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Review

# Premature adrenarche: Etiology, clinical findings, and consequences

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ABSTRACT

Adrenarche means the morphological and functional change of the adrenal cortex leading to increasing production of adrenal androgen precursors (AAPs) in mid childhood, typically at around 5–8 years of age in humans. The AAPs dehydroepiandrosterone (DHEA) and its sulfate conjugate (DHEAS) are the best serum markers of adrenal androgen (AA) secretion and adrenarche. Normal ACTH secretion and action are needed for adrenarche, but additional inherent and exogenous factors regulate AA secretion. Inter-individual variation in the timing of adrenarche and serum concentrations of DHEA(S) in adolescence and adulthood are remarkable. Premature adrenarche (PA) is defined as the appearance of clinical signs of androgen action (pubic/axillary hair, adult type body odor, oily skin or hair, comedones, acne, accelerated statural growth) before the age of 8 years in girls or 9 years in boys associated with AAP concentrations high for the prepubertal chronological age. To accept the diagnosis of PA, central puberty, adrenocortical and gonadal sex hormone secreting tumors, congenital adrenal hyperplasia, and exogenous source of androgens need to be excluded. The individually variable peripheral conversion of circulating AAPs to biologically more active androgens (testosterone, dihydrotestosterone) and the androgen receptor activity in the target tissues are as important as the circulating AAP concentrations as determinants of androgen action. PA has gained much attention during the last decades, as it has been associated with small birth size, the metabolic and polycystic ovarian syndrome (PCOS), and thus with an increased risk for type 2 diabetes and cardiovascular diseases in later life. The aim of this review is to describe the known hormonal changes and their possible regulators in on-time and premature adrenarche, and the clinical features and possible later health problems associating with PA.



**Contents**



## 1. Introduction

The term adrenarche was introduced in the 1940s [1], and it means the morphological and functional change of the adrenal cortex leading to increasing production of adrenal androgen precursors (AAPs) in mid childhood, typically at around 5–8 years of age. This increase in AAP production coincides with the

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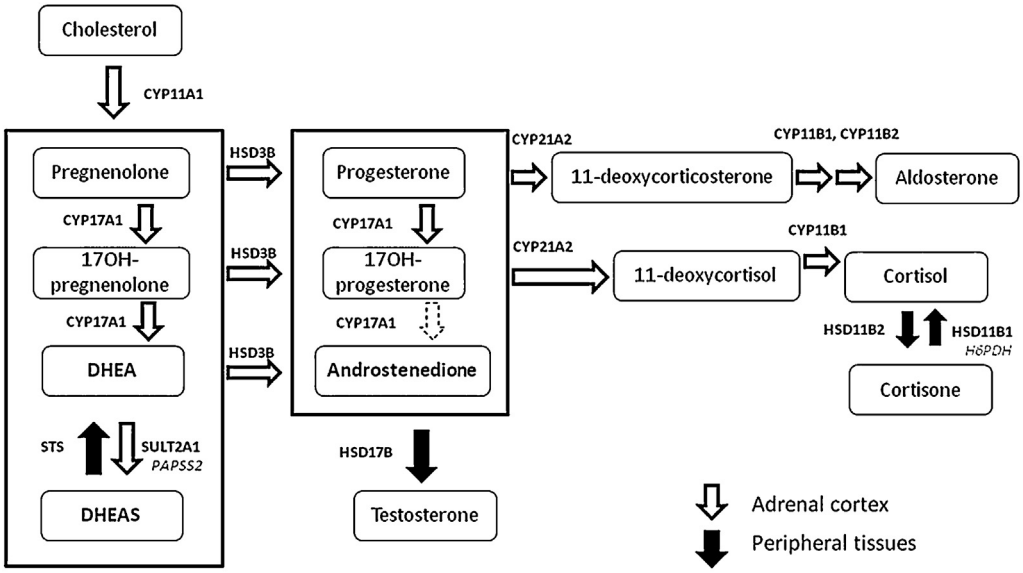


**Fig. 1.** Steroid synthesis pathways in the human adrenal cortex with some peripheral metabolic pathways of adrenal steroids included. CYP11A1, 20,22-desmolase; CYP11B1, 11β-hydroxylase; CYP11B2, aldosterone synthase; CYP17A1, 17α-hydroxylase/17,20-lyase; CYP21A2, 21-hydroxylase; HSD3B, 3β-hydroxysteroid dehydrogenase; HSD11B1, 11β-hydroxysteroid dehydrogenase 1; HSD11B2, 11β-hydroxysteroid dehydrogenase 2; HSD17B, 17β-hydroxysteroid dehydrogenase; STS, sulfatase; SULT2A1, sulfotransferase; PAPSS2, PAPS synthase type 2; H6PDH, hexose-6-phosphate dehydrogenase.

