

Precocious Puberty

COMPETENCY: The resident should be able to define precocious puberty, know the differential diagnosis of precocious puberty, and distinguish between variations of normal and precocious puberty. Additionally, the resident should be able to devise a diagnostic and therapeutic plan for a patient with precocious puberty.

CASE: A 9-year-old boy is brought to you because of the appearance of facial, axillary, and pubic hair. Physical examination reveals that both the testes and the penis are enlarged to a size appropriate for Tanner stage IV sexual maturation. Pubic hair is adult in character and is confined to the suprapubic region. The parents ask if this development is normal.

QUESTIONS:

1. What is the definition of precocious puberty?
2. What is the differential diagnosis of precocious puberty?
3. What are acceptable variations of normal pubertal development?
4. What lab tests aid in the diagnosis of precocious puberty?
5. What is the current treatment of precocious puberty?

REFERENCES:

1. Ghai, K and Rosenfield, R: Disorders of Pubertal Development: Too Early, Too Much, Too Late, or Too Little. *Adolescent Medicine: State of the Art Reviews*. 1994; 5: 19-35.
2. Root, A: Precocious Puberty. *Pediatrics in Review*. 2000; 21: 10-19.
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QUESTIONS:

1. What is the definition of precocious puberty?

Precocious puberty is defined as the appearance of secondary sexual characteristics before the ages of 8 years in girls and 9 years in boys. Before elaborating on this point, a review of normal pubertal development is indicated.

In girls, breast budding (thelarche) is usually the first sign of puberty; pubic hair growth (pubarche) is the initial sign in 15% of girls. Menarche occurs an average of 2 years after thelarche, with a range of 1 to 5 years. Peak height velocity occurs immediately prior to menarche at an average of 12 years in girls.

In boys, the earliest physical sign of puberty is testicular enlargement (long diameter >2.5cm, volume >4ml). Pubertal development progresses at a relatively slow pace through Tanner stage III male genital development and then accelerates. Approximately 4 years elapse between genital stages II and V. Peak height velocity occurs at an average age of 14 years.

Precocious puberty can be further categorized as either complete or incomplete. Complete (also referred to as central or true) precocious puberty results from premature activation of the normal hypothalamic-pituitary-gonadal axis. Pulsatile hypothalamic secretion of gonadotropin-releasing hormone (GnRH) stimulates pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Complete precocious puberty is always appropriate for the sex of the individual (isosexual precocity). Incomplete (also referred to as peripheral) precocity results from extrapituitary secretion of gonadotropin or gonadotropin-independent secretion of gonadal steroids. This condition sometimes causes secondary sexual characteristics contrary to the phenotypic sex (contrasexual precocity).

2. What is the differential diagnosis of precocious puberty?

Complete

Idiopathic

Neurogenic

- Hypothalamic hamartoma
- Neoplasms
- Irradiation
- Posttraumatic
- Postinfectious
- Congenital anomalies

Advanced somatic maturation

- Virilizing disorders
- Feminizing disorders

Incomplete

Normal variant

- Premature thelarche
- Premature adrenarche

Neuroendocrine

- Hypothyroidism
- Isolated excess of LH or hCG

Gonadal

- Autonomous thyroid secretion
- McCune-Albright, testotoxicosis, tumor

Adrenal

- Congenital adrenal hyperplasia
- Autonomous steroid secretion: tumor

Ectopic

- Autonomous hCG secretion

Exogenous

- Anabolic or contraceptive medication

Factitious

- Trauma, tumor

Complete Precocious Puberty:

The manifestations of puberty result from pituitary secretion of LH and FSH. LH stimulates theca/interstitial cells to produce androgens, causing development of pubic hair. In girls/boys respectively, FSH stimulates granulosa/Sertoli cells to produce estrogen/testosterone, causing breast development/testicular enlargement. If the excess of sex hormones is substantial and sustained, puberty is rapidly progressive, with increased height velocity and rate of skeletal maturation. Premature epiphyseal fusion then leads to the paradox of short adult stature in spite of tall stature in childhood.

Precocious puberty occurs about 5 times more commonly in girls than in boys. In approximately 90% of girls, the precocity is idiopathic and seems to represent the extreme end of the bell-shaped curve for the age of onset of normal puberty. Conversely, 90% of boys with complete precocity have a CNS insult or structural abnormality. The diagnosis of idiopathic true precocious puberty is made by exclusion when no CNS etiology is found.

