NORMAL AND PREMATURE ADRENARCHE

Alicia Belgorosky; María Sonia Baquedano; Gabriela Guercio; Marco A. Rivarola.
Servicio de Endocrinologia, Hospital de Pediatria Garrahan, Buenos Aires, Argentina

1. INTRODUCTION

Adrenarche occurs only in higher primates, typically at 6-8 y of age in humans, when the innermost layer of adrenal cortex, the zona reticularis, develops. This is an event of posnatal sexual maturation in which there is an increase in the secretion of adrenal androgens, mainly dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), not accompanied by an increase in cortisol secretion (1). The zona reticularis (ZR) is in theory the morphological equivalent of the fetal zone of adrenal cortex. The primate adrenal produces large amounts of DHEA and DHEAS during fetal development, which decrease rapidly after birth, since the fetal zone virtually disappears during the first few months of postnatal life (2-6). Thereafter, longitudinal studies have shown a progressive increase in serum concentration of DHEA and DHEAS in healthy boys and girls, beginning at 6 to 8 years of age, roughly in parallel with an increase in skeletal age (7-15). However, in contrast to the latter proposal, adrenarche might begin earlier in childhood, as suggested by studies performed in healthy children measuring DHEA, as well as the DHEA metabolites in 24-h urine samples (16).
Even though adrenarche might be a multifactorial event, the main process regulating the production of adrenal androgens continues to represent one of the most intriguing mysteries in adrenal functional differentiation. Although a non-ACTH pituitary factor, stimulating adrenal androgen production has been proposed to work in concert with ACTH today, no circulating factor has been found that might initiate this process. Moreover, according to recent studies, it has been suggested that the increment of adrenal androgen production is associated to the enlargement of ZR (18-21). In addition, the regulation of adrenal steroidogenesis in zona reticularis is a complex process, since adrenarche requires both the acquisition of 17, 20-lyase activity of P450c17 and a decrease of 3beta HSD expression (18-20,22-27). Several factors, such as the IGF system, insulin, the immune system, and also a possible modulatory role of the adrenal medulla have been proposed, among others, to be involved in the regulation of the functional differentiation of adrenal ZR cells (18-28). However, the mechanism of adult adrenal cortex remodeling and zonation has to be elucidated.

The fact that adrenarche is confined to higher–order primates indicates that this phenomenon is a relatively recent evolutionary development. Even thought the importance of the fetal production of DHEA and DHEAS is related to their role as substrates for the massive rise in estrogens biosynthesis during gestation (29), the significance of adrenarche in human physiology remains unknown. In addition, although no DHEA receptor has been genetically cloned, there are strong data to support the possibility of the existence of a plasma membrane receptor for DHAS (30-31).

Adrenarche can be considered as the puberty of the adrenal gland, but the two processes (adrenal and gonadal puberty) are independent. However, androgens of adrenal origin had been postulated to be able to initiate activation of the hypothalamic-pituitary–gonadal axis, because central precocious puberty often occurs in children untreated or poorly treated for congenital adrenal hyperplasia (1,15,32), suggesting a possible relationship between adrenarche and gonadarche. On the contrary, the adrenal insufficiency does not represent a limiting factor for the development of gonadarche (33).

Pubarche has often been taken as the clinical sign of adrenarche, therefore, the terms adrenarche and pubarche have been usually used as synonyms (15,33). However, dissociation between pubarche and biochemical markers of adrenarche can occur in girls with precocious puberty, who have pubarche long before adrenarche (34-35). The
FIGURE 1. The newborn adrenal gland still retains the regressing fetal zone. The medulla has not reach yet an uniforme layer. Cell renewal of all zones takes place in the sub-capsular region.

opposite situation has been reported in some girls with Turner syndrome, mainly in those with premature ovarian failure (35).

Premature adrenarche, the early increase in adrenal androgen production might be associated with ovarian hyperandrogenism and polycystic ovarian syndrome in females, as well as with insulin resistance in the two sexes, during puberty development, adult life and even in childhood (15,18, 36-42). Then, improving our knowledge on the mechanism involved in the regulation of adrenarche represents an important challenge for medical science.

