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Definition, etiology, and evaluation of precocious puberty

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INTRODUCTION — Precocious puberty is the onset of pubertal development at an earlier age than is expected based upon established normal standards. The cause of precocious puberty may range from a variant of normal development (eg, premature adrenarche or isolated premature thelarche) to pathologic conditions with significant risk of morbidity and even death (eg, malignant germ-cell tumor and astrocytoma).

The clinician faced with a child who presents with early sexual development should consider the following questions.

- Is the child too young to have reached the pubertal milestone in question? To answer this question, the clinician needs to know the normal ages for pubertal milestones and the line between normal and abnormal development.
- What is causing the early sexual development? To answer this question, the physician ascertains whether the sexual development is attributable to androgen or estrogen excess, and whether the source of excess sex hormone is centrally mediated through the hypothalamic-pituitary-gonadal axis, or from an autonomous peripheral origin, or has an exogenous basis.
- Is therapy indicated, and, if so, what therapy?

The definition of precocious puberty and its causes and evaluation will be reviewed here. The treatment of precocious puberty is discussed separately. (See "Treatment of precocious puberty".)

NORMAL PUBERTAL DEVELOPMENT — The hypothalamic-pituitary-gonadal axis is biologically active in infancy with peak activity between six and eight weeks of age. This state yields sex steroid levels comparable with those seen in early-to-mid puberty, but without peripheral effects. Known as the “mini-puberty of infancy,” its biological relevance is unknown.

The neonatal stage is followed by a long period of pre-puberty, which is a state of active suppression of the hypothalamic-pituitary-gonadal axis. Children enter puberty when the suppression is released, which permits re-activation of the hypothalamic-pituitary-gonadal axis. The physiologic and genetic mechanisms that affect timing of pubertal maturation are discussed separately. (See "Normal puberty", section on 'Sequence of pubertal maturation'.)

In 1969 and 1970, Marshall and Tanner defined the standards of normal pubertal development in children and adolescents, known as sexual maturity ratings or “Tanner stages” (table 1) [1,2]. These studies reported that the first sign of puberty in English girls was breast development at an average age of 11 years (thelarche), followed by pubic hair growth (pubarche) and menarche. In English boys, the first sign was testicular enlargement at an average age of 11.5 years followed by penile growth and pubic hair growth (table 2). (See "Normal puberty".)

Since these reports by Marshall and Tanner, several studies in the United States suggest that children, especially overweight children, are entering puberty at a younger age than previously [3-7]. In addition, there are racial differences with puberty occurring earlier in African-American children compared with non-Hispanic white and Hispanic children. These data and the proposed explanations for the trends are discussed separately. (See "Normal

puberty", section on 'Trends in pubertal timing'.)

DEFINITION — Precocious puberty is usually defined as the onset of secondary sexual development before the age of eight years in girls and nine years in boys [8]. These limits are chosen to be 2.5 to 3 standard deviations (SD) below the mean age of onset of puberty. In most populations, attainment of pubertal milestones is normally distributed, with a standard deviation of approximately one year, and the mean age of onset of puberty is about 10.5 years of age in girls and 11.5 years in boys (figure 1A-B) [1-6,8].

Threshold for evaluation — In 1999, the Lawson Wilkins Pediatric Endocrine Society (LWPES) recommended that evaluation for a pathologic cause of precocious puberty be reserved for white girls who have breast and/or pubic hair development before seven years of age and black girls who have these findings before six years of age [9]. This recommendation was based on a study describing the first signs of pubertal development among approximately 18,000 girls in the United States and Puerto Rico, which occurred at a younger age than had been previously reported (figure 2) [7]. The study did not distinguish between girls with isolated thelarche or adrenarche from those with true precocious puberty. This same study did not show that menarche was occurring any earlier (ie, approximately 12.5 years) than had been thought since the 1940s [10].

This recommendation has been controversial because of concerns that lowering the age threshold for evaluation of precocious puberty will result in failure to identify some children with pathologic disease [11,12]. As an example, a retrospective review of 223 girls referred to a tertiary center for evaluation of pubertal development before eight years of age found that utilization of the LWPES guidelines would have resulted in failure to identify a substantial number of patients with treatable disease [12]. Twelve percent of these girls were ultimately diagnosed with an endocrinopathy that was amenable to early intervention, including congenital adrenal hyperplasia, McCune-Albright syndrome, pituitary adenoma, and neurofibromatosis.

We believe careful evaluation is warranted in children presenting with signs of secondary sexual development younger than the age of eight years in girls or nine years in boys. The level of concern and extent of evaluation should increase with decreasing age at presentation. In girls who are between the ages of seven and eight and boys who are between the ages of eight and nine, a comprehensive history and physical examination may be sufficient initially if this examination does not raise any additional concerns. (See 'Evaluation' below.)

Classification — Precocious puberty can be classified based upon the underlying pathologic process.

- **Gonadotropin-dependent precocious puberty** – Gonadotropin-dependent precocious puberty (GDPP, also known as central precocious puberty or true precocious puberty), is caused by early maturation of the hypothalamic-pituitary-gonadal axis. GDPP is characterized by sequential maturation of breasts and pubic hair in girls, and of testicular enlargement and pubic hair in boys. In these patients, the sexual characteristics are appropriate for the child's gender (isosexual). GDPP is idiopathic in more than 80 percent of cases, and almost all idiopathic cases occur in girls (table 3). (See 'Causes of gonadotropin dependent precocious puberty (GDPP)' below.)

- **Gonadotropin-independent precocious puberty** – Gonadotropin-independent precocious puberty (GIPP, also known as peripheral precocious puberty or pseudo-precocious puberty) is caused by excess secretion of sex hormones (estrogens or androgens) derived either from the gonads or adrenal glands, exogenous sources of sex steroids, or ectopic production of gonadotropin from a germ cell tumor (eg, human chorionic gonadotropin, hCG) (table 4). This form of puberty may be appropriate for the child's gender (isosexual) or inappropriate, with virilization of girls and feminization of boys (contrasexual). (See 'Causes of gonadotropin independent precocious puberty (GIPP)' below.)

- **Incomplete precocious puberty** – Incomplete precocious puberty is defined as isolated breast development in girls (premature thelarche), or isolated male hormone-mediated sexual characteristics (such as pubic and/or axillary hair, acne, and apocrine odor) in boys or girls that results from increased adrenal androgen production (premature adrenarche) (table 5). Both of these disorders can be a variant of normal puberty. However, these children should be monitored because some progress to precocious puberty. (See 'Types of

incomplete precocious puberty' below.)

EPIDEMIOLOGY — The traditional definition of precocious puberty as onset of any pubertal development before age eight in girls and nine in boys yields markedly different rates depending on the population studied:

- In a population-based study, breast and/or pubic hair development was present at age eight in 48 percent of African-American girls and 15 percent of White girls [7]. At seven years of age, the proportions were 27 percent and 7 percent, respectively.
- In a population-based study that reviewed data from Danish national registries from 1993 to 2001, the incidence of precocious puberty was 20 per 10,000 girls and less than 5 per 10,000 boys [13]. The diagnostic age limit utilized in this study was eight years for girls and nine for boys. About half the patients had GDPP and the remaining cases were results of isolated premature thelarche or adrenarche, or early normal pubertal development. (See "Premature adrenarche".)

Because precocious puberty is statistically defined as 2.5 to 3.0 SDs below the average age of onset of puberty in healthy children, one would expect that the prevalence rate should be 0.6 percent, or 1 in 160 children, which is considerably lower than the rate in the US study cited above and considerably higher than the Danish study. These observations suggest that the current definition of precocious puberty is problematic, at least in girls, and that selection of children for evaluation should depend on clinical features and perhaps on the rate of progression of observed pubertal changes in the population, which may be related to race/ethnic factors and obesity rates [14]. (See 'Definition' above and 'Threshold for evaluation' above.)

There is a strong female predominance of precocious puberty [15]. As an example, in a retrospective review from a tertiary care center the female to male ratio was 23:1 [16]. About half of the 197 girls and one quarter of the boys had GDPP. An etiology was found in all 16 boys and only in 6 girls (3 percent).

CAUSES OF GONADOTROPIN DEPENDENT PRECOCIOUS PUBERTY (GDPP) — Gonadotropin-dependent precocious puberty (central precocious puberty) is caused by early maturation of hypothalamic-pituitary-gonadal axis. As described above, GDPP affects 10 to 20 times more girls than boys [15,16]. Although the onset is early, the pattern and timing of pubertal events usually progresses in the normal sequence. These children have accelerated linear growth for age, advanced bone age, and pubertal levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) and of estradiol in girls and testosterone in boys.

GDPP is typically treated with a gonadotropin releasing hormone (GnRH) agonist, which produces a prepubertal hormonal state and stops the progression of secondary sexual development, accelerated growth, and bone age advancement. (See "Treatment of precocious puberty", section on 'Treatment for GDPP'.)

Idiopathic — GDPP is idiopathic in more than 80 percent of cases, and almost all idiopathic cases occur in girls [16,17]. As a result, this idiopathic category is responsible for the striking female predominance of GDPP.

CNS lesions — Although GDPP is usually idiopathic, some cases are caused by lesions of the central nervous system (CNS) (table 3). This association mandates that a contrast-enhanced magnetic resonance imaging (MRI) be performed even in the absence of any neurologic abnormalities [17-19]. (See 'Imaging and laboratory tests' below.)

Any type of intracranial disturbance can cause precocious puberty including the following:

- Hamartomas – Hamartomas of the tuber cinereum are benign tumors that are the most frequent type of CNS tumor to cause precocious puberty in very young children. One speculative explanation is the presence of GnRH neurons that act as ectopic hypothalamic GnRH pulse generator [20]. In most cases, the mechanism is unknown. Some hamartomas may produce transforming growth factor alpha (TGF alpha), which is thought to mediate release of GnRH [21].
- Other CNS tumors – Other CNS tumors associated with precocious puberty include astrocytoma [21], ependymoma, pinealomas, and optic and hypothalamic gliomas. Sexual precocity in patients with

neurofibromatosis is usually, but not always, associated with an optic glioma [22]. (See "Clinical manifestations and diagnosis of central nervous system tumors in children".)

- CNS irradiation – Precocious puberty caused by CNS irradiation also is commonly associated with growth hormone (GH) deficiency [23]. GH reserve should be tested and, if deficient, treated with GH, combined with GnRH agonist therapy. (See "Endocrinopathies in the childhood cancer survivor", section on 'Growth hormone (GH) deficiency'.)

- Other CNS lesions – Precocious puberty has been associated with hydrocephalus, cysts, trauma, CNS inflammatory disease, and congenital mid-line defects, such as optic nerve hypoplasia. (See "Congenital anomalies and acquired abnormalities of the optic nerve", section on 'Hypoplasia'.)

Genetics — Specific genetic mutations have been associated with GDPP, although each appears to be a rare cause of precocious puberty:

- Gain-of-function mutations in the Kisspeptin 1 gene (KISS1) [24] and its G protein-coupled receptor KISS1R (formerly known as GPR54) [25] have been implicated in the pathogenesis of some cases of GDPP, while loss-of function mutations in KISS1R can cause hypogonadotropic hypogonadism. These observations suggest that KISS1R is essential for gonadotropin-releasing hormone physiology and for initiation of puberty [26]. (See "Congenital gonadotropin-releasing hormone deficiency (idiopathic hypogonadotropic hypogonadism)", section on 'Kisspeptin 1 receptor gene (KISS1R, formerly GPR54)'.)

- GDPP also can be caused by loss-of-function mutations in MKRN3, an imprinted gene in the Prader-Willi syndrome critical region. Paternally-inherited mutations in MKRN3 were identified in five of 15 families with GDPP, and the mutations affected pubertal onset in both boys and girls [27].

Previous excess sex steroid exposure — Children who have been exposed to high serum levels of sex steroid (eg, those with poorly controlled congenital adrenal hyperplasia and McCune Albright Syndrome) may sometimes develop superimposed GDPP, either from the priming effect of the GIPP-derived sex steroid on the hypothalamus or from sudden lowering of the sex steroid levels following improvement in the control of the GIPP [28-30]. (See 'McCune-Albright syndrome' below.)

Primary hypothyroidism — Children with severe, long-standing primary hypothyroidism occasionally present with precocious puberty. In girls, findings include early breast development, galactorrhea, and recurrent menstrual bleeding; and in boys, premature testicular enlargement [31-33]. Historically this has been referred to as the "overlap" or Van Wyk-Grumbach syndrome [34]. The signs of pubertal development regress with thyroxine therapy. (See "Acquired hypothyroidism in childhood and adolescence".)

