

Premature Pubarche

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Premature pubarche refers to the precocious appearance of pubic hair without other signs of puberty or virilization. The age limit until recently has been considered 8 years in girls and 9 years in boys. However, the results of a large cross-sectional study carried out in 1997, suggest that the appearance of pubic hair in girls may be considered normal when it occurs after 7 years of age in white subjects, and after 6 years of age in African-Americans (1). Axillary hair, apocrine odor, and acne may or may not be present. Growth velocity may be increased, and slightly advanced bone maturation usually well correlated with the height age, is often present. The transient acceleration of growth and bone maturation has no negative effects on the onset and progression of puberty, and on final height. The precise etiology of premature pubarche is not known. Generally, it has been attributed to an early maturation of the zona reticularis of the adrenal cortex leading to an increase of adrenal androgens to levels normally seen in early puberty and, in turn, to the premature appearance of pubarche. Because half of PP patients have normal androgen levels, a hypersensitivity of the hair follicle to steroid hormones has also been proposed.

The diagnosis of premature pubarche is based on the exclusion of true precocious puberty and the nonclassic forms of congenital adrenal hyperplasia. The incidence of 21-hydroxylase deficiency, the most frequent enzymatic defect, in children with premature pubarche is extremely variable, ranging from 0% in some reports to 40% in others, probably due to the varying ethnic background of the populations studied. Recently, Type II 3 β hydroxysteroid dehydrogenase gene mutations were also identified in patients with premature pubarche and extremely elevated ACTH-stimulated 17-hydroxypregnenolone plasma levels.

Since idiopathic precocious puberty is generally characterized by pubertal progression of the hypothalamic-pituitary-gonadal axis function, it can usually be clinically distinguished from premature pubarche. The plasma concentrations of DHEA, DHEA-S and Δ 4-androstenedione as well as the levels of the 17-ketosteroids and their urinary metabolites, may be increased for age in children with premature pubarche, and similar to those normally found in children with Tanner stage II of pubertal development. ACTH stimulation

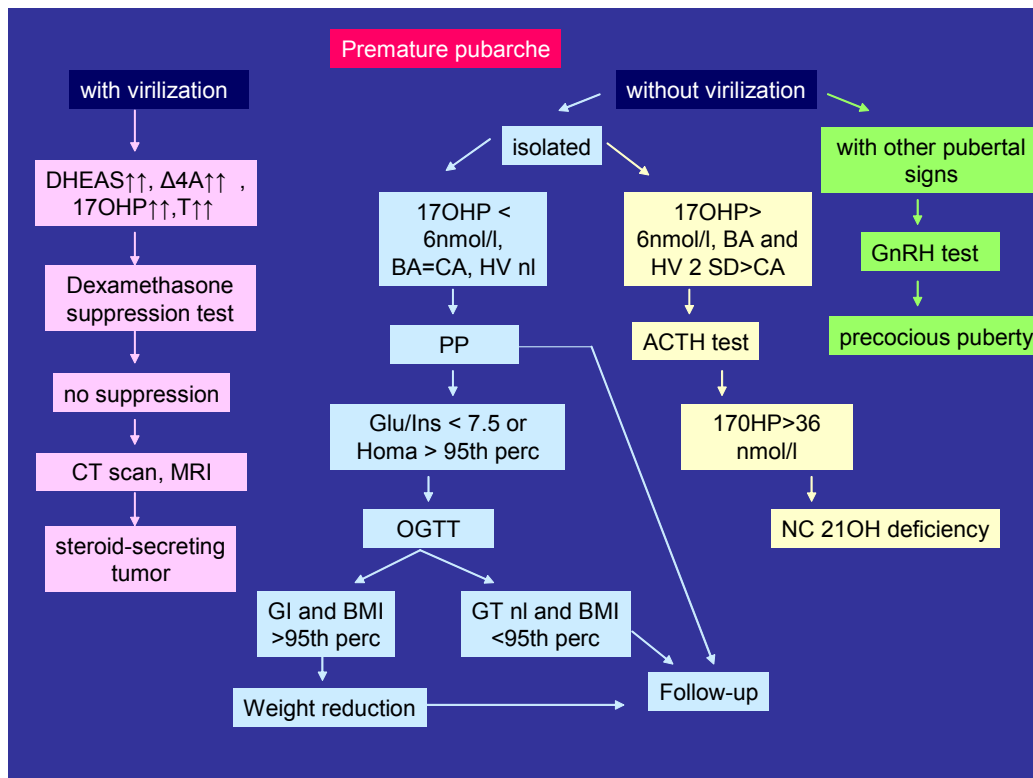
test rules out nonclassic congenital adrenal hyperplasia but not the carrier state. Gonadotropin levels are in the prepubertal normal range both at basal state and after stimulation with gonadotropin-releasing hormone.