Hamartomas of the tuber cinereum are the most frequent type of CNS tumor causing precocious puberty. These nonprogressive congenital overgrowths of a heterotopic mass of GnRH neurons cause ectopic production of GnRH. With advances in CT and MRI, hamartomas are increasingly found in patients previously thought to have idiopathic precocious puberty. Neoplasms or other destructive processes disinhibit the GnRH pulse generator by disruption of the inhibitory neural pathways that impinge on the hypothalamus. The precocity may be a direct tumor effect or a consequence of cranial surgery or radiotherapy.

Advanced somatic maturation results from a virilizing or feminizing condition that advances bone age to a pubertal level. It is associated with early maturation of the neuroendocrine system and precocious puberty. This condition may occur after effective treatment for virilizing or feminizing disorders such as congenital adrenal hyperplasia or McCune-Albright syndrome.

Incomplete Precocious Puberty:

Normal variants constitute the most common forms of incomplete precocity. **Premature thelarche** is defined as premature breast enlargement with no other signs of sexual maturation. Breast enlargement may regress after a few months or persist with little change. Normal pubertal development does not occur until the usual age. Idiopathic premature thelarche appears to result from slight overactivity of the hypothalamic-pituitary-ovarian axis and represents one end of the spectrum of neuroendocrine activation; the other end is rapidly progressive true sexual precocity. Follow-up is indicated to rule out progressive precocity.

Premature adrenarche causes most cases of premature pubarche (isolated appearance of pubic or axillary hair) with no other signs of puberty or virilization. Premature adrenarche is due to an incomplete precocious puberty of the adrenal glands in which the adrenal cortex prematurely acquires the ability to secrete 17-ketosteroids in response to ACTH. Levels of dehydroepiandrosterone sulfate (DHEAS) over 40 mcg/dl indicate that adrenarche has begun. Follow-up is indicated to rule out progression to exaggerated adrenarche, as discussed below.

Juvenile hypothyroidism on rare occasions causes precocious breast development, galactorrhea, and multicystic ovaries. All symptoms are reversed by thyroxine replacement. The unique feature of this syndrome is that sexual maturation is associated with growth arrest. A potential explanation for this phenomenon relates to the hormonal overlap in the negative feedback regulation of TSH and other pituitary hormone secretion, with increased LH and FSH as a consequence of primary hypothyroidism.

McCune-Albright syndrome is characterized by the triad of irregularly edged (“coast of Maine”) café-au-lait spots, fibrous dysplasia of skull and long bones, and precocity due to autonomously functioning ovarian cysts. It is seen more commonly in girls than boys and sometimes is associated with other endocrine hyperfunction, such as hyperthyroidism, Cushing’s syndrome, hyperprolactinemia, or pituitary gigantism.

Familial testotoxicosis (familial gonadotropin-independent sexual precocity in males) causes pubertal levels of plasma testosterone with a prepubertal gonadotropin profile and response to GnRH testing. The condition is indistinguishable from true precocious puberty on physical examination because the onset of sexual precocity is accompanied by bilateral testicular enlargement. Sex-limited autosomal dominant inheritance is noted. In adulthood, affected individuals achieve normal LH dynamics, and fertility almost always occurs. Mutation of the LH receptor, rendering it constitutively active, seems to underlie most pedigrees.

Hormone-secreting gonadal tumors in girls are most often benign feminizing follicular cysts that may wax and wane spontaneously. Recurrence has been prevented by GnRH agonist treatment, suggesting that the tumors arise as a consequence of gonadotropin stimulation but then become autonomous. Surgical intervention is rarely indicated. Granulosa cell tumor of the ovary is the most common estrogenic neoplasm; some cases mimic true precocity by elaborating moderate amounts of androgen as well. Testicular neoplasms or adrenal rests are usually characterized by irregular nodular enlargement of the testes.

Adrenal androgen secretion is caused by congenital adrenal hyperplasia or androgen-producing tumors. Virilizing CAH caused by a deficiency of 21-hydroxylase is the most common cause of GnRH-independent sexual precocity, and androgens are suppressible by glucocorticoids. Nonclassic CAH can be difficult to distinguish from exaggerated adrenarche on the basis of baseline data, as discussed below. Virilizing adrenal neoplasms secrete disproportionately large amounts of dehydroandrostenedione. Unlike CAH, this secretion of androgens is not suppressible by glucocorticoids.