A few patients have had high serum FSH or LH concentrations as the underlying pathology. Another proposed mechanism is stimulation of the FSH receptor by high serum thyrotropin (TSH) concentrations [35]. Activating mutations of the FSH receptor have been reported in women with spontaneous ovarian hyperstimulation during pregnancy; the receptors were highly sensitive to stimulation by hCG, and in vitro, by TSH. It was hypothesized that similar mutations would be seen in children with severe primary hypothyroidism and gonadal hyperstimulation, but in two studies of 12 children with the disorder, none had an FSH receptor mutation [36,37].

CAUSES OF GONADOTROPIN INDEPENDENT PRECOCIOUS PUBERTY (GIPP) — Gonadotropin-independent precocious puberty (also known as peripheral precocious puberty or pseudo-precocious puberty) is caused by excess secretion of sex hormones (estrogens or androgens) derived either from the gonads or adrenal glands or from exogenous sources (table 4). Further characterization is based upon whether the sexual characteristics are appropriate for the child's gender (isosexual) or inappropriate, with virilization of girls and feminization of boys (contrasexual). FSH and LH levels are suppressed (in the prepubertal range) and do not increase with GnRH stimulation.

Treatment for GIPP depends on the cause. GnRH agonist therapy is ineffective, in contrast to patients with GDPP. (See "Treatment of precocious puberty", section on 'Treatment for GIPP'.)

In the following discussion, the causes of GIPP are described based upon gender.

Girls

Ovarian cysts — A large functioning follicular cyst of the ovaries is the most common cause of GIPP in girls [38]. Affected patients often present after an episode of vaginal bleeding. These cysts may appear and regress spontaneously, so conservative management is usually appropriate. Large cysts may predispose to ovarian torsion.

Ovarian tumors — Ovarian tumors are a rare cause of GIPP in girls. Granulosa cell tumors can cause isosexual GIPP; Sertoli/Leydig cell tumors (arrhenoblastoma), pure Leydig cell tumors, and gonadoblastoma may make androgens and cause contrasexual GIPP [39-41].

Boys — In boys, causes of isosexual GIPP include:

Leydig cell tumors — Leydig cell tumor should be considered in any boy with asymmetric testicular enlargement. Even if a distinct mass cannot be palpated and none is evident on ultrasonography, the larger testis should be biopsied if it enlarges during follow-up. These testosterone-secreting tumors are almost always benign, and are readily cured by surgical removal [42]. Radical orchiectomy is the recommended procedure; however, successful treatment by direct enucleation of the tumor with sparing of the testis has been reported [43].

Human chorionic gonadotropin (hCG) secreting germ cell tumors — Germ-cell tumors secrete hCG, which activates LH receptors on the Leydig cells. This results in increased testosterone secretion [44]. The increase in testicular size correlates poorly with the serum testosterone concentration because most of the testis is made up of tubular elements whose maturation depends upon FSH.

These tumors occur in the gonads, brain (usually in the pineal region), liver, retroperitoneum, and posterior mediastinum, reflecting sites of embryonic germ cells before their coalescence in the gonadal ridge [44]. The histology of hCG-secreting tumors ranges from dysgerminoma, which respond readily to therapy, to the more malignant embryonal cell carcinoma and choriocarcinoma. All males with mediastinal germinomas should be karyotyped because these tumors are frequently associated with Klinefelter syndrome. (See "Clinical manifestations, diagnosis, and staging of testicular germ cell tumors" and "Pathology of mediastinal tumors", section on 'Germ cell tumors'.)

Familial male-limited precocious puberty — This rare disorder (also known as familial GIPP or testotoxicosis) is caused by an activating mutation in the LH receptor gene, which results in premature Leydig cell maturation and testosterone secretion [45]. Although inherited as an autosomal dominant disorder, girls are not affected clinically because activation of both the FSH and LH receptors is required for estrogen biosynthesis, so the disorder is considered "male-limited" [46]. Affected boys present at one to four years of age.

Treatment of this disorder is discussed separately. (See "Treatment of precocious puberty", section on 'Familial male-limited precocious puberty'.)

Both girls and boys — The following causes of GIPP can occur in either girls or boys. Sexual changes either may be isosexual or contrasexual depending on the gender of the child and the type of sex hormone produced. Excess estrogen will cause feminization, while excess androgen will result in virilization.

Exogenous estrogen — Feminization has been attributed to excess estrogen exposure from creams, ointments, and sprays (eg, estradiol transdermal spray) [47]. Caretakers using these topical estrogens to treat menopausal symptoms may inadvertently expose children to the hormones [48]. Other possible sources of estrogen exposure include contamination of food with hormones, phytoestrogens (eg, in soy), and folk remedies such as lavender oil and tea tree oil [49,50]. A food source was suspected for local “epidemics” of early thelarche in Italy and Puerto Rico during the 1980s, but no single causative substance was found in food samples [51-53].

Adrenal pathology — Adrenal causes of excess androgen production include androgen-secreting tumors and enzymatic defects in adrenal steroid biosynthesis (congenital adrenal hyperplasia). Boys who have an adrenal cause for their precocity will not have testicular enlargement (<4 mL testicular volume or <2.5 cm in diameter). (See

"Genetics and clinical presentation of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency".)

Premature pubarche may be the presenting feature of an inherited disorder of adrenal steroid metabolism, including 11-beta hydroxylase deficiency, 3-beta hydroxysteroid dehydrogenase type 2 deficiency, hexose-6-phosphate dehydrogenase deficiency and PAPSS2 deficiency. (See "Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency".)

Adrenal estrogen-secreting tumors can lead to feminization. Rarely, adrenal tumors may produce androgen and estrogen, the latter because of intra-adrenal aromatization of androgen (or enough androgen that is peripherally aromatized to estrogen), causing both male and female pubertal changes [54]. (See "Clinical presentation and evaluation of adrenocortical tumors".)

Pituitary gonadotropin-secreting tumors — These tumors are extremely rare in children and are associated with elevated levels of FSH and/or LH [55,56].

McCune-Albright syndrome — McCune-Albright Syndrome (MAS) is a rare disorder defined as the triad of peripheral precocious puberty, café-au-lait skin pigmentation (picture 1), and fibrous dysplasia of bone (image 1). MAS should be considered in girls with recurrent formation of follicular cysts and cyclic menses [57]. The skin manifestations and bone lesions may increase over time. In girls presenting with vaginal bleeding, the ovarian enlargement has often been mistaken for an ovarian tumor, leading to unnecessary oophorectomy [58]. Girls presenting with premature vaginal bleeding should be carefully evaluated for features of McCune-Albright syndrome to avoid this potential mistake.

Patients with MAS have a somatic (postzygotic) mutation of the alpha subunit of the G3 protein that activities adenylate cyclase [59-61]. This mutation leads to continued stimulation of endocrine function (eg, precocious puberty, thyrotoxicosis, gigantism or acromegaly, Cushing syndrome, and hypophosphatemic rickets), in various combinations. Mutations can be found in other nonendocrine organs (liver and heart) resulting in cholestasis and/or hepatitis, intestinal polyps, and cardiac arrhythmias, respectively. A heightened risk of malignancy has also been reported [62]. Germline mutations of this mutation would be lethal [59,61,63,64].

The clinical phenotype varies markedly, depending on which tissues are affected by the mutation, but precocious puberty is the most commonly reported manifestation [65]. As in other forms of GIPP, the sequence of pubertal progression may be abnormal, in that vaginal bleeding often precedes significant breast development [66]. Prolonged exposure to elevated levels of sex steroids may cause accelerated growth, advanced skeletal maturation, and compromised adult height. Although the precocious puberty is typically GIPP, a secondary component of GDPP may develop, also because of prolonged exposure to sex steroids [67]. (See 'Previous excess sex steroid exposure' above.)

McCune-Albright syndrome is more common in girls than in boys. Affected girls tend to overproduce estrogens, whereas affected boys overproduce androgens. Therefore, treatment also varies by gender and clinical phenotype. (See "Treatment of precocious puberty", section on 'McCune-Albright syndrome'.)

TYPES OF INCOMPLETE PRECOCIOUS PUBERTY — Incomplete precocious puberty is the early development of secondary sexual characteristics and usually is a variant of normal puberty (often referred to as idiopathic) (table 5). Radiologic determination of bone age should be performed to confirm that epiphysial maturation is not unduly accelerated. If the bone age is normal or only marginally advanced, and the age of onset and other clinical characteristics are typical, no other tests are usually required. Nonetheless, monitoring of children with this condition is needed to ensure that they do not develop GDPP.

Premature thelarche — Most cases of premature thelarche are idiopathic and present around two years of age (but may start at birth) and either remit spontaneously or are very slowly progressive. Most of these girls have no other signs of pubertal development and their growth rate is normal. Their serum estradiol concentrations are typically in the prepubertal range. The cause is not known. Premature thelarche can progress to true isosexual

precocious puberty in 14 to 20 percent of these children [68,69].

Key features of premature thelarche are:

- Isolated breast development, either unilateral or bilateral
- Absence of other secondary sexual characteristics
- Normal linear growth
- Normal bone age

Premature thelarche occurs in two peaks: one during the first two years of life and the other at six to eight years of age. It may be more common in Black or Hispanic children, particularly if they are overweight [70-72]. In most instances, no cause can be found. Soy-based infant formulas have been implicated, although the evidence is weak and the consequence may be only a slower waning of breast tissue during infancy [73-75]. Use of lavender oil, tea tree oil, or hair care products that contain placental extract has also been implicated in some cases of premature thelarche [49].

Generally premature thelarche requires only sympathetic reassurance. However, to identify any patient with progressive puberty, the patient should be followed regularly at six month intervals. The patient should be examined for signs of additional pubertal development, and growth data should be plotted; an accelerated height velocity would suggest progressive puberty and requires further evaluation. (See 'Evaluation' below.)

Consultation with a pediatric endocrinologist is warranted if any of the following is present [76]:

- Progressive secondary sexual development
- Increasing growth velocity
- Accelerated bone maturation
- Onset after three years of age

Neonates — Breast hypertrophy can occur in female and male neonates. It is caused by stimulation from maternal hormones and usually resolves spontaneously within a few weeks or months. While in most cases, neonatal thelarche disappears over the first months of life, failure to do so almost never has any pathologic significance. Breast development at birth in both sexes is sometimes quite prominent and may also be associated with galactorrhea ("witch's milk"), which also resolves spontaneously [77]. (See "Overview of breast masses in children and adolescents", section on 'Neonates and infants'.).

Premature adrenarche — Premature adrenarche is characterized by the appearance of pubic and/or axillary hair (pubarche) prior to the age of eight years in girls and nine years in boys. It is more common in girls, Black females, and individuals with obesity and insulin resistance. Premature adrenarche is considered a variant of normal development but is a risk factor for polycystic ovary disease in girls. Follow up of all children with premature adrenarche is, therefore, recommended [78]. (See "Premature adrenarche" and "Definition, clinical features and differential diagnosis of polycystic ovary syndrome in adolescents".)

Evaluation of a child with premature pubarche begins with bone age determination. If the bone age is normal or slightly advanced, then no further workup is needed, but the child should be monitored for further pubertal progression. If the bone age is advanced by more than 20 percent of chronological age, then further evaluation should be performed (algorithm 1). The diagnosis of idiopathic premature adrenarche is best supported by documentation that the child's serum dehydroepiandrosterone sulfate (DHEAS) concentration is appropriate for pubic hair stage and that levels of early morning (8 to 9 AM) 17-hydroxyprogesterone and testosterone are in age-appropriate normal ranges; these tests are performed to assess for pathologic sources of excess androgen, such as congenital adrenal hyperplasia. (See "Premature adrenarche", section on 'Evaluation of premature pubarche'.)

EVALUATION

Guiding principles — The evaluation for precocious puberty focuses on answering the following questions:

- Who should be evaluated? – We believe careful evaluation is warranted in children presenting with signs of secondary sexual development younger than the age of eight (girls) or nine (boys) years. The concern and extent of evaluation should increase with decreasing age at presentation. In girls who are between the ages of seven and eight and boys who are between the ages of eight and nine, a comprehensive history and physical examination may be sufficient if this examination does not raise any additional concerns.

- Is the cause of precocity central or peripheral? – The sequence and pace of pubertal development in children with gonadotropin-dependent precocious puberty (GDPP, central precocious puberty) recapitulates normal pubertal development but at an earlier age (figure 1A-B). By contrast, individuals with gonadotropin-independent precocious puberty (GIPP) have a peripheral source of gonadal hormones and are more likely to display deviations from the normal sequence and pace of puberty. As an example, a girl who progresses to menstrual bleeding within one year of the onset of breast development is more likely to have ovarian disease (a cause of GIPP) than GDPP [79,80].

- How quickly is the puberty progressing? – The pace of pubertal development reflects the degree and duration of sex steroid action.