In this chapter the following topics will be discussed:


3. Premature adrenarche.
2. NORMAL ADRENARCHE

2.1 DEVELOPMENT AND ZONATION OF THE HUMAN ADRENAL GLAND

The developmental program that gives rise to the adrenal gland begins early during embryogenesis and continues into adult life. There are undeniable species-specific differences in the structural and functional organization of the human and great primate adrenal cortex compared to non-primate species (43).

The fetal adrenal cortex derives from a common adrenogonadal precursor lineage that also gives rise to the steroid-secreting cells of the gonads. In human embryos, these adrenogonadal progenitors first appear in the fourth week of gestation. Cells destined to generate the adrenal cortex migrate from the coelomic epithelium forming the primitive adrenal gland by eight weeks of gestation. This rudimentary adrenal gland contains an inner cluster of large, eosinophil cells, termed the fetal zone. Shortly thereafter, a second group of cells develops to form a densely packed
After 2 years of age the adrenal medulla form a continuous layer.

outer zone of cells, the definitive zone. At the same time, the adrenal cortex becomes encapsulated and chromaffin cells originating from the neural crest migrate through the fetal cortex to progressively colonize the center of the gland to form the future medulla (43-44). However, it is not until 12 to 18 months of age that the medulla becomes adult-like in appearance (45).

Genes encoding a number of transcription factors have been linked to adrenocortical cell development and to modulation of steroidogenic function (44,46). The large inner fetal zone expressing cholesterol side-chain cleavage enzyme (CYP11A) and 17α-hydroxylase (CYP17), but not 3β-hydroxysteroid dehydrogenase, is the site of synthesis of large amounts of DHEA and DHEA-S since early in development (47). Definitive zone cells have a proliferation phenotype that persists throughout gestation, and they acquire mineralocorticoid synthesis capacity only late in
gestation. A third zone, the transitional zone, develops between the definitive and fetal zone around midgestation, and it expresses enzymes required for the synthesis of cortisol (47).

After birth, a strong remodeling of the adrenal gland occurs; the medullary islands coalesce to form a rudimentary medulla, the fetal zone regresses (Figure 1) by the third postnatal month, primarily by apoptosis (3,48), and the definitive zone develops into the adult adrenal. These morphologic changes are accompanied by a rapid drop in DHEA and DHEA-S production due to the involution of the fetal zone. In preadrenarche children, the zona glomerulosa (ZG) and the zona fasciculata (ZF) are clearly present (Figure 2) but only focal islands of ZR cells, that do not express the enzymes needed to maintain high levels of DHEA-S production, can be identified at age 3 to 5 years of age (Figure 3) (4,19-20,49). After adrenarche, there is a development and thickening of a continuous ZR associated with detectable increases in circulating DHEA and DHEA-S (Figure 4) (4,11,50).
Peak levels of DHEA and DHEA-S occur at age 20 to 25 years and decline thereafter (51). This decrease in adrenal androgens with aging is often called adrenopause. There appears to be a reduction in the width of the ZR with aging, without overall changes in the width of the adrenal cortex. This suggests that this phenomenon is specific to the ZR, and not global atrophy of the adrenal gland with aging (51, 52).

The origin of the adrenocortical zones and the regulation of their proliferation are incompletely understood. At present there are three theories for the zonation of the adrenal cortex (53). The transformational field theory involves the replacement of zonal tissue by ZF (54-59). The zonal theory involves the equal proliferation of all three zones (55). The third, the progenitor cell proliferation/migration theory, and the most accepted one, proposes that proliferation of cortical cells takes place in the outermost layers of the adrenal cortex. The theory would be valid for differentiation of ZG and ZF during fetal life, as well as for ZR during postnatal life. Hence, all cells of the adrenal cortex would have a common origin, which becomes functionally differentiated in the appropriate zone environment.

Although the accumulated data point strongly to the progenitor cell proliferation/migration theory in adrenal gland differentiation, the evidence is not direct. On the other hand, at the other age spectrum of human life, there are few data concerning the mechanisms responsible for the apparent shrinkage of ZR with aging.