Ectopic sources of gonadotropins are typified by human chorionic gonadotropin (hCG)-secreting tumors. Specific assays for the beta subunit of hCG confirm that elevation of LH is due to hCG. Virilization due to excessive production of hCG causes slight testicular enlargement in boys that is indistinguishable from early true precocity. Either cranial tumors (most commonly chorioepitheliomas of the hypothalamus or pineal germinomas) or extracranial tumors (most commonly hepatomas or hepatoblastomas, followed by teratoma) secrete hCG. The prevalence of hCG-secreting tumors is increased in 47 XXY Klinefelter's syndrome. Plasma alpha fetoprotein is a useful marker of germ-cell tumors.

Exogenous sources of sex hormones must be considered in the work-up for sexual precocity. Cosmetic creams containing estrogens in the form of placental extract may feminize. Premature pubic hair growth can result from anabolic steroids.

Factitious puberty can result from neurofibroma of the clitoris or breast. Foreign body and sexual abuse are the prime considerations when vaginal bleeding occurs without breast development.

3. What are acceptable variations of normal pubertal development?

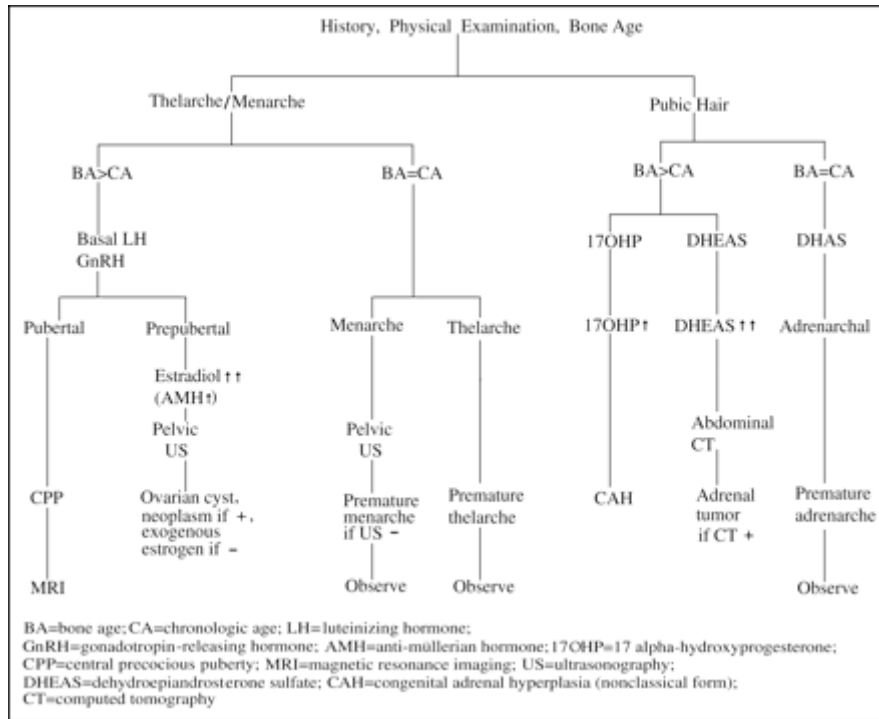
See above for a description of premature thelarche and premature adrenarche. In children with premature thelarche, the bone age is similar to or only modestly advanced (<2 years) over chronologic age; serum levels of LH, FSH, and estradiol are within the prepubertal ranges; and pelvic ultrasonography reveals prepubertal uterine and ovarian sizes and echogenic patterns (<3 cysts <5 mm in diameter). Clinical judgment dictates the extent of evaluation of a girl with isolated premature thelarche, with watchful observation often being the most appropriate.

In children with premature adrenarche, bone age is usually less than 2 years in advance of chronologic age, growth rate is not increased markedly, and DHEA (>50ng/dL) and DHEAS (>20 mcg/dL) levels are within adrenarchal ranges.