    - A rapid rate of linear growth and skeletal maturation (measured as advanced bone age) suggests either GDPP or GIPP due to ovarian or testicular disease with high concentrations of sex steroids (table 6). Pubertal progression would be considered slow if there is minimal or no change in stage of breast, pubic hair, or genital development during six or more months of observation. Height velocity is considered accelerated if it is more than the 95th percentile for age.

    - By contrast, a child with normal linear growth and skeletal maturation (bone age normal or minimally advanced) suggests idiopathic premature adrenarche with low concentrations of sex steroids, rather than GDPP or GIPP (figure 3).

- Is the precocity because of excess estrogen or androgen? – Are the secondary sexual characteristics virilizing or feminizing? In girls, isolated virilization excludes a central etiology; in boys, feminization excludes both a central and most testicular etiologies. A rare ovarian cause of virilization is ovarian arrhenoblastoma (Sertoli-Leydig cell tumor) [81]; a rare testicular cause of feminization is a feminizing Sertoli cell tumor, which may be associated with Peutz-Jeghers syndrome [82].

Initial evaluation — The evaluation of a patient suspected to have precocious puberty begins with a history and physical examination, followed by radiographic measurement of bone age to determine whether there is a corresponding increase in epiphysial maturation.

- Medical history – The history focuses on when the initial pubertal changes were first noted for the patient, as well as the timing of pubertal onset in his or her parents and siblings. In addition, other questions are directed toward evidence of linear growth acceleration, the presence of headaches, seizures or abdominal pain (indicative of either CNS or ovarian process) and previous history of CNS disease or trauma. The possibility of exposure to exogenous sex steroids (medicinal or cosmetic sources) or compounds with sex-steroid-like properties should always be explored [47].

- Physical examination – The physical examination includes measurements of height, weight, and calculation of height velocity (cm/yr). Girls with precocious puberty compared with normal girls display an early growth acceleration pattern that can be a useful clue in early identification [83]. The physical examination should include a funduscopic examination to evaluate for papilledema (which would suggest increased intracranial pressure), restricted visual fields (suggestive of a CNS mass), and a thorough dermatological exam to evaluate for cafe-au-lait spots (which would suggest neurofibromatosis or McCune-Albright syndrome).

- Pubertal staging – Secondary sexual development should be assessed as objectively as possible to determine the sexual maturity rating (Tanner stage) of pubertal development (table 1). This means staging breast development in girls (picture 2), genital development in boys, and pubic hair development in both sexes

(picture 3A-B). In girls, the diameter of glandular breast tissue (by direct palpation including compression to differentiate from adipose tissue) and the nipple-areolar complex should be assessed. In boys, measurements are made of the testicular volume (figure 4) and penile size (stretched length of the non-erect penis, measuring from the pubic bone to tip of glans, excluding the foreskin). Accurate measurements are critical to determine whether further radiologic or laboratory testing is necessary. (See "Normal puberty", section on 'Sexual maturity rating (Tanner stages)'.)

- Bone age – Patients who have early secondary sexual findings confirmed by physical examination should be evaluated for skeletal maturation by radiographic assessment of bone age. Further evaluation is warranted if the bone age is >20 percent older than chronological age (table 7) (approximately 2 standard deviations [SD]).

  If the patient has a normal bone age, he or she is unlikely to have GDPP or GIPP. If the clinical findings are consistent with incomplete precocious puberty (eg, isolated breast development in girls, or isolated premature pubarche in boys or girls) and the bone age is normal, follow-up rather than further evaluation usually is appropriate. (See 'Types of incomplete precocious puberty' above.)

Further evaluation — Once the diagnosis of precocious puberty has been made, further evaluation is needed to determine the cause of precocious puberty, whether therapy is needed, and if so which treatment is appropriate.

The first step is to measure basal LH levels and LH levels following administration of GnRH. The results are used to differentiate between GDPP and GIPP, which then guides additional testing.

Serum LH concentrations after GnRH agonist stimulation — Children with GDPP can be distinguished from those with GIPP (and from normal prepubertal children) on the basis of measurements of serum LH concentrations, at baseline and after administration of exogenous gonadotropin-releasing hormone (GnRH) or GnRH agonist. Interpretation of basal levels is confounded by the secretory pattern of LH, which is pulsatile and predominantly nocturnal in early puberty. LH levels, either basally or after GnRH stimulation, are most easily interpreted if the ultrasensitive assays are employed.

If basal levels of LH are markedly elevated (eg, more than 5 mIU/mL [where IU – International Units]) in a child with precocious puberty, then a diagnosis of GDPP can be made without proceeding to a GnRH stimulation test. However, patients with low or intermediate basal levels of LH should have a GnRH stimulation test to clarify the diagnosis.

GnRH is not available in the United States; a GnRH agonist may be used instead. Levels of LH and sex steroids should be measured using ultrasensitive assays with detection limits adapted to the pediatric age group (ie, LH detection limits near 0.3 mIU/mL). In most laboratories, prepubertal levels of LH are below 0.1 mIU/mL.

- In GDPP, basal levels of LH and FSH are often at pubertal levels and will increase with GnRH stimulation. Peak LH levels above 5 to 8 mIU/mL suggest GDPP.
- In GIPP, LH and FSH levels are low at baseline (prepubertal range) and will not increase with GnRH stimulation.

Several different protocols have been used for this test. Blood is sampled at baseline for LH, FSH, and either estradiol or testosterone. A single dose of the GnRH agonist leuprolide acetate is then given at a dose of 20 mcg/kg. LH is measured as a single sample at 60 minutes (or, in some protocols, 30 minutes) [84-86]. Other protocols employ sampling every 30 minutes for up to two hours. Girls with nonprogressive precocious puberty tend to have a delayed rise in LH and lower LH/FSH ratios than those with GDPP [84,87].

The optimal cutoff value of LH for identifying children with GDPP has not been established, and varies somewhat among assays. However, for most current LH assays a value of 3.3 to 5 mIU/mL defines the upper limit of normal for stimulated LH values in prepubertal children [84]. In addition, measurement of the appropriate sex steroid 24 hours after the leuprolide injection often yields supportive information. Note that neither basal nor stimulated FSH levels are useful for distinguishing the prepubertal state from that of puberty but are measured to assure bioactivity

of the injected leuprolide.

The diagnostic value of a GnRH stimulation test was shown in a study comparing results of 100 normal prepubertal children with those of 10 children with GIPP and 58 children with GDPP. The mean basal serum LH concentration was <0.6 mIU/mL (the sensitivity limit of the assay) in the first two groups, but was 1.6 mIU/mL in 58 children with GDPP [88]. The peak serum LH responses to GnRH in the three groups were 3.1 mIU/mL, 1.5 mIU/mL, and 22 mIU/mL, respectively. The values for serum FSH overlapped much more in the three groups. The specificity and positive predictive value of high basal and GnRH-stimulated serum LH concentrations for the diagnosis of GDPP were 100 percent.

Imaging and laboratory tests

- GDPP – Patients with GDPP, as indicated by elevated basal or stimulated serum LH concentrations, require brain imaging to determine whether there is an identifiable CNS cause (table 7) [84]. Contrast-enhanced magnetic resonance imaging (MRI) is necessary to detect hypothalamic and infundibular lesions [89,90]. However, there is no clear-cut evidence that pituitary microadenomas are associated with GDPP, so magnetic resonance imaging without contrast is probably sufficient in most cases [91]. There is some controversy about whether imaging is required for certain low-risk groups, such as girls presenting after age six [89]. One series found no CNS lesions among a group of girls with pubertal onset after age six and serum estradiol concentrations <45 pmol/L (12 pg/mL) [18], while a second series reported CNS abnormalities in over 15 percent of girls with onset of puberty between six and nine years of age [91]. Therefore, there is insufficient information to confidently exclude this group of patients from imaging.

  In addition, estradiol and testosterone levels should be measured to establish the degree of biochemical pubertal advancement, thyroid function studies should be performed if there is any clinical evidence of hypothyroidism, and children who have received cranial radiation should be evaluated for the possibility of concomitant growth hormone deficiency. (See 'Causes of gonadotropin dependent precocious puberty (GDPP)' above.)

- GIPP – In patients with GIPP, the following laboratory tests are used to identify the peripheral cause of precocious puberty: testosterone, estradiol, LH, FSH, cortisol (drawn in the afternoon, to screen for Cushing syndrome which occasionally causes hyperandrogenism), DHEA, DHEAS, and 17-hydroxyprogesterone. In boys, human chorionic gonadotropin (hCG) should be measured to evaluate for the possibility of an hCG-secreting tumor; if a tumor is found in the mediastinum, a karyotype should be performed to evaluate for Klinefelter syndrome because of its association with mediastinal germinoma [44].

  An abdominal and pelvic ultrasound should be performed to identify the presence of an ovarian cyst or tumor (table 7). Pelvic ultrasound also may be used to monitor pubertal progress in girls; uterine volume changes above 2 mL suggest progressive puberty. Ultrasound examination of the testes is indicated in boys with GIPP to evaluate for the possibility of Leydig-cell tumor.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient information: Early puberty (The Basics)")

SUMMARY

- Precocious puberty is defined as the onset of pubertal development more than 2.5 to 3 standard deviations (SD) earlier than the average age (figure 1A-B). (See 'Definition' above.)
- Because of the trend of earlier pubertal development, there is controversy about the lower age limit for normal pubertal development. We recommend careful evaluation in children presenting with signs of secondary sexual development younger than the age of eight years in girls or nine years in boys (figure 2). (See 'Definition' above and 'Evaluation' above.)
- The etiology of precocious puberty is classified by the underlying pathogenesis into three categories: Gonadotropin dependent precocious puberty (GDPP, also known as central precocious puberty), gonadotropin independent precocious puberty (GIPP), and incomplete precocious puberty. (See 'Classification' above.)
- Gonadotropin dependent precocious puberty (GDPP) is caused by an early activation of normal pubertal development mediated through central activation of the hypothalamic-pituitary-gonadal axis. Although more than 80 percent of these patients have idiopathic GDPP (a diagnosis of exclusion), others will have an underlying CNS lesion that may be amenable to treatment (table 3). Thus all patients with GDPP should have brain imaging. (See 'Causes of gonadotropin dependent precocious puberty (GDPP)' above and 'Further evaluation' above.)
- Gonadotropin independent precocious puberty (GIPP) is caused by peripheral secretion of sex hormones either from the gonads or adrenal glands, ectopic hCG production by a germ cell tumor, or by exogenous sources of sex steroids, and is independent from the hypothalamic-pituitary-gonadal axis (table 4).
- GDPP can be distinguished from GIPP by measuring LH levels: (See 'Serum LH concentrations after GnRH agonist stimulation' above.)
    - In GDPP, basal LH levels are often elevated into the pubertal range and show a pubertal (heightened) response to GnRH stimulation.
    - In GIPP, the LH level is low at baseline and fails to respond to GnRH stimulation.
- Incomplete (idiopathic) precocious puberty consists of isolated breast development (premature thelarche) or isolated characteristics such as pubic hair development (premature adrenarche) (table 5). Either of these patterns usually is a variant of normal puberty and requires no intervention. However, some of these patients will develop precocious puberty, and close follow-up is recommended. (See 'Types of incomplete precocious puberty' above.)

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REFERENCES

1. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969; 44:291.
2. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970; 45:13.
3. Harlan WR, Harlan EA, Grillo GP. Secondary sex characteristics of girls 12 to 17 years of age: the U.S. Health Examination Survey. J Pediatr 1980; 96:1074.
4. Harlan WR, Grillo GP, Cornoni-Huntley J, Leaverton PE. Secondary sex characteristics of boys 12 to 17 years of age: the U.S. Health Examination Survey. J Pediatr 1979; 95:293.
5. Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 1985; 107:317.
6. Sun SS, Schubert CM, Chumlea WC, et al. National estimates of the timing of sexual maturation and racial

differences among US children. Pediatrics 2002; 110:911.