2.2 REGULATORS OF ADRENAL ANDROGEN PRODUCTION

The pituitary hormone adrenocorticotrophin (ACTH) is the primary regulator of both fetal adrenal development and adult adrenal cortex homeostasis and steroidogenic function (56, 57-59). Given the variety of biological events triggered by ACTH in the adrenal cortex, it appears that most of these effects are induced by a variety of related proteins synthesized and secreted by the different zones of the cortex, and/or that locally produced factors may synergize or antagonize the direct biological effects of ACTH in order to generate combinatorial responses in the different cell subpopulations.

Several experiments and clinical observations have shown that ACTH is necessary but not sufficient to induce adrenarche. Patients with ACTH resistance fail to undergo adrenarche (60, 61), and patient with ACTH deficiency have undetectable DHEA-S levels (62). However, ACTH levels do not change at times when circulating DHEA levels change.
drastically, such as during adrenarche or aging (63) suggesting that other factors must be involved in the specific regulation of DHEA and DHEAS synthesis in the adrenal gland. These factors should be involved either in regulation of adrenal enzyme expression and action or in the growth and trophic maintenance of the ZR itself.

The roles of several growth factors have been examined. Insulin-like growth factors I and II (IGF-I and IGF-II), acting through type 1 IGF receptor (IGF-R1), affect growth and differentiation of a wide variety of cell types and can act as autocrine, paracrine, or endocrine factors (64). While IGF-I mediates many of the postnatal somatotropic actions of growth hormone (GH), IGF-II has been involved in the regulation of fetal development. Both IGF-I and IGF-II enhance steroidogenic enzyme activity of P450c17 and 3-HSD (65). In this regard, a recent study of IGF-I, IGF-II and IGF-R1 mRNA expression and immunolocalization in human adrenals from early infancy to late puberty shows a very low IGF-R1 expression in the ZR suggesting that the IGF system is not directly involved in the regulation of adrenal androgen via ZR cells (21). However, it has been proposed that IGF-I and perhaps IGF-II, by autocrine, paracrine or endocrine stimulation, could be a factor involved in the postnatal mechanisms of progenitor adrenal cell proliferation and migration (21). Although IGF-II circulating and tissue levels are highest during fetal life and decrease postnatally (21, 65) a postnatal role of IGF-II in adrenal gland could not be discarded (21, 66).

Basic fibroblast growth factor (bFGF) is a potent mitogen in primary cultures of bovine adult adrenal cortical cells (67). It also stimulates proliferation of cultured fetal and definitive zone cells (68). As bFGF is also a potent angiogenic and neurotrophic factor, its trophic effects could be also due to effects on the growth and maintenance of the vascularization and innervation of the adrenal cortex. Nevertheless, little is know about the expression and role of bFGF in postnatal human adrenal gland function, including adrenarche.

The possible role of the transforming growth factor-1 (TGF-1) in adrenarche is not clear. TGF-1 stimulates 3-HSD2 activity in adult human adrenal cells. A local decrease of TGF-1 production might be involved in the steroid hormone changes observed at adrenarche (69).

Interleukin-6 (IL-6) also appears to be a local factor that stimulates DHEA secretion. Interestingly, IL-6 receptor is expressed with high density in the ZR (70). Cytokines produced by the inner zones of the human adrenal cortex, such as
tumor necrosis factor (TNF) (71), would participate in the differentiation and apoptosis of the ZR (72, 73). Recently, an inhibitory effect TNF on the HSD3B2 promoter has been shown, which is in agreement with the low expression of 3 HSD2 in the ZR at adrenarche (74).

A potential role for steroids, particularly estradiol, in promoting adrenal androgen production has been suggested. High concentrations of estradiol enhance basal and ACTH stimulated DHEA and DHEA-S production by human fetal adrenal cells in culture (75, 76). The mechanism of action seems to be a direct inhibition of 3β-HSD2 enzyme activity by high estrogen levels (77). Besides, it has been shown that estradiol increases cell proliferation in the human cell line H295R (78). However, children with gonadal dysgenesis have a normal rise of DHEA-S with chronological age (33). Furthermore, there are no significant sex differences in the age of adrenarche which supports that estrogens are not a major factor. However, estrogen is no solely an endocrine factor, but instead is produced in a number of extragonadal sites and acts locally in a paracrine and intracrine fashion. Within these sites, aromatase action can generate high levels of estradiol locally without significantly affecting circulating levels (79). Taking this into account, it is of interest that a preliminary study described the presence of aromatase expression in prepubertal and pubertal human adrenal glands, as well as the immunolocalization of estrogen receptor in the ZR (80).