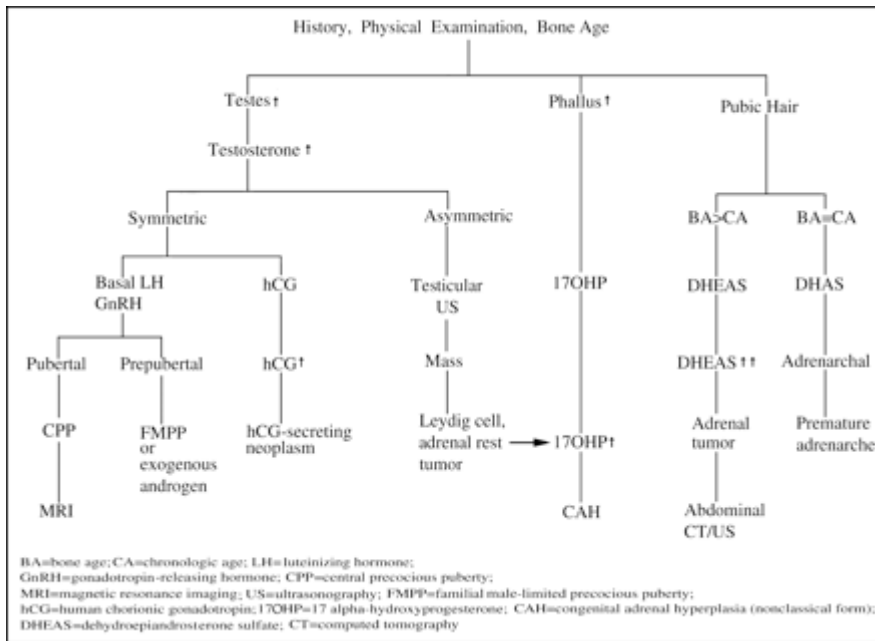
4. What lab tests aid in the diagnosis of precocious puberty?

After separating out normal variants (premature thelarche and adrenarche), lab work-up begins with determination of bone age and assessment for degree of estrogenization (plasma estradiol and vaginal cytology) or virilization (plasma testosterone and DHAS). Precocious puberty is noted by bone age greater than chronologic age and pubertal levels of sex hormones. Advanced skeletal maturation reflects long-standing sex hormone action. In most patients who have complete precocious puberty, the bone age is more than 2 years in advance of chronologic age. In children who have incomplete precocious puberty, bone age more closely approximates or is only slightly more mature than chronologic age.

Figures/Tables:



Evaluation of the female who has isosexual precocious puberty



*Evaluation of the male who has isosexual precocious **puberty***

Although random levels of LH and FSH are seldom useful diagnostically, levels after GnRH stimulation can help distinguish between complete and incomplete forms of precocious puberty. In patients with complete precocious puberty, LH levels should increase after stimulation with GnRH (to 8 IU/L). Conversely, in patients with incomplete precocious puberty, LH levels should remain suppressed or prepubertal despite GnRH stimulation.

In girls with complete precocious puberty, basal serum concentrations of estradiol are often elevated appropriately for the Tanner stage of breast development. In girls who have estrogen-secreting ovarian cysts or granulosa cell tumors, estradiol levels often exceed 100 pg/ml. Similarly, boys with complete precocious puberty have serum testosterone levels appropriate for the noted Tanner stage of male genital development while those with testicular neoplasms have substantially elevated levels. MRI of the CNS is essential in all patients who have complete precocious puberty to identify any specifically treatable CNS lesion.

Boys who have 21-hydroxylase deficient CAH will exhibit elevated serum concentrations of 17 alpha hydroxyprogesterone that decline after administration of cortisol. In those who have deficiency of 11 beta-hydroxylase, serum levels of 11-deoxycortisol are increased. Patients who have virilizing adrenal tumors have markedly elevated serum levels of DHEA and DHEAS. Those who have familial testotoxicosis often present with a positive family history, symmetrically but only slightly (5 to 6 ml) enlarged testes, pubertal serum testosterone levels that increase further after hCG administration, prepubertal basal and post GnRH concentrations of LH and FSH, and testosterone secretion that is not suppressible by GnRH agonists. Leydig cell tumors usually are

identified as unilateral testicular masses; testosterone concentrations are pubertal and nonsuppressible.

5. What is the current treatment of precocious puberty?

Most patients and families simply require reassurance that the premature development is an extreme variation of normal – a normal process happening early. About one-third of the patients with true sexual precocity have a mild, slowly progressive, idiopathic process that does not adversely affect height potential or psychosocial well-being. If the ratio of bone age to height age is less than 1.2 and remains so, normal height potential is likely to be maintained, and no pharmacotherapy is indicated.

GnRH agonists are the medical treatment of choice for rapidly progressive complete precocious puberty