7. 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.
8. Boepple PA, Crowley WF Jr. Precocious puberty. In: Reproductive Endocrinology, Surgery, and Technology, Adashi EY, Rock JA, Rosenwaks Z (Eds), Lippincott-Raven, Philadelphia 1996. Vol 1, p.989.
9. Kaplowitz PB, Oberfield SE. Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment. Drug and Therapeutics and Executive Committees of the Lawson Wilkins Pediatric Endocrine Society. Pediatrics 1999; 104:936.
10. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. Pediatrics 2008; 121 Suppl 3:S172.
11. Rosenfield RL, Bachrach LK, Chernausek SD, et al. Current age of onset of puberty. Pediatrics 2000; 106:622.
12. Midyett LK, Moore WV, Jacobson JD. Are pubertal changes in girls before age 8 benign? Pediatrics 2003; 111:47.
13. Teilmann G, Pedersen CB, Jensen TK, et al. Prevalence and incidence of precocious pubertal development in Denmark: an epidemiologic study based on national registries. Pediatrics 2005; 116:1323.
14. Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. Pediatrics 2009; 123:84.
15. Pescovitz OH, Comite F, Hench K, et al. The NIH experience with precocious puberty: diagnostic subgroups and response to short-term luteinizing hormone releasing hormone analogue therapy. J Pediatr 1986; 108:47.
16. Bridges NA, Christopher JA, Hindmarsh PC, Brook CG. Sexual precocity: sex incidence and aetiology. Arch Dis Child 1994; 70:116.
17. Chemaitilly W, Trivin C, Adan L, et al. Central precocious puberty: clinical and laboratory features. Clin Endocrinol (Oxf) 2001; 54:289.
18. Chalumeau M, Chemaitilly W, Trivin C, et al. Central precocious puberty in girls: an evidence-based diagnosis tree to predict central nervous system abnormalities. Pediatrics 2002; 109:61.
19. Ng SM, Kumar Y, Cody D, et al. Cranial MRI scans are indicated in all girls with central precocious puberty. Arch Dis Child 2003; 88:414.
20. Mahachoklertwattana P, Kaplan SL, Grumbach MM. The luteinizing hormone-releasing hormone-secreting hypothalamic hamartoma is a congenital malformation: natural history. J Clin Endocrinol Metab 1993; 77:118.
21. Jung H, Carmel P, Schwartz MS, et al. Some hypothalamic hamartomas contain transforming growth factor alpha, a puberty-inducing growth factor, but not luteinizing hormone-releasing hormone neurons. J Clin Endocrinol Metab 1999; 84:4695.
22. Listernick R, Charrow J, Gutmann DH. Intracranial gliomas in neurofibromatosis type 1. Am J Med Genet 1999; 89:38.
23. Ogilvy-Stuart AL, Clayton PE, Shalet SM. Cranial irradiation and early puberty. J Clin Endocrinol Metab 1994; 78:1282.
24. Silveira LG, Noel SD, Silveira-Neto AP, et al. Mutations of the KISS1 gene in disorders of puberty. J Clin Endocrinol Metab 2010; 95:2276.
25. Teles MG, Bianco SD, Brito VN, et al. A GPR54-activating mutation in a patient with central precocious puberty. N Engl J Med 2008; 358:709.
26. Seminara SB, Messager S, Chatzidaki EE, et al. The GPR54 gene as a regulator of puberty. N Engl J Med 2003; 349:1614.
27. Abreu AP, Dauber A, Macedo DB, et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. N Engl J Med 2013; 368:2467.
28. Pescovitz OH, Hench K, Green O, et al. Central precocious puberty complicating a virilizing adrenal tumor: treatment with a long-acting LHRH analog. J Pediatr 1985; 106:612.

29. Pescovitz OH, Cassorla F, Comite F, et al. LHRH analog treatment of central precocious puberty complicating congenital adrenal hyperplasia. Ann N Y Acad Sci 1985; 458:174.
30. Holland FJ, Kirsch SE, Selby R. Gonadotropin-independent precocious puberty ("testotoxicosis"): influence of maturational status on response to ketoconazole. J Clin Endocrinol Metab 1987; 64:328.
31. Van Wyk JJ, Grumbach MM. Syndrome of precocious menstruation and galactorrhea in juvenile hypothyroidism: an example of hormonal overlap in pituitary feedback. J Pediatr 1960; 57:416.
32. Castro-Magaña M, Angulo M, Cañas A, et al. Hypothalamic-pituitary gonadal axis in boys with primary hypothyroidism and macroorchidism. J Pediatr 1988; 112:397.
33. Cabrera SM, DiMeglio LA, Eugster EA. Incidence and characteristics of pseudoprecocious puberty because of severe primary hypothyroidism. J Pediatr 2013; 162:637.
34. Bhansali A, Kashyap A, Lodha S, et al. Isosexual precocity: uncommon presentation of a common disorder. Postgrad Med J 2000; 76:177.
35. Anasti JN, Flack MR, Froehlich J, et al. A potential novel mechanism for precocious puberty in juvenile hypothyroidism. J Clin Endocrinol Metab 1995; 80:276.
36. Ryan GL, Feng X, d'Alva CB, et al. Evaluating the roles of follicle-stimulating hormone receptor polymorphisms in gonadal hyperstimulation associated with severe juvenile primary hypothyroidism. J Clin Endocrinol Metab 2007; 92:2312.
37. Suarez EA, d'Alva CB, Campbell A, et al. Absence of mutation in the follicle-stimulating hormone receptor gene in severe primary hypothyroidism associated with gonadal hyperstimulation. J Pediatr Endocrinol Metab 2007; 20:923.
38. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 47-1989. A six-year-old girl with sexual precocity. N Engl J Med 1989; 321:1463.
39. Lack EE, Perez-Atayde AR, Murthy AS, et al. Granulosa theca cell tumors in premenarchal girls: a clinical and pathologic study of ten cases. Cancer 1981; 48:1846.
40. Young RH, Dickersin GR, Scully RE. Juvenile granulosa cell tumor of the ovary. A clinicopathological analysis of 125 cases. Am J Surg Pathol 1984; 8:575.
41. Arhan E, Cetinkaya E, Aycan Z, et al. A very rare cause of virilization in childhood: ovarian Leydig cell tumor. J Pediatr Endocrinol Metab 2008; 21:181.
42. Urban MD, Lee PA, Plotnick LP, Migeon CJ. The diagnosis of Leydig cell tumors in childhood. Am J Dis Child 1978; 132:494.
43. Henderson CG, Ahmed AA, Sesterhenn I, et al. Enucleation for prepubertal leydig cell tumor. J Urol 2006; 176:703.
44. Englund AT, Geffner ME, Nagel RA, et al. Pediatric germ cell and human chorionic gonadotropin-producing tumors. Clinical and laboratory features. Am J Dis Child 1991; 145:1294.
45. Shenker A, Laue L, Kosugi S, et al. A constitutively activating mutation of the luteinizing hormone receptor in familial male precocious puberty. Nature 1993; 365:652.
46. Egli CA, Rosenthal SM, Grumbach MM, et al. Pituitary gonadotropin-independent male-limited autosomal dominant sexual precocity in nine generations: familial testotoxicosis. J Pediatr 1985; 106:33.
47. Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. Pediatr Endocrinol Rev 2011; 8:208.
48. Food and Drug Administration safety communication, 7/29/10: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220185.htm (Accessed on October 06, 2010).
49. Henley DV, Lipson N, Korach KS, Bloch CA. Prepubertal gynecomastia linked to lavender and tea tree oils. N Engl J Med 2007; 356:479.
50. Henley DV, Korach KS. Physiological effects and mechanisms of action of endocrine disrupting chemicals that alter estrogen signaling. Hormones (Athens) 2010; 9:191.
51. Partsch CJ, Sippell WG. Pathogenesis and epidemiology of precocious puberty. Effects of exogenous

oestrogens. Hum Reprod Update 2001; 7:292.

52. Fara GM, Del Corvo G, Bernuzzi S, et al. Epidemic of breast enlargement in an Italian school. Lancet 1979; 2:295.
53. Sáenz de Rodríguez CA, Bongiovanni AM, Conde de Borrego L. An epidemic of precocious development in Puerto Rican children. J Pediatr 1985; 107:393.
54. Phornphutkul C, Okubo T, Wu K, et al. Aromatase p450 expression in a feminizing adrenal adenoma presenting as isosexual precocious puberty. J Clin Endocrinol Metab 2001; 86:649.
55. Faggiano M, Criscuolo T, Perrone L, et al. Sexual precocity in a boy due to hypersecretion of LH and prolactin by a pituitary adenoma. Acta Endocrinol (Copenh) 1983; 102:167.
56. Ambrosi B, Bassetti M, Ferrario R, et al. Precocious puberty in a boy with a PRL-, LH- and FSH-secreting pituitary tumour: hormonal and immunocytochemical studies. Acta Endocrinol (Copenh) 1990; 122:569.
57. Frisch LS, Copeland KC, Boepple PA. Recurrent ovarian cysts in childhood: diagnosis of McCune-Albright syndrome by bone scan. Pediatrics 1992; 90:102.
58. Nabhan ZM, West KW, Eugster EA. Oophorectomy in McCune-Albright syndrome: a case of mistaken identity. J Pediatr Surg 2007; 42:1578.
59. Weinstein LS, Shenker A, Gejman PV, et al. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 1991; 325:1688.
60. Shenker A, Weinstein LS, Moran A, et al. Severe endocrine and nonendocrine manifestations of the McCune-Albright syndrome associated with activating mutations of stimulatory G protein GS. J Pediatr 1993; 123:509.
61. Lumbroso S, Paris F, Sultan C, European Collaborative Study. Activating Gsalpha mutations: analysis of 113 patients with signs of McCune-Albright syndrome--a European Collaborative Study. J Clin Endocrinol Metab 2004; 89:2107.
62. Chanson P, Salenave S, Orcel P. McCune-Albright syndrome in adulthood. Pediatr Endocrinol Rev 2007; 4 Suppl 4:453.
63. Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome. Proc Natl Acad Sci U S A 1992; 89:5152.
64. Grant DB, Martinez L. The McCune-Albright syndrome without typical skin pigmentation. Acta Paediatr Scand 1983; 72:477.
65. de Sanctis C, Lala R, Matarazzo P, et al. McCune-Albright syndrome: a longitudinal clinical study of 32 patients. J Pediatr Endocrinol Metab 1999; 12:817.
66. Haddad N, Eugster E. An update on the treatment of precocious puberty in McCune-Albright syndrome and testotoxicosis. J Pediatr Endocrinol Metab 2007; 20:653.
67. Schmidt H, Kiess W. Secondary central precocious puberty in a girl with McCune-Albright syndrome responds to treatment with GnRH analogue. J Pediatr Endocrinol Metab 1998; 11:77.
68. Pasquino AM, Pucarelli I, Passeri F, et al. Progression of premature thelarche to central precocious puberty. J Pediatr 1995; 126:11.
69. Zhu SY, Du ML, Huang TT. An analysis of predictive factors for the conversion from premature thelarche into complete central precocious puberty. J Pediatr Endocrinol Metab 2008; 21:533.
70. Herman-Giddens ME, Kaplowitz PB, Wasserman R. Navigating the recent articles on girls' puberty in Pediatrics: what do we know and where do we go from here? Pediatrics 2004; 113:911.
71. Freedman DS, Khan LK, Serdula MK, et al. Racial and ethnic differences in secular trends for childhood BMI, weight, and height. Obesity (Silver Spring) 2006; 14:301.
72. Biro FM, Galvez MP, Greenspan LC, et al. Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. Pediatrics 2010; 126:e583.
73. Zung A, Glaser T, Kerem Z, Zadik Z. Breast development in the first 2 years of life: an association with soy-based infant formulas. J Pediatr Gastroenterol Nutr 2008; 46:191.
74. Mendez MA, Anthony MS, Arab L. Soy-based formulae and infant growth and development: a review. J Nutr

2002; 132:2127.

75. Freni-Titulaer LW, Cordero JF, Haddock L, et al. Premature thelarche in Puerto Rico. A search for environmental factors. Am J Dis Child 1986; 140:1263.
76. Hoffman P, Pescovitz OH. Premature thelarch. In: Saunders Manual of Pediatric Practice, Findberg L, Kleinman RE (Eds), WB Saunders, Philadelphia 2002. p.745.
77. Madlon-Kay DJ. 'Witch's milk'. Galactorrhea in the newborn. Am J Dis Child 1986; 140:252.
78. Saenger P. Premature adrenarche. In: Saunders Manual of Pediatric Practice, 2nd ed, Fineberg L, Kleinman R (Eds), WB Saunders, Philadelphia 2002. p.833.
79. Heller ME, Dewhurst J, Grant DB. Premature menarche without other evidence of precocious puberty. Arch Dis Child 1979; 54:472.
80. Hill NC, Oppenheimer LW, Morton KE. The aetiology of vaginal bleeding in children. A 20-year review. Br J Obstet Gynaecol 1989; 96:467.
81. Tavassoli FA, Norris HJ. Sertoli tumors of the ovary. A clinicopathologic study of 28 cases with ultrastructural observations. Cancer 1980; 46:2281.
82. Alikasifoglu A, Gonc EN, Akcoren Z, et al. Feminizing Sertoli cell tumor associated with Peutz-Jeghers syndrome. J Pediatr Endocrinol Metab 2002; 15:449.
83. Papadimitriou A, Beri D, Tsialla A, et al. Early growth acceleration in girls with idiopathic precocious puberty. J Pediatr 2006; 149:43.
84. Carel JC, Eugster EA, Rogol A, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009; 123:e752.
85. Houk CP, Kunselman AR, Lee PA. The diagnostic value of a brief GnRH analogue stimulation test in girls with central precocious puberty: a single 30-minute post-stimulation LH sample is adequate. J Pediatr Endocrinol Metab 2008; 21:1113.
86. Kandemir N, Demirbilek H, Özön ZA, et al. GnRH stimulation test in precocious puberty: single sample is adequate for diagnosis and dose adjustment. J Clin Res Pediatr Endocrinol 2011; 3:12.
87. Chi CH, Durham E, Neely EK. Pharmacodynamics of aqueous leuprolide acetate stimulation testing in girls: correlation between clinical diagnosis and time of peak luteinizing hormone level. J Pediatr 2012; 161:757.
88. Brito VN, Batista MC, Borges MF, et al. Diagnostic value of fluorometric assays in the evaluation of precocious puberty. J Clin Endocrinol Metab 1999; 84:3539.
89. Carel JC, Léger J. Clinical practice. Precocious puberty. N Engl J Med 2008; 358:2366.
90. Bladowska J, Biel A, Zimny A, et al. Are T2-weighted images more useful than T1-weighted contrast-enhanced images in assessment of postoperative sella and parasellar region? Med Sci Monit 2011; 17:MT83.
91. Mogensen SS, Aksglaede L, Mouritsen A, et al. Pathological and incidental findings on brain MRI in a single-center study of 229 consecutive girls with early or precocious puberty. PLoS One 2012; 7:e29829.