histological development of the zona reticularis, the innermost zone of the adrenal cortex [2]. Dehydroepiandrosterone (DHEA), its sulfate conjugate (DHEAS), and androstenedione are the most important AAPs. Adrenarche occurs only in humans and some other higher primates [3–5], which has limited the clarification of its significance and regulation. The clinical manifestations caused by the increasing secretion of AAPs and their conversion to biologically active androgens appear slightly later than the hormonal changes of adrenarche in serum or urine samples can be detected. Because central puberty may start simultaneously or soon after adrenarche, the clinical signs of adrenarche cannot always be separated from those caused by gonadarche which means the induction of ovarian or testicular sex hormone production in response to the central pubertal activation of the hypothalamo-pituitary-gonadal (HPG) axis.

The clinical condition premature (or precocious) adrenarche (PA) is usually defined as the appearance of clinical signs of androgen action before the age of 8 years in girls or 9 years in boys together with serum AAP concentrations (or urinary AAP metabolite excretion) high for prepubertal chronological age but appropriate for normal Tanner pubertal developmental stage II–III. PA offers a possibility to study the influence and significance of adrenal androgens (AAs) and AAPs in childhood. To accept the "diagnosis" of PA, central puberty (leading to gonadarche), adrenocortical and gonadal sex hormone secreting tumors, and congenital adrenal hyperplasia due to enzyme defects in cortisol biosynthesis have to be excluded as causes of excessive androgen production for age. Originally, precocious appearance of "sexual hair" (pubic and/or axillary) named premature pubarche (PP) [6] was considered the main or only clinical manifestation of PA. This is probably at least one reason why PP is still often erroneously described as a synonym for PA (discussed in [7]). Several studies since 1970s have revealed that in addition to PP, other signs of androgen action are quite common in PA. These include adult type body odor, oily hair or skin, comedones, acne, and slightly increased statural growth [8–13].

The aim of this review is to describe briefly the physiological changes occurring in adrenocortical function during adrenarche, and the clinical features and possible later health problems associating with PA. The readers are advised to see previously published reviews of adrenarche [14–17] and PA [13,18–20] written from different perspectives.

## 2. Morphological, functional, and molecular changes in the adrenal cortex during the human life span

During fetal life, the human adrenal glands are huge (nearly as big as the kidneys) compared to their proportional size in later life. The major part of the human fetal adrenal cortex (about 80% of its total volume) is formed by the innermost fetal zone (FZ) that regresses during the first few months of postnatal life. The outermost zone of the fetal adrenal cortex is called the definitive (or permanent) zone (DZ) and a narrow third layer between the FZ and DZ is called the transitional zone (TZ) (reviewed in [21]). Figs. 1 and 2 outline the steroid synthesis pathways in the human adrenal cortex with some peripheral further metabolic routes of adrenal steroids included (Fig. 1). The fetal adrenal does not express *HSD3B* (3β-hydroxysteroid dehydrogenase, 3β-HSD) enzyme before

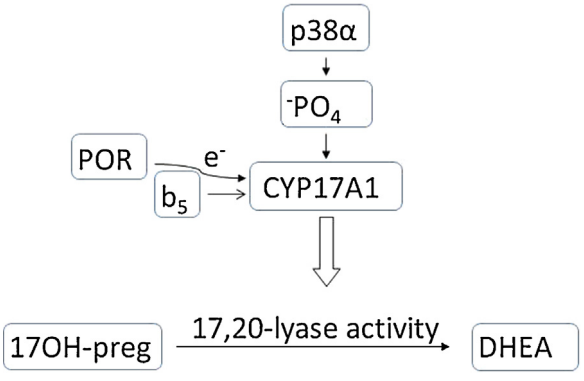


**Fig. 2.** Regulation of 17,20-lyase activity of CYP17A1. This activity is regulated by *P450* oxidoreductase (POR) mediating electrons ($e^-$), and the interaction between POR and CYP17A1 is promoted by the allosteric action of cytochrome b5 (b5). Furthermore, kinase p38α stimulates phosphorylation of CYP17A1, leading to increased 17,20-lyase activity [36].