More recently, other candidate hormones, related to control of body mass, such as insulin and leptin, have been suggested as the triggers of adrenal growth and adrenarche. In vitro, leptin has been shown to increase the 17, 20 lyase activity of the P450c17 enzyme in human adult adrenal cells, presumably through P450c17 phosphorylation (81).

It is worth mentioning that components of extracellular matrix can induce intracellular cell signals or interact with hormonal or growth factor transduction pathways, leading to specific adrenocortical cell behavior, such as proliferation, migration, apoptosis, and gene expression (82-84).

Finally, the integrated control of adrenocortical function involves cortico-medullary interactions, the gland’s vascular supply, its neural input, the immune system, growth factors, as well as signals provided by the extracellular microenvironment (28, 85). Although the physiological triggers of adrenarche remain speculative, it is reasonable to speculate that adrenarche is probably the result of the interplay of several factors.
2.3 THE IGF SYSTEM AND INSULIN SENSITIVITY

There are some evidences that the GH – IGF system and insulin might be regulating factors of adrenal androgen production at adrenarche. For instance, serum IGF-1 levels rise and fall in a pattern similar to serum DHEAS, and normal puberty is characterized by a state of transient insulin resistance associated with an increase of, not only gonadal sex steroid production, but also adrenal androgens. Thereby, a role has been proposed for the GH - IGF system and insulin on the developmental changes taking place at adrenarche (86-92). As it has been described above, several In vitro studies showed that the IGFsystem and insulin might modulate adrenal steroidogenesis, not only cortisol but also DHEAS secretion.

The GH/IGF system and adiposity have been considered the major contributors of insulin resistance at puberty (90, 93-97). Several studies have shown pubertal female-male differences in insulin sensitivity, normal girls being less insulin sensitive than normal boys (90, 96-100). However, we found that these sex differences were clearly evident in late prepuberty, when girls became more insulin-resistant than boys, (98, 100). In addition, a similar finding was described by Hoffman et al (97) in a small sample of subjects.

In vivo studies of the implications of insulin-resistance and the GH/IGF system on the regulation of adrenal androgen secretion, in normal children at adrenarche are scarce. Bloch et al (101) have found that healthy children at adrenarche were more insulin-resistant than younger ones, and an inverse relationship between insulin sensitivity and DHEAS levels were also found .On the contrary, no relationship between DHEAS levels and Insulin sensitivity was observed in normal prepubertal and adolescent subjects of both sexes, by Caprio et al (102). Finally, while Smith et al (103) described a positive correlation between DHEAS levels and basal or stimulated Insulin responses when prepubertal and pubertal children were analysed together, they were unable to detect a significant correlation in the prepubertal group alone.

In adult men, in contrast to adult women, DHEAS concentrations correlate positively with insulin sensitivity (104), suggesting a physiological sexual dimorphism. We have studied the relationships between the GH/IGF-1, insulin sensitivity, and adrenal androgens in normal prepubertal and pubertal boys and girls (98, 100). In our study we found
that, as previously described (105, 106), serum DHEAS levels increased during prepuberty in both sexes. However, as it is shown in figure 3, and in contrast to Denburg et al. (42), in prepubertal boys, no correlation was found between serum DHEAS levels and insulin sensitivity, or serum DHEAS levels and serum IGF-1 levels, suggesting that neither the GH/IGF-1 axis nor insulin sensitivity are involved in adrenarche. Insulin sensitivity decreased in the transition from early to late puberty in boys following changes in BMI and correlating with DHEAS levels, suggesting that peripheral Insulin could be involved in adrenal androgen steroidogenesis, particularly during early puberty in boys.