Topic 5812 Version 22.0

GRAPHICS

Sexual maturity rating (Tanner stages) of secondary sexual characteristics

Boys - Development of external genitalia
Stage 1: Prepubertal
Stage 2: Enlargement of scrotum and testes; scrotal skin reddens and changes in texture
Stage 3: Enlargement of penis (length at first); further growth of testes
Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker
Stage 5: Adult genitalia
Girls - Breast development
Stage 1: Prepubertal
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
Stage 3: Further enlargement of breast and areola; no separation of their contour
Stage 4: Areola and papilla form a secondary mound above level of breast
Stage 5: Mature stage: projection of papilla only, related to recession of areola
Boys and girls - Pubic hair
Stage 1: Prepubertal (the pubic area may have vellus hair, similar to that of forearms)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes
Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5: Adult female in type and quantity, with horizontal upper border

Graphic 55329 Version 7.0

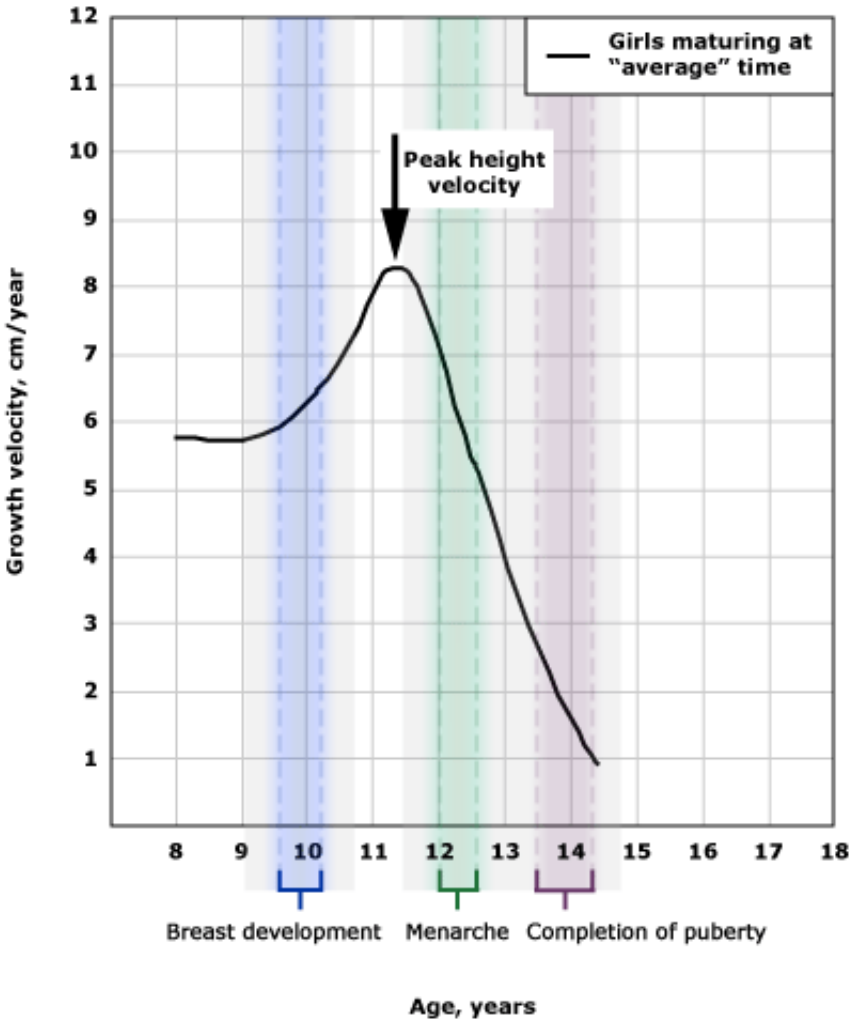
Normal testicular length and volume, by age

Age, yr	Length, cm (mean ± SD)	Volume, mL (approximate)
< 2	1.4 ± 0.4	
2 - 4	1.2 ± 0.2	
4 - 6	1.5 ± 0.6	1
6 - 8	1.8 ± 0.3	
8 - 10	2.0 ± 0.5	2
10 - 12	2.7 ± 0.7	5
12 - 14	3.4 ± 0.8	10
14 - 16	4.1 ± 1.0	20
16 - 18	5.0 ± 0.5	29
18 - 20	5.0 ± 0.3	29

Adapted from Keefer JR. Endocrinology. In: Harriet Lane Handbook, 15th ed, Siberry GK, Iannone R (Eds), Mosby, St. Louis 2000. p.227.

Graphic 76651 Version 2.0

Sequence of puberty in girls

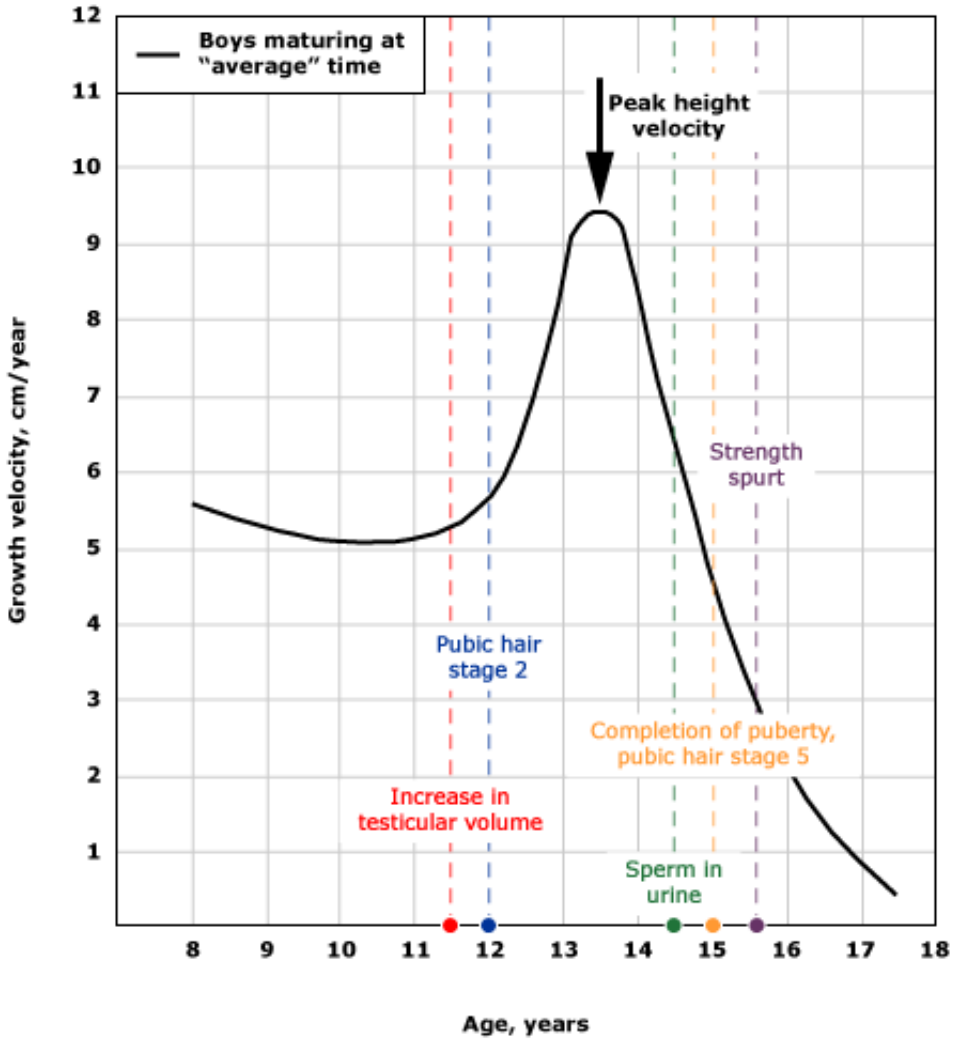


Sequence of events in girls with average timing of pubertal development in the United States. Black girls tend to reach a milestone at a younger age (left-hand side of the bracket) than white girls (right-hand side of the bracket). The median length of time between the onset of puberty (breast tanner stage 2) and menarche is 2.6 years, and the 95th percentile is 4.5 years.

Data from: Biro FM, Huang B, Lucky AW, et al. Pubertal correlates in black and white US girls. J Pediatr 2006; 148:234, and from: Tanner JM, Davies PS. J Pediatr 1985; 107:317.

Graphic 52047 Version 4.0

Sequence of puberty in boys

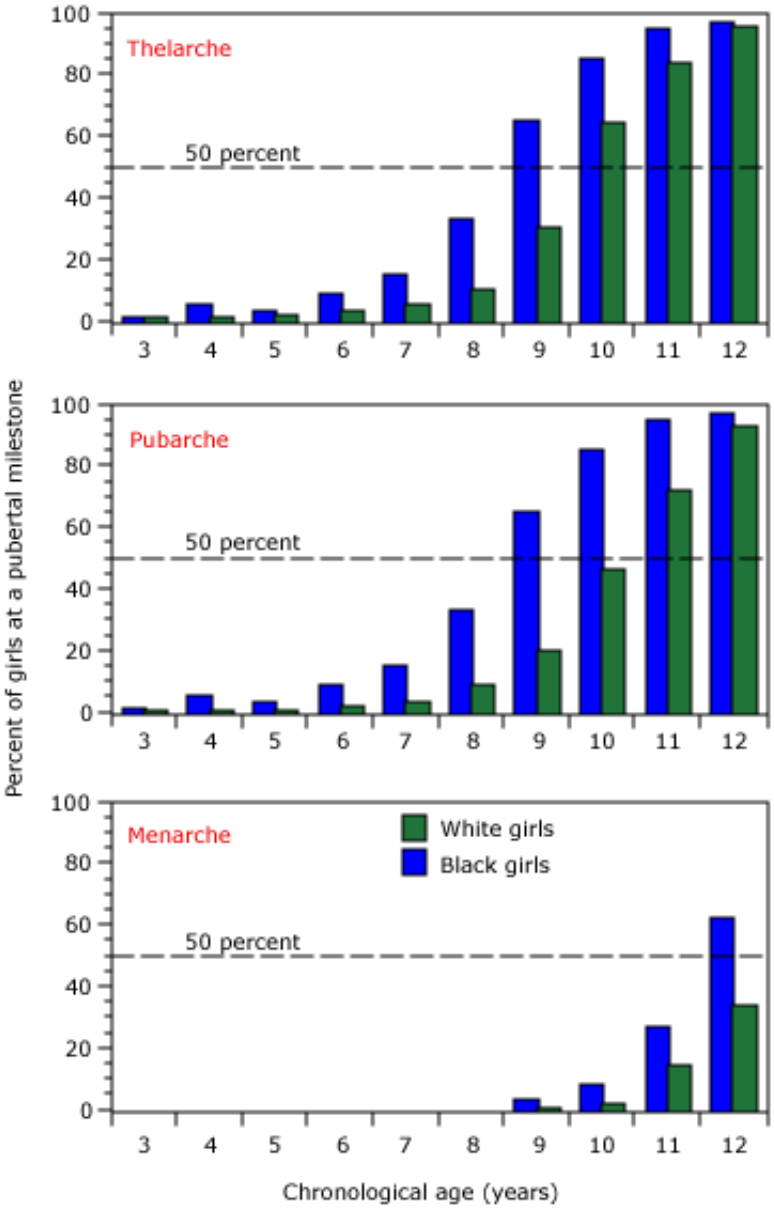


Sequence of pubertal events in boys with average timing of pubertal development in the United States.

Data from: Biro FM et al, Pubertal staging in boys. J Pediatr 1995;127:100; Karpati AM et al, Stature and pubertal stage assessment in American boys: the 1988-1994 Third National Health and Nutrition Examination Survey. J Adolesc Health 2002;30:205-12; Dore E et al. Gender differences in peak muscle performance during growth. Int J Sports Med 2005; 26:274; Neu CM et al. Influence of puberty on muscle development at the forearm. Amer J Physiol Endocrin Metab 2002;283:E103; and Tanner et al. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr 1985; 107:317.

Graphic 72046 Version 1.0

Timing of puberty in white and black girls in the United States



In this study, the first signs of puberty occurred at a younger age than had been previously reported; the mean age of onset was earlier for black versus white girls.

Data from Herman-Giddens, ME, Slora, EJ, Wasserman, RC, et al, Pediatrics 1997; 99:505.

Graphic 72226 Version 1.0

Evaluation of gonadotropin-dependent ("central") precocious puberty

Etiology	Gonadotropin levels	LH response after GnRH stimulation	Sex steroid hormone levels	Clinical features	Additional evaluation
Idiopathic *(80 percent of girls with GDPP)* or CNS tumor	Pubertal levels, with prominent LH pulses during sleep: LH >0.6 IU/L	Pubertal response: LH level post GnRH >7 IU/L	Pubertal values of estradiol (>9 pg/mL), testosterone (20-1200 ng/dL), and DHEAS	Pubertal development accelerated, but proceeds in normal timing and sequence Enlargement of ovary/uterus (by ultrasound) or testes (by exam) Bone age >height age >chronological age Responsive to GnRH agonist therapy	Contrast-enhanced MRI of brain to rule out CNS abnormality In boys, measure hCG to exclude an hCG-secreting tumor Skin examination and skeletal survey to rule out McCune-Albright syndrome

LH: luteinizing hormone; GnRH: gonadotropin-releasing hormone; CNS: central nervous system; DHEAS: dehydroepiandrosterone sulfate; MRI: magnetic resonance imaging; hCG: human chorionic gonadotropin.

Graphic 52565 Version 9.0

Evaluation of gonadotropin-independent ("peripheral") precocious puberty

Etiology	Gonadotropin levels	LH response after GnRH stimulation	Sex steroid hormone levels	Clinical features	Additi evalua
Congenital adrenal hyperplasia (untreated)	Prepubertal	Absent LH response	Sex hormone levels vary depending on the adrenal enzyme block	Boys have prepubertal testes with enlarged phallus and pubic hair development. Girls with "nonclassic" CAH may present with early pubic and/or axillary hair, and other signs of androgen excess.	After ther with glucocort GDPP ma develop a require G agonist th
Leydig cell tumor (boys)	Suppressed	Absent LH response	Very high levels of testosterone	Irregular and asymmetrical enlargement of testes	Tumor ma be palpab testicular ultrasoun in diagno
Ovarian cyst	Suppressed	Absent LH response	Normal or elevated estradiol; occasionally elevated androgens	Pubertal development accelerated; occasionally presents with ovarian torsion and abdominal pain	Abdomina ultrasoun and/or MI
hCG-secreting germ cell tumors (boys)	High hCG or positive pregnancy test	Absent LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm diameter (>4 mL volume), but smaller than expected for the degree of pubertal development Precocious puberty is seen	These tur may occu gonads, l liver, retroperit or medias When in a mediastir karyotype be perfor because

				only in boys as hCG only activates LH receptors (estrogen biosynthesis in the ovaries requires both FSH and LH receptor activation)	strong associatio this findir Klinefelte syndrome
Familial male-limited (gonadotropin-independent) precocious puberty (boys)	Suppressed	Absent LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm diameter (>4 mL volume), but smaller than expected for degree of pubertal development; spermatogenesis may occur Familial: Male-limited autosomal dominant trait Precocious puberty is seen only in boys as there is only activation of the LH receptors, and ovarian estrogen biosynthesis requires both FSH and LH receptor activation	
McCune-Albright syndrome (girls>>boys)	Suppressed	Absent LH response	Pubertal values of estradiol in girls and testosterone in boys	Ovaries: Enlarged for age and usually containing multiple large cysts Testes: Symmetric and >2.5 cm	Ultrasour Ovaries enlarged, follicular c May have hyperacti endocrine disorders thyrotoxi

				diameter (>4 mL volume), but smaller than expected for pubertal development Skin: Multiple irregular-edged café-au-lait spots Bone: Polyostotic fibrous dysplasia	and/or gi
Virilizing adrenal tumor	Suppressed	Absent LH response	High DHEA or DHEAS*; high androstenedione and testosterone	Testes prepubertal	CT, MRI, c ultrasoun adrenal g to locate if still undetecta selective sampling androger
Adrenal cancer	Suppressed	Absent LH response	High DHEA or DHEAS*; high 17-ketosteroids in urine	May present with signs of glucocorticoid excess, and may be associated with hereditary cancer syndromes	CT, MRI, c ultrasoun adrenal g to locate if still undetecta selective sampling androger
Exogenous sex steroids (eg, testosterone creams and estradiol spray or creams)	Suppressed	Absent LH response	Elevated testosterone in boys and estradiol in girls	Estrogen preparations cause feminization, while topical androgens cause virilization in both sexes	Clinical hi explores exogenou steroids b caretaker folk reme Monitor s steroid h levels an clinical st after rem inciting a

GDPP: gonadotropin-dependent precocious puberty; LH: luteinizing hormone; GnRH: gonadotropin-releasing hormone; CAH: congenital adrenal hyperplasia; hCG: human chorionic gonadotropin; FSH: follicle-stimulating hormone; DHEAS: dehydroepiandrosterone sulfate; CT: computed tomography; MRI: magnetic resonance imaging; 17-OHP: 17-hydroxyprogesterone.
* If adrenal tumor tissue loses sulfokinase activity, DHEAS may not be elevated.

Graphic 59268 Version 8.0

Clinical findings and evaluation strategy in apparent idiopathic forms of incomplete precocious puberty

Etiology	Clinical features	Bone age*	Sex steroid hormone levels (if performed)	Stimulation testing (if performed) ¶Δ◇	Additional evaluation
Premature adrenarche (boys or girls)	Isolated pubarche, with normal growth rate. Gonads prepubertal in size and no breast development in girls. Onset usually after 6 years of age. Associated more frequently with obesity, having been born SGA, or brain injury.	Bone age may be normal or slightly advanced (about 10 to 20 percent more than chronological age)*	DHEAS values elevated for age (ie, at Tanner 2 levels).§ Prepubertal levels of 17-OHP and testosterone.§	ACTH stimulation test¶ (if performed): 17-OHP response is consistent with early puberty (versus marked elevations, which suggest CAH).	Monitor for possible further progression to full puberty.
Premature thelarche (girls)	Isolated breast development, with no other signs of pubertal development and normal growth rate. Typical onset at 1 to 3 years of age.	Bone age is normal or slightly advanced (about 10 to 20 percent more than chronological age)*	Prepubertal levels of estradiol¥	GnRH stimulation test◇ (if performed): No or minimal LH and estradiol response.	Monitor for possible further progression to full puberty.

SGA: small for gestational age; DHEAS: dehydroepiandrosterone sulfate; 17-OHP: 17-hydroxyprogesterone; ACTH: adrenocorticotropic hormone; CAH: congenital adrenal hyperplasia; GnRH: gonadotropin-releasing hormone.

* If bone age is normal and clinical features are consistent with idiopathic premature adrenarche or idiopathic premature thelarche, follow-up rather than further evaluation usually is appropriate. If

the bone age is advanced, or if age of onset is atypical, then further evaluation for precocious puberty should be performed, as described below.

¶ For boys or girls with premature pubarche, an ACTH stimulation test is performed if DHEAS, testosterone and/or 17-OHP results are **not** consistent with idiopathic isolated premature adrenarche, to further evaluate for CAH.

Δ For children with premature pubarche, a GnRH stimulation test is performed only if there is rapid growth velocity and bone age maturation, **and** concomitant testicular enlargement in boys, or breast development and ovarian enlargement in girls.

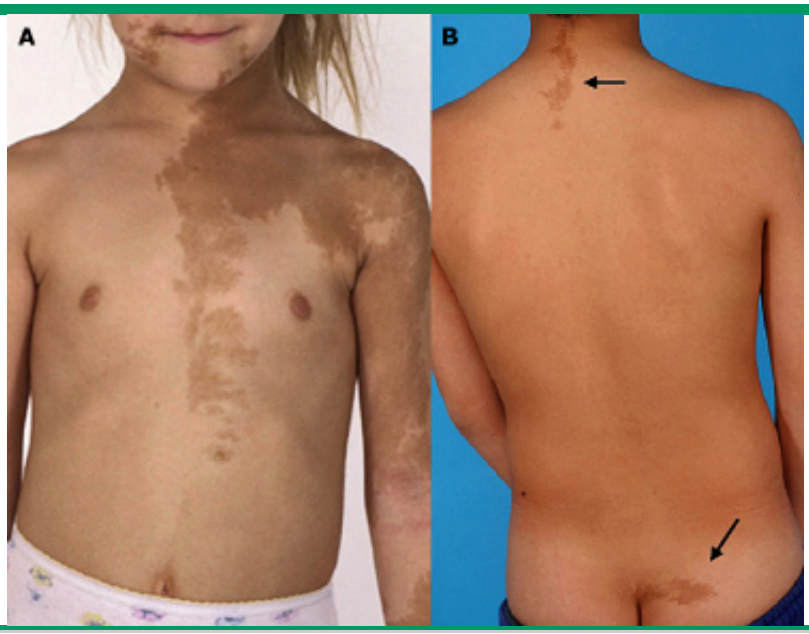
◇ For girls with premature thelarche, a GnRH stimulation test (including measurements of basal and stimulated LH and estradiol) is performed only if the bone age is advanced and/or if there are clinical features that raise concern for premature puberty (eg, rapid pubertal progression, growth velocity, bone age maturation, or ovarian enlargement on ultrasound).

§ Boys or girls with isolated pubarche and moderately advanced bone age (>20 percent of chronological age) should be further evaluated by measuring DHEAS, 17-OHP, and testosterone in the early morning (8 to 9 AM). These tests assess for pathologic causes of excess androgen, such as CAH. Idiopathic premature adrenarche is characterized by DHEAS concentrations between 40 and 115 micrograms/dL (1.1 to 3.1 micromol/L), with testosterone ≤20 ng/dL (0.7 nmol/L), and 17-OHP <200 ng/dL (6 nmol/L).

¥ For girls with idiopathic premature thelarche, early morning (8 to 9 AM) estradiol levels should be in the prepubertal range <45 pmol/L (12 pg/mL).

Graphic 72054 Version 7.0

Café-au-lait spots in McCune-Albright syndrome



A) A typical lesion on the face, chest, and arm of a five-year-old girl with McCune-Albright syndrome, which demonstrates jagged "coast of Maine" borders and the tendency for the lesions to both respect the midline and follow the developmental lines of Blaschko (a configuration of skin lesions characterized by arcs on the upper chest, S shapes on the abdomen, and V shapes over the posterior midline, caused by patterns of x-chromosome inactivation).
B) Typical lesions that are often found on the nape of the neck and crease of the buttocks are shown (arrows).

