR, P450 oxidoreductase; HSD3B2, 3β-hydroxysteroid dehydrogenase type 2; HSD11B1, 11β-hydroxysteroid dehydrogenase; H6PDH, hexose-6-phosphate dehydrogenase; G6P, glucose-6-phosphate; 6PGL, 6-phosphogluconate; PAP, 3'-phosphoadenosine-5'-phosphate; PAPS, 3'-phosphoadenosine-5'-phosphosulphate; PAPSS2, PAPS synthase 2; SULT2A1, DHEA sulphotransferase; THF, tetrahydrocortisol; THE, tetrahydrocortisone. Androgens are shown in blue, glucocorticoids in orange and mineralocorticoids in green.

www.eje-online.org
We recently reported a case about a girl who presented with PA manifesting with pubic hair development at the age of 6 years (136). She subsequently developed acne and hirsutism at 11 years of age and secondary amenorrhoea at 13 years of age, i.e. a phenotype progressing from PA to a presentation resembling PCOS. Lab investigations revealed increased serum androstenedione and mildly elevated testosterone, as frequently seen in early onset androgen excess, with her body weight progressing from overweight to the obese range. However, of note, her serum DHEAS levels were undetectable throughout, whereas serum DHEA was at the upper limit of normal, suggestive of impaired DHEA sulfation as the driver of androgen excess. Surprisingly, genetic analysis did not reveal any mutations in the SULT2A1 gene, which prompted us to explore further mechanisms potentially impacting DHEA sulphation. For catalytic activity, SULT2A1 to examine male family members and learned that affected female individuals suffered from infertility.

Of note, our patient also showed very mild signs of bone dysplasia that was not clinically apparent but revealed by X-ray. A previously reported consanguineous Pakistani kindred carrying a homozygous PAPSS2 nonsense mutation void of any catalytic function presented with severe spondyloepimetaphyseal dysplasia (149). An androgen phenotype in that kindred was not reported, but the researchers were only allowed to examine male family members and learned that affected female individuals suffered from infertility. These findings indicate that PAPSS2 deficiency has to be considered a multi-system disorder, which, in principle, is not surprising, as sulfation is a major metabolic reaction occurring in multiple tissue types and organs such as liver, bone and cartilage and is also involved in endocrine pathways such as neuropeptide, thyroid and catecholamine signalling (150). Importantly, PAPSS2 deficiency reveals DHEA sulphation as a major regulator of human androgen synthesis, with impaired sulfation of DHEA to DHEAS resulting in increased conversion of DHEA to active androgens and subsequent androgen excess, which manifests with PA and PCOS. Of note, the biochemical phenotype in our patient, low DHEAS and increased androstenedione, would have previously been labelled as ‘ovarian hyperandrogenism’ while androgen excess in our patient clearly stems from an adrenal cause. Previous studies have found low or undetectable DHEAS in 5–10% children with PP (55, 151), suggestive of a potentially significant role of dysregulation of this pathway in the pathogenesis of PA.
Conclusions and future directions

We feel that given the available evidence of PA can no longer routinely be considered a benign extreme of normal variation. Early onset androgen excess, whether presenting with PA or adolescent PCOS, appears to represent a significant risk factor for the development of MS. In an age of increasing numbers of childhood obesity and considering the intriguing links between the insulin–IGF1 system and androgen regulation, we may be set to observe an increasing number of patients with early onset androgen excess. The recent elucidation of several conditions manifesting with early androgen excess including PA and PCOS has provided with novel mechanistic insights into the underlying pathophysiology and it is likely that the coming years will show the elucidation of further distinct causes underlying PA, which first and foremost requires careful phenotyping and use of nomenclature (Fig. 3) to identify potentially novel entities. Systematic longitudinal studies in children with PA are warranted to address the apparent link between early onset androgen excess, insulin resistance and metabolic risk and will also elucidate the frequency of novel monogenic causes of childhood androgen excess, i.e. (apparent) cortisone reductase and DHEA sulphation deficiencies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This review was supported by the Wellcome Trust (Project Grant 092283, to W Arlt; Programme Grant 066357, to P M Stewart; Clinician Scientist Fellowship GR079865MA to N Krone), the Medical Research Council (MRC Research Training Fellowship to J Idkowiak), the European Society for Paediatric Endocrinology (ESPE Research Fellowship to J Idkowiak), and the Biotechnology and Biological Sciences Research Council (BBSRC David Philips Fellowship to G G Lavery).