Contrarily to boys, Guercio et al. found a significant decrease of insulin sensitivity in normal prepubertal girls as well during pubertal development (100). Although we have not determined serum estradiol in this study, we believe that the sex differences in insulin sensitivity that we have found, might be secondary to differences in the estrogen milieu, since sex steroids, androgens as well as estrogens, can regulate insulin sensitivity (107-109) and adipogenesis (110, 111) in opposite ways. In girls, Guercio et al. (100) found a significant negative correlation between serum DHEAS levels and insulin sensitivity during prepubertal and pubertal development, and a positive one between serum DHEAS levels and serum IGF-I, but limited to the prepubertal period. These data suggested that in normal girls insulin is involved in the regulation of adrenal androgen steroidogenesis during the life span and might be one of the peripheral regulators involved in the mechanism of adrenarche in girls. The study of Guercio et al. (100) also suggests that the GH/IGF axis might be an important metabolic signal involved in the maturational changes of human adrenal at the time of adrenarche.

Information regarding to serum adrenal androgen levels in growth hormone (GH) deficiency individuals has been conflicting, and limited to a small number of reports, mainly derived from studies performed in children (112-118). It has been proposed that the presence of an intact ACTH reserve is a necessary feature of the GH–dependent action (119). However, in the few studies available in children, this point was not carefully considered.

Although the available data are not conclusive, as it is shown in the scheme in figure 5, we propose that GH might stimulate adrenal androgen production directly or throughout the modification of peripheral or intradrenal IGF system.
However, an inhibitory effect of GH on 11beta–HSD type 1(120) activity leading to decreased peripheral cortisol production, and subsequent activation of hypothalamo-pituitary axis has to be ruled out.

3. PREMATURE ADRENARCHE

3.1 DEFINITION. CLINICAL AND LABORATORY CHARACTERISTICS

Premature pubarche is a clinical term used to describe the appearance of pubic hair before the age of 8/9 years in girls/boys, respectively, in the absence of other clinical signs of puberty. Premature or exaggerated adrenarche is defined as the elevation of adrenal androgens above prepubertal levels in children with premature pubarche, provided that the elevation is not due to defined disorders of the gonads or adrenals, such as gonadal precocious puberty, tumors or enzymatic defects of steroidogenesis (121). As published by Guercio et al. (100), in prepubertal girls the normal mean±SD serum dehydroepiandrosterone sulfate level, the main marker of zona reticularis function, was 0.24±0.22 µmol/liter (mean±SD age 5.0±3.08 years). However, there was an age difference during prepuberty. In early prepubertal girls (2.2±1.45 years old), serum dehydroepiandrosterone sulfate was 0.08±0.09 while in late prepuberty (7.5±1.5 years old), values were 0.39±0.22 µmol/liter. The corresponding level in prepubertal boys (169), with a mean±SD age of 5.22±2.29 years, was similar to girls: 0.31±0.33 µmol/liter. An age difference within prepuberty was also found in boys: early prepuberty (3.19±1.0 years old) 0.16±0.20, and late prepuberty (7.13±1.25 years old) 0.46±0.22 µmol/liter.

It should be stressed that the increase of serum dehydroepiandrosterone sulfate detected in late prepuberty is the initiation of a long-term biological process of a gradual increment in the serum levels of the steroid, peaking in the early twenties, and followed by a slower and gradual decrement during the next decades to reach very low levels at senescence.

3.2 DIFFERENTIAL DIAGNOSIS

The differential diagnosis of premature pubarche has important clinical implications. It is more common in girls than in boys (122), and it might be associated with other signs of mild androgen action, such as acné, body hair or advanced bone age. It is mandatory to discard several conditions leading to excessive androgen production. Congenital
defects of steroidogenesis are classically present before birth and, therefore, female external genitalia are masculinized to varying degrees. Mild defects, however, might induce minimal masculinization, and should be discarded. Most commonly, premature pubarche is the first sign of nonclassical 21-hydroxylase deficiency (123). Other congenital defects of steroidogenesis are also possible. Virilizing ovarian or adrenal tumors are extremely rare, but they should be included in the differential diagnosis. One diagnosis to discard is idiopathic precocious puberty. Usually, this condition starts with breast development (telarche) and, therefore, it is easy to diagnose. However, as it occasionally happens with normal puberty, the onset of pubic hair might precede breast development. Occasionally, medications for CNS disorders might induce the development of premature pubic hair.

In boys also, the first condition to differentiate from, is simple virilizing congenital adrenal hyperplasia due to 21-hydroxylase deficiency. These boys do not lose salt, and premature pubarche might be the first sign of androgen excess. Clinically, there is growth acceleration and increased bone age. The external genitalia are usually stimulated, contrasting with small testes, in the first years of life. Later on, chronic androgen excess leads to early maturation of the hypothalamic GnRH pulse generator and development of true precocious puberty. As in girls, virilizing adrenal tumors should be discarded. Testicular disorders are rare. Testicular tumors are usually palpable, and might be single (usually Leydig cell tumor) or multiple (Sertoli-Leydig cell tumors). Finally, other conditions, such as familial male precocious puberty produced by gain-of-function mutations of the LH receptor (testotoxicosis), or stimulation of the testes by an hCG-secreting choriocarcinoma should be considered.

Imaging studies and laboratory hormonal tests are helpful to establish a correct diagnosis, in the two sexes. Adrenal and ovarian tumors can be detected by appropriate image diagnosis. Since the etiology of idiopathic premature pubarche is unknown, the diagnosis is supported by the detection of a moderate elevation of serum adrenal androgens (usually dehydroepiandrosterone sulfate), along with the exclusion of the above mentioned disorders. For the detection of 21-hydroxylase deficiency, it is important to determine the basal serum concentration of 17-hydroxyprogesterone along with serum androgens. If they were not elevated, the 17-hydroxyprogesterone response to an iv ACTH test is
useful for detecting nonclassical 21-hydroxylase deficiency (124). Finally, analysis of the CYP21 gene will confirm the diagnosis.

3.3 ASSOCIATION OF PREMATURE ADRENARCHE WITH RISK OF CHRONIC DISEASE AS ADULT

Mounting evidence, arisen in epidemiological studies, indicates that events occurring in the earliest stages of human development, such as fetal growth restriction, may influence the development of several disorders in adulthood, such as central distribution of body fat, insulin resistance, the metabolic syndrome, type 2 diabetes, hypertension and ischemic cardiovascular disease (125). It has been suggested that lower birth weight could result in re-programming a number of metabolic pathways which might have long-term unfavorable consequences on body health. In 1998, Ibañez et al. (40) reported that premature pubarche (and exaggerated adrenarche), hyperinsulinism and ovarian hyperandrogenism were associated with low birth weight, in girls. This finding linked exaggerated adrenarche with the risk of developing central obesity, hyperinsulinism and polycystic ovary syndrome. More recent studies found that the relationship between lower birth weight and higher childhood adrenal androgen levels was similar in boys and girls. Furthermore, adrenal androgen levels were highest in small for gestational age infants who gained weigh rapidly during childhood (126). Charkaluk et al. (127) studied a large population of children with premature pubarche (n = 216) classified according to their sex and age at onset of pubarche. They confirmed that premature pubarche was rare in boys (13.4 % of the cohort). They suggested that premature pubarche occurring in children aged less than 2 years is probably different from that occurring in older ones. In agreement with previous reports, 4 to 7.9 year old girls with premature pubarche tended to be obese and had a higher incidence of intrauterine growth retardation.

Indeed, insulin resistance and hyperinsulinemia are common features seen in prepubertal girls with premature adrenarche. In many of these girls, significantly high ACTH-stimulated ∆5-steroid levels (17-hydroxypregnenolone and DHEA), associated with low SHBG, low IGFBP-1, high IGF-1 levels and an altered lipid profile have been reported. It has been shown that ACTH-stimulated hormones correlated inversely with insulin sensitivity and directly with IGF-1 levels, suggesting that hyperandrogenism might be linked to Insulin resistance and the IGF system (36-39,128-130). Administration of metformin to girls with premature pubarche appears to prevent the increase in DHEAS levels (131).
Obesity was more frequently reported in girls with precocious pubarche and the correlations between DHEAS levels and adiposity indexes suggests that overweight might influences the onset of adrenarche (38, 39, 130-133). Moreover, in normal children, a greater increase in urinary DHEAS during the period of the greatest rise in BMI was found (134). These effects might be related to an increased of insulin and leptin levels, associated with an increased adiposity (134, 135). Leptin has been implicated in adrenarche by modulating CYP17 phosphorylation (81). However, in girls with precocious adrenarche, serum leptin levels have been found to be similar (136) or higher (132) than in controls.