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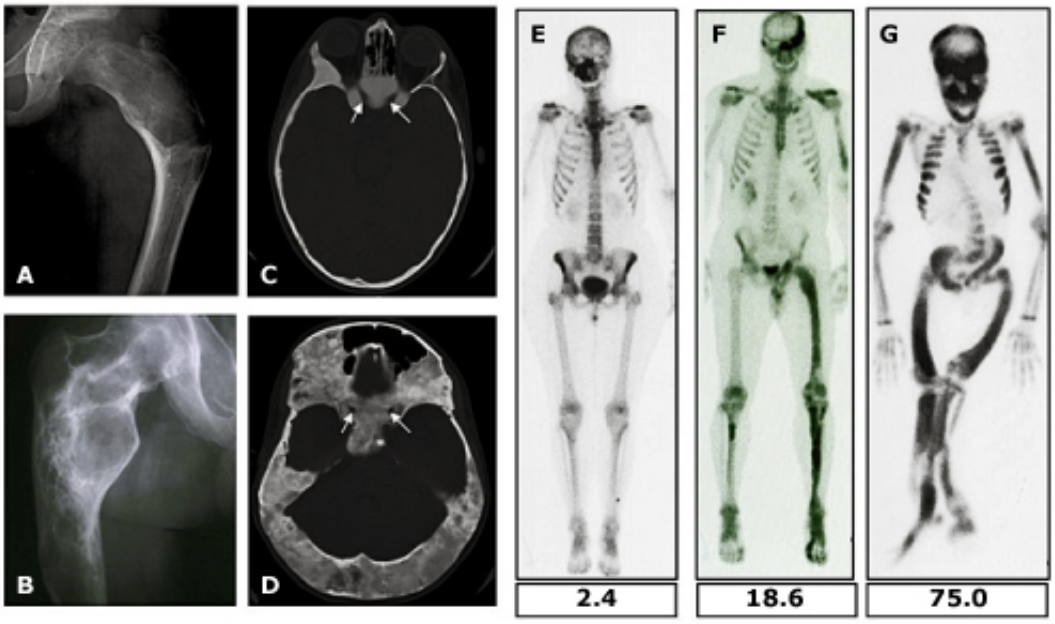
Graphic 80844 Version 5.0

Radiographic appearance of fibrous dysplasia in McCune-Albright syndrome



A) A proximal femur with typical ground glass appearance and shepherd's crook deformity characteristic of fibrous dysplasia (FD) in a 10-year-old child. B) The appearance of FD in the femur of an untreated 40-year-old man demonstrates the tendency for FD to appear more sclerotic with time. C) The typical ground glass appearance of FD in the craniofacial region on a CT image of a 10-year-old child is shown. The white arrows indicate the optic nerves, which are typically encased with FD. D) A CT image in a 40-year-old woman demonstrates the typical appearance of craniofacial FD in an older person, with mixed solid and "cystic" lesions. The Hounsfield Unit measurements of "cystic" lesions are quite useful in distinguishing soft tissue "cystic" lesions from true fluid-filled cysts, which are much more uncommon and tend to behave aggressively with rapid expansion and compression of vital structures. E-G) Bone Scintigraphy in FD. Representative 99Tc-MDP bone scans which show tracer uptake at affected skeletal sites, and the associated skeletal disease burden score are shown. E) A 50-year-old woman with monostotic FD confined to a single focus involving contiguous bones in the craniofacial region. F) A 42-year-old man with polyostotic FD shows the tendency for FD to be predominantly (but not exclusively) unilateral, and to involve the skull base and proximal femur. G) A 16-year-old boy with McCune-Albright syndrome and involvement of virtually all skeletal sites (panostotic) is shown.

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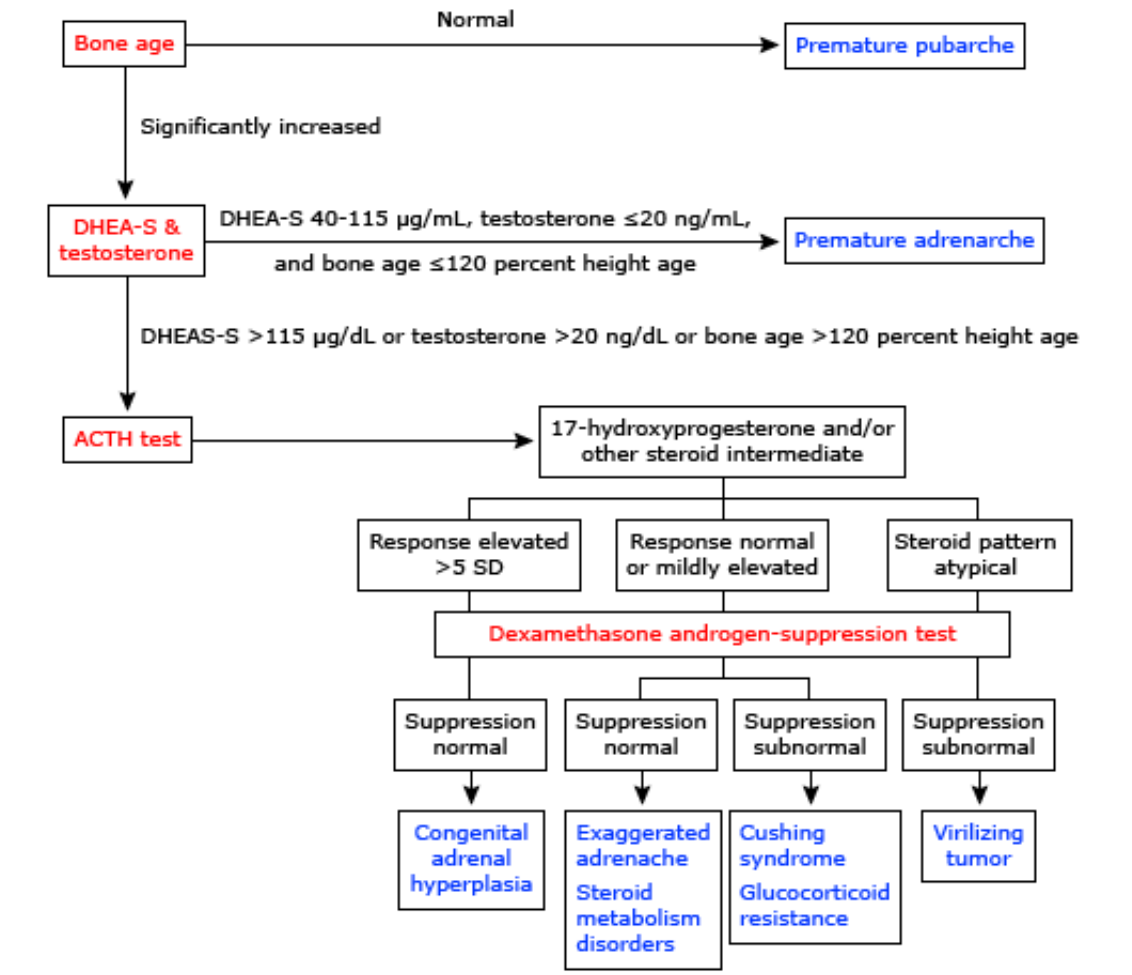
Graphic 81627 Version 2.0

An approach to the diagnostic evaluation for isolated premature pubarche



A significantly advanced bone age is an indication for a screening work-up, consisting of early morning DHEA-S and testosterone levels. A bone age/height age ratio >1.2 (which indicates compromised height potential) or DHEA-S or testosterone level above the normal adrenarchal range (115 mcg/dL and 20 ng/dL, respectively) suggests that the premature pubarche may be caused by a hyperandrogenic disorder rather than ordinary premature adrenarche.
In this case we suggest the following tests:

1. ACTH test (measuring the responses of cortisol precursors). A 17-hydroxyprogesterone (17OHP) level may be substituted for the ACTH test as a screening test for congenital adrenal hyperplasia if it is obtained by 8:00 AM.
2. Dexamethasone androgen-suppression testing (measuring the suppression of elevated androgen levels).

Even if these tests are normal, clinical follow-up is indicated to rule out inordinate progression of pubarche or evidence of virilization or true puberty. This is because bone age interpretation and the precision of testosterone assays at low levels are often problematic, and because abnormal responses to these tests are not necessarily present in very rare disorders of steroid metabolism (eg, apparent/cortisone reductase deficiency and apparent DHEA

sulfotransferase deficiency). See topic text for details about the ACTH stimulation test and dexamethasone androgen-suppression test.

DHEA-S: dehydroepiandrosterone sulfate; ACTH: adrenocorticotropic hormone; SD: standard deviations.

Courtesy of Robert Rosenfield, MD.

Graphic 89151 Version 2.0

Clinical characteristics of nonprogressive versus progressive precocious puberty

	Nonprogressive precocious puberty	Gonadotropin-dependent (central) precocious puberty	Gonadotropin-independent (peripheral) precocious puberty
Physical examination: Advancement through pubertal stages (Tanner stage)	No progression in Tanner staging during 3 to 6 months of observation	Progression to next pubertal stage in 3 to 6 months	Progression
Growth velocity	Normal for bone age and relationship to peak height velocity	Accelerated (>6 cm per year)*	Accelerated*
Bone age	Normal	Advanced for height age	Advanced for height age
Serum estradiol concentration (girls)•	Undetectable	Measurable, variable, and increasing	Measureable, variable, and increasing
Serum testosterone concentration (boys, or girls with virilization)•	Prepubertal	Pubertal and increasing	Pubertal and increasing
Basal (unstimulated) serum LH concentration•	Normal (prepubertal)Δ	Normal or elevated (as compared to prepubertal levels)Δ	Suppressed or normal (prepubertal)Δ
GnRH (or GnRHa) stimulation test•	LH peak in the prepubertal range◇	LH peak elevated (in the pubertal range)◇	No change from baseline, or LH peak in the prepubertal range

* UNLESS the patient has already passed his or her peak height velocity at the time of evaluation, in which case growth velocity may be normal or decreased for chronological age.

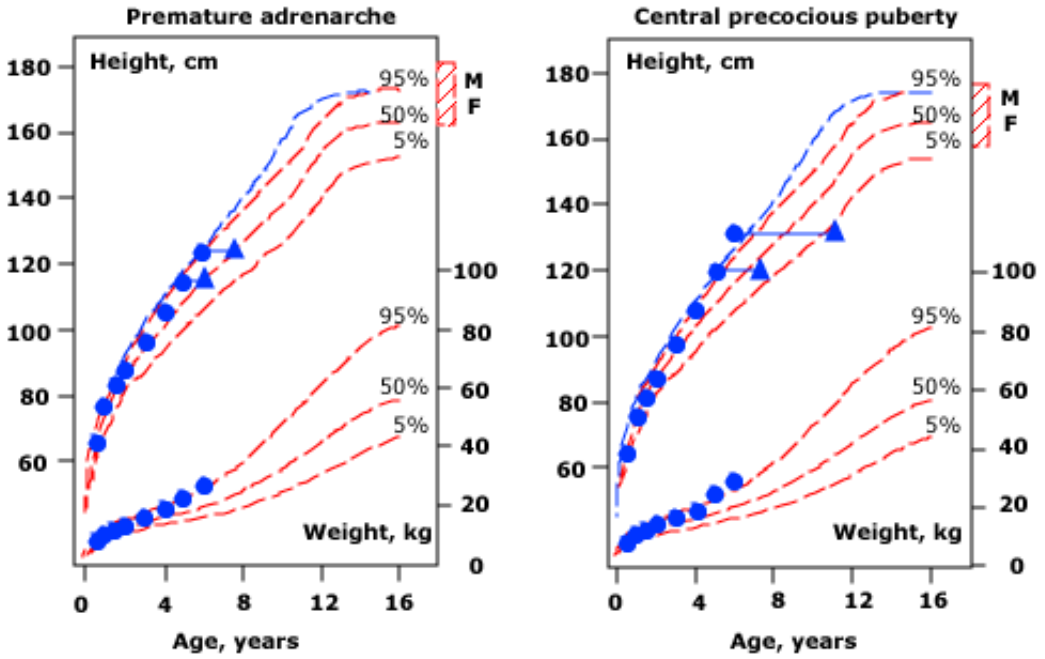
• Serum concentrations of gonadal steroids and LH should be measured using ultrasensitive assays with detection limits adapted to the pediatric age group (ie, LH detection limits near 0.1 mIU/mL).

Δ In most laboratories, basal prepubertal concentrations of LH are below 0.1 mIU/mL.

◇ In most laboratories, the upper limit of normal for LH after GnRH stimulation is 3.3 to 5.0 mIU/mL.

Graphic 72017 Version 2.0

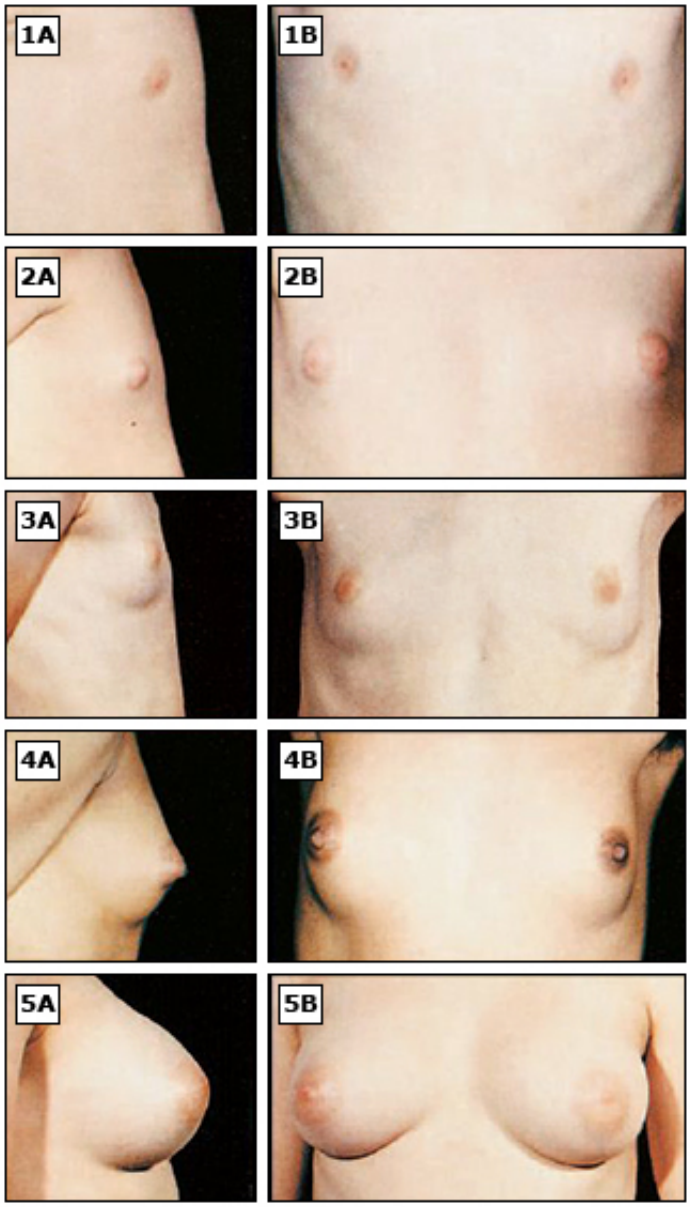
Growth patterns relevant to the assessment of precocious puberty in girls



Height (upper curves) and weight (lower curves) plotted versus age against the backdrop of normal expectations for growth. The triangles reflect height versus bone age, and the shaded box on right hand y axis represents the 95 percent confidence limits for adult height based on parents' heights (M = mother's height centile; F = father's height centile). In the left panel, a child with premature adrenarche has had a modest acceleration of linear growth and skeletal maturation consistent with the impact of relatively weak adrenal androgens. Her "height age" and bone age are equal (both approximately a year in advance of chronological age). In the right panel, the more dramatic impact of gonadal steroid production is evident in a girl with gonadotropin dependent (central) precocious puberty. The linear growth rate is more accelerated and the skeletal maturation dramatically advanced (bone age >> height age > chronological age).

Graphic 60956 Version 2.0

Sexual maturity rating (Tanner staging) of breast development in girls

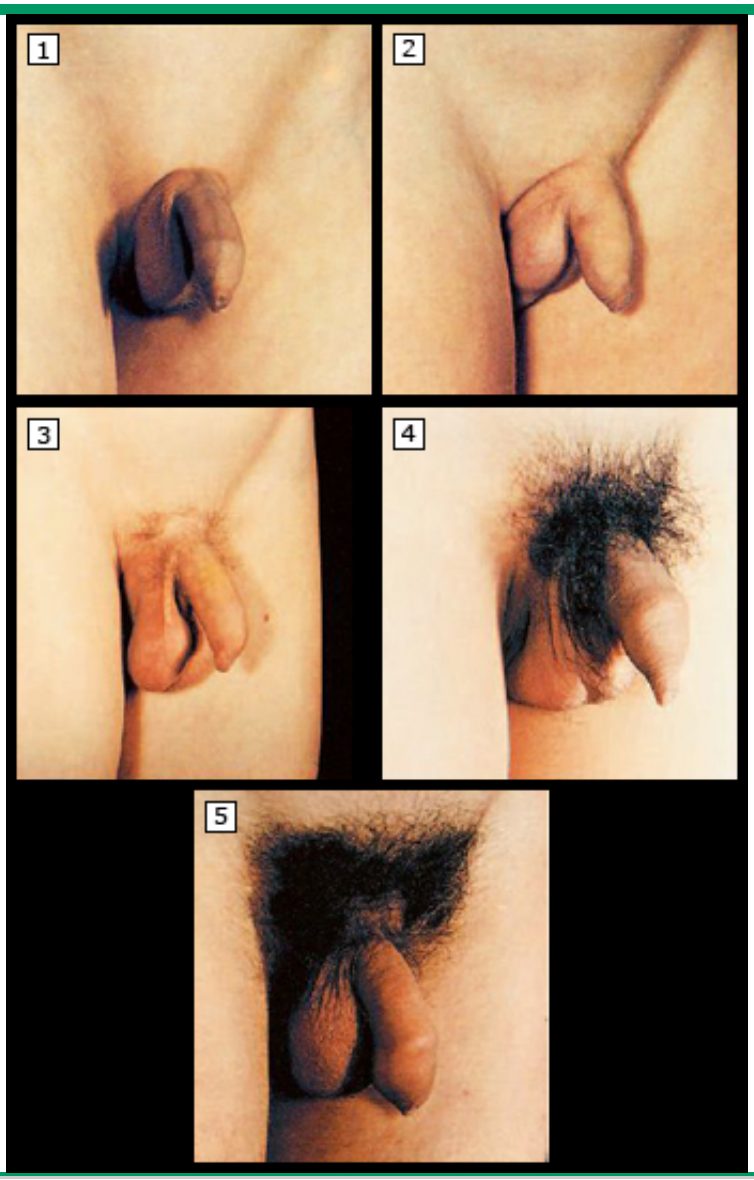


Stages in breast development in girls.
Stage 1: Prepubertal, with no palpable breast tissue.
Stage 2: Development of a breast bud, with elevation of the papilla and enlargement of the areolar diameter.
Stage 3: Enlargement of the breast, without separation of areolar contour from the breast.
Stage 4: The areola and papilla project above the breast, forming a secondary mound.
Stage 5: Recession of the areola to match the contour of the breast; the papilla projects beyond the countour of the areola and breast.

Figure from: Roede MJ, van Wieringen JC. Growth diagrams 1980: Netherlands third nation-wide survey. Tijdschr Soc Gezondheids 1985; 63:1. Reproduced with permission from the author.

Graphic 72038 Version 7.0

Sexual maturity rating (Tanner staging) of pubic hair development in boys



Stages of pubic hair development in boys. Stage 1: Prepubertal, with no pubic hair. Stage 2: Sparse, straight pubic hair along the base of the penis. Stage 3: Hair is darker, coarser, and curlier, extending over the mid-pubis. Stage 4: Hair is adult-like in appearance, but does not extend to thighs. Stage 5: Hair is adult in appearance, extending from thigh to thigh.

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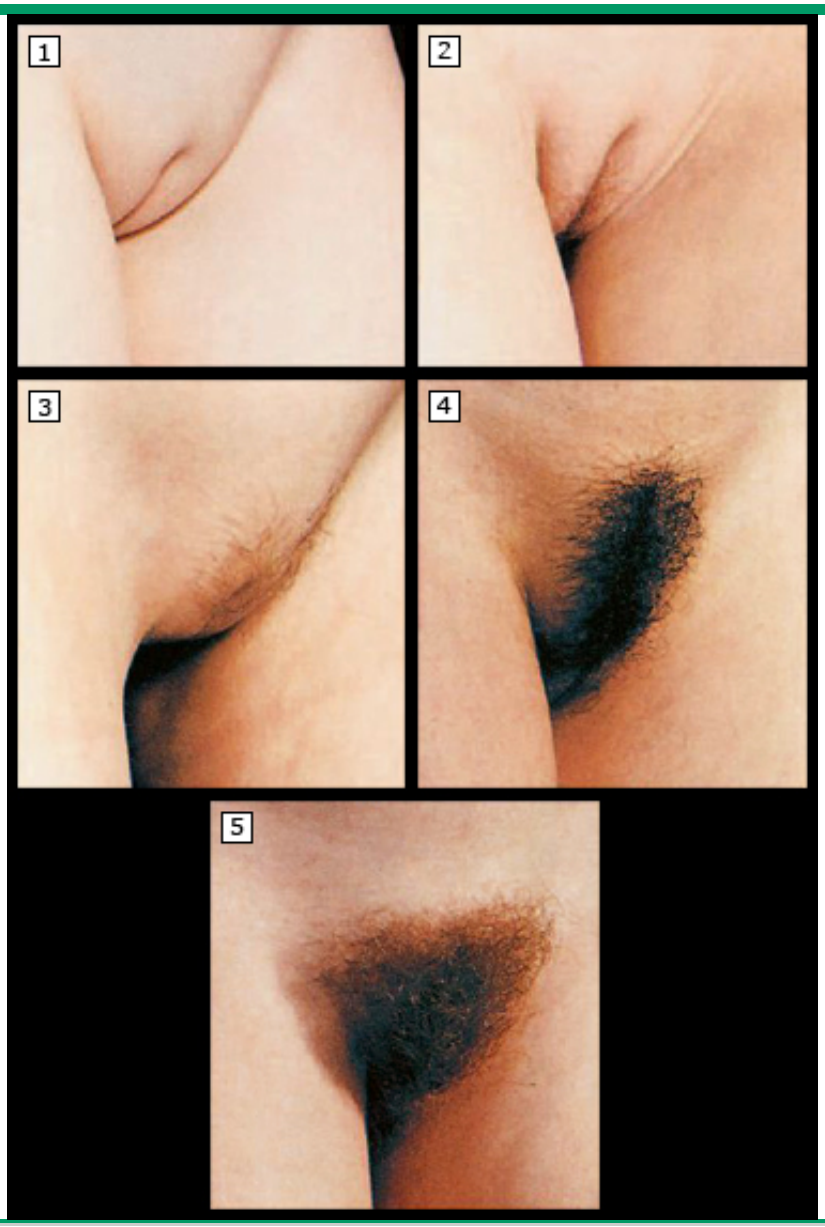
Graphic 80005 Version 4.0

Sexual maturity rating (Tanner staging) of pubic hair development in girls



Stages of development in pubic hair in girls.
Stage 1: Prepubertal with no pubic hair.
Stage 2: Sparse, straight hair along the lateral vulva.
Stage 3: Hair is darker, coarser, and curlier, extending over the mid-pubis.
Stage 4: Hair is adult-like in appearance, but does not extend to the thighs.
Stage 5: Hair is adult in appearance, extending from thigh to thigh.

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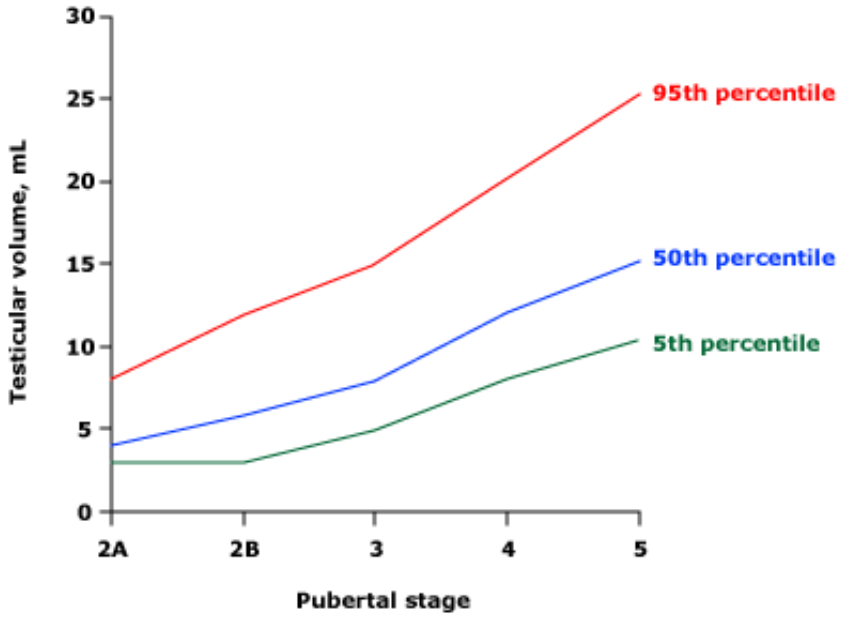
Graphic 79782 Version 4.0

Testicular volume in each pubertal stage



Testicular volume in adolescents as a function of pubertal stage. These data are from serial evaluations of 539 boys, ages 10 to 15 years; the subjects were evaluated every 6 months over 3 years. Pubertal stage represents the sexual maturity rating (Tanner stage of pubertal development).

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Radiological evaluation of precocious puberty

	Bone age	Other
Gonadotropin dependent precocious puberty (GDPP)	↑ ↑	Cranial MRI
		Gonadal ultrasound
Primary hypothyroidism	↓	
Gonadotropin independent precocious puberty (GIPP)		
Gonadotropin-secreting tumors		
Germ-cell tumor (hCG)	↑ ↑	Tumor search: brain, liver, testes, peritoneum, mediastinum
		Pituitary MRI
Gonadotropin-secreting adenoma	↑	
Gonadal autonomy	↑ ↑	Gonadal ultrasound; skeletal survey, bone scan
Adrenal pathology	↑ ↑	Adrenal CT if tumor suspected
Incomplete precocious puberty		
Premature thelarche	slightly ↑	
Premature adrenarche	↑	

hCG: human chorionic gonadotropin; MRI: magnetic resonance imaging; CT: computerized tomography.

Graphic 61907 Version 4.0

Disclosures

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