Acknowledgements

This article is partly based on the presentation for the European Journal of Endocrinology Prize Lecture 2009 by W Arlt at the European Congress of Endocrinology Meeting at Istanbul, Turkey.

References


9 Silverman SH, Migeon C, Rosenberg E & Wilkins L. Precocious growth of sexual hair without other secondary sexual development; premature pubarche, a constitutional variation of adolescence. *Pediatrics* 1952 10 426–432.


15 Sizonenko PC & Paumier L. Hormonal changes in puberty III: correlation of plasma dehydroepiandrosterone, testosterone, FSH, and LH with stages of puberty and bone age in normal boys and girls and in patients with Addison’s disease or hypogonadism or with premature or late adrenarche. *Journal of Clinical Endocrinology and Metabolism* 1975 41 894–904. (doi:10.1210/jcem-41-5-894)


19 Marshall WA & Tanner JM. Variations in the pattern of pubertal changes in boys. *Archives of Disease in Childhood* 1970 45 13–23. (doi:10.1136/adc.45.3.13)


25 Sklar CA, Kaplan SL & Grumbach MM. Evidence for dissociation


33 Parker LN & Odell WD. Control of adrenal androgen secretion. Endocrine Reviews 1980 1 392–410. (doi:10.1210/edrv-1-4-392)


36 Taha D, Mullis PE, Baizée L & De Zegher F. Absent or delayed adrenarche in Pit-1/POU1F1 deficiency. Hormone Research 2005 64 175–179. (doi:10.1159/000088793)


73 Ibanez L, Potau N, Zampolli M, Rique S, Saenger P & Carrascosa A. Hyperinsulinemia and decreased insulin-like growth factor-binding protein-1 are common features in prepubertal and pubertal girls with a history of premature pubarche. *Journal of Clinical Endocrinology and Metabolism* 1997 82 2283–2288. (doi:10.1210/jc.82.7.2283)


77 Denburg MR, Silfen ME, Maniho AM, Chin D, Levine LS, Ferlin M, McMahon DJ, Go C & Oberfield SE. Insulin sensitivity and the


92 Scherer PE. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* 2006 55 1537–1545. (doi:10.2337/db06-0263)


95 Oberfield SE. Elevated free IGF-I levels in prepubertal Hispanic girls with premature adrenarche: relationship with hyperandrogenism and insulin sensitivity. *Journal of Clinical Endocrinology and Metabolism* 2002 87 398–403. (doi:10.1210/jc.81.11.3892)

96 Oberfield SE. Elevated free IGF-I levels in prepubertal Hispanic girls with premature adrenarche: relationship with hyperandrogenism and insulin sensitivity. *Journal of Clinical Endocrinology and Metabolism* 2002 87 398–403. (doi:10.1210/jc.81.11.3892)


100 Ibanez L, Lopez-Bermejo A, Suarez L, Marcos MV, Diaz M & de Zegher F. Visceral adiposity without overweight in children

www.eje-online.org

115 Ibanez L, Lopez-Bermejo A, Diaz M, Suarez I, & de Zegher F. Low-birth weight children develop lower sex hormone binding globulin and higher dehydroepiandrosterone sulfate levels and aggravate their visceral adiposity and hypodiplopectinemia between six and eight years of age. *Journal of Clinical Endocrinology and Metabolism* 2009 94 3696–3699. (doi:10.1210/jc.2009-0789)