On the other hand, the GH-IGF-1 system might modulate adrenal androgens (137). Indeed, a report by Silfen et al. (39) found that insulin levels in hispanic girls with premature adrenarche did not differ from that of control girls, but IGF-1 was higher and IGFBP-1 lower in premature adrenarche.

It is then evident that premature adrenarche shares many characteristics with PCOS, suggesting that they might be different expression of similar underlying disorders. Therefore, the risk of developing PCOS at adolescence or soon thereafter in girls with premature adrenarche should alert primary care physicians to follow the evolution of sexual development, age of menarche and menstrual cycles in these girls.

On the basis of the evidence discussed above, premature pubarche has to be included among conditions prone to develop central obesity, insulin resistance and its complications for adult life. It is advisable, then, in clinical practice to study these children in terms of body mass index, insulin sensitivity and lipid profile to assess the feasibility of implementing preventing measures involving quality and quantity of food intake, recreational activities and exercise.

4. FINAL COMMENTS

The mechanism behind precocious adrenarche is as intriguing as that behind normal adrenarche. From a cellular perspective, adrenarche depends on the mechanisms regulating post natal zonation of ZR. As stated above, the migration theory of zonal formation assumes that, starting at the age of 6 years, proliferation of progenitor cells would take place in the periphery of the cortex, followed by migration of these cells toward the center of the gland. Upon arrival, these cells would place themselves adjacent to focal areas of ZR cells, already present, and they would acquire
expression of genes specific for ZR cells. This process of cell accumulation would result in the formation of a new zone. In premature pubarche, ZR formation would start earlier and/or it is exaggerated. The trigger for this earlier activation of ZR differentiation could act at the level of progenitor cell proliferation, migration, cell differentiation or, perhaps, at several levels.

It is interesting that adrenarche requires the permissive presence of basal levels of ACTH, but that ACTH is not the primary stimulator. On the other hand, under an acute iv ACTH stimulation (post adrenarche) there is no response of serum DHEAS during the first hours, but there is a response after several days, suggesting that the response might need proliferation of ZR cells. Activation of IGF-1 R by high levels of insulin in patients with insulin resistance, or by IGF-1 in other subjects (39), might induce proliferation of adrenal progenitor cells in some girls with premature or exaggerated adrenarche.

Estrogens might participate in the mechanism of premature adrenarche at the level of ZR cell differentiation through activation of ER. To explain the higher incidence of premature pubarche in girls compared to boys, it might be proposed that peripheral estrogens could be added to local estrogens synthesized by adrenal medulla aromatase, to act on ER (80). Furthermore, DHEA itself, but not DHEAS, can be an agonistic ligand for ER (137), suggesting the existence of a positive feedback system within ZR. Other potential candidate factors playing a role in normal differentiation of ZR cells, such as cytokines (IL-6, TNF), leptin, components of the extracellular matrix or of adrenal medulla, might be responsible of premature adrenarche.

Until recently, the secretion of adrenal androgens, as well as the growth of pubic hair in children, was considered as a trivial physiological event, and premature pubarche a minor deviation of normality. However, the numerous recent studies discussed in this review have changed our concept of these events. However, many questions remain with incomplete answers, such as, 1) the mechanisms of adrenarche and premature adrenarche, 2) the physiological actions of adrenal androgens, acting as either direct ligands or pro-hormones, and 3) the relationship between activation of adrenal androgen secretion, growth restriction during fetal life and chronic diseases in adulthood, transforming adrenal
androgens in markers of diseases important for human health. Future research might contribute to provide responses for a better understanding of these questions.

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