Once precocious puberty and nonclassic congenital adrenal hyperplasia are ruled out, no treatment is needed. However, a long-term follow-up of these patients is warranted. Recent data, in fact, indicate that girls with premature pubarche may not have a benign outcome. Forty percent of postpubertal girls diagnosed with premature pubarche during childhood have an increased incidence of functional ovarian hyperandrogenism (2). Furthermore, hyperinsulinemia is a common feature in adolescent patients with premature pubarche and functional ovarian hyperandrogenism, and is directly related to the degree of androgen excess (3). Although the mechanisms linking the triad of hyperinsulinemia, premature pubarche, and ovarian hyperandrogenism remain enigmatic, this frequent concurrence may result, at least in part, from a common genetic or early origin, as the result of in utero growth retardation. It was suggested that programming of the endocrine axes occurs during critical phases of fetal development and is affected by intrauterine growth retardation. Ibanez et al. reported significantly lower birth weight in Spanish girls with premature pubarche and ovarian hyperandrogenism (3). However, other studies did not confirm these results. Specifically, in a Dutch population of short children born small for gestational age, only 2.2% of the girls examined had premature pubarche. This is comparable with the incidence of premature pubarche in the normal population, in which the incidence in white girls is 2.8%. Moreover, in a smaller group of Italian patients with premature pubarche all girls had birth weights appropriate for gestational age (4). It was also shown in a cohort of French young women that intrauterine growth retardation predisposes to insulin resistance but not to hyperandrogenism. It is plausible that there are two distinct forms of premature pubarche, one characterized by the association of premature pubarche with low birth weight, hyperinsulinism, and hyperandrogenism, and one by premature pubarche alone in the absence of other clinical and/or biochemical abnormalities (isolated premature pubarche). The prevalence of these distinct forms of premature pubarche may vary in the different populations. The pathogenetic mechanisms underlying the two forms of premature pubarche may also be different. In children with premature pubarche and low birth weight, hyperandrogenism, and hyperinsulinism the concurrence of these clinical and biochemical features may result from a common origin as an effect of early exposure of the fetus to poor nutrition leading to permanent changes in insulin metabolism and body fat deposition, according to the thrifty phenotype

hypothesis. These are the patients most probably at higher risk of developing PCOS and the metabolic syndrome in adulthood and deserve a careful follow-up. Recent short-term studies suggested that an insulin-sensitizing therapy in these patients may prevent the progression from premature pubarche to PCOS (5). However, since no data regarding safety of long-term use of insulin-sensitizers in children and adolescents, and no long-term studies to document acceptable risk:benefit profile are available, the use of such agents in children with PP is not recommended outside of experimental clinical trials.

In patients with isolated premature pubarche in the absence of biochemical and metabolic abnormalities, a hypersensitivity of the pilosebaceous unit to androgens as a result of increased androgen receptor activity may be responsible for the isolated precocious appearance of pubic hair (6). These are patients who most probably are not at risk of developing endocrine or metabolic abnormalities in adulthood. However, since data on the outcome are not available, a long-term follow-up of these patients is also warranted to ascertain the benign outcome of the disease.

Algorithm for Premature Pubarche



- PP: premature pubarche
- DHEAS: dehydroepiandrosterone sulfate
- Δ4A: androstenedione
- 17OHP: 17-hydroxyprogesterone
- T: testosterone
- Glu/Ins: Glucose/Insulin
- OGTT: oral glucose tolerance test
- GI: glucose intolerance
- GT: glucose tolerance
- NC: nonclassic

Essential references

1. Herman-Giddens ME, Slora EJ, Wasserman RC, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network. *Pediatrics* 1997; 99: 505-512.
2. Ibanez L, Potau N, Virdis R, et al. Postpubertal outcome in girls diagnosed of premature pubarche during childhood : increased frequency of functional ovarian hyperandrogenism. *J Clin Endocrinol Metab* 1993; 76: 1599-1603.
3. Ibanez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls : relation to reduced fetal growth. *J Clin Endocrinol Metab* 1998; 83: 3558-3562
4. Ghizzoni L, Milani S. The Natural History of Premature Adrenarche. *J Pediatr Endocrinol Metab* 2000; 13: 1247-1251.
5. Ibanez L, Valls C, Marcos MV, Ong K, Dunger DB, De Zegher F. Insulin sensitization for girls with precocious pubarche and with risk for polycystic ovary syndrome: effects of prepubertal initiation and postpubertal discontinuation of metformin treatment. *J Clin Endocrinol Metab.* 2004 Sep;89(9):4331-7.
6. Vottero A, Capelletti M, Giuliadori S, Viani I, Ziveri M, Bernasconi S, Ghizzoni L. Decreased androgen receptor gene methylation in premature pubarche: a novel pathogenetic mechanism? *J Clin Endocrinol Metab.* 2006 Mar;91(3):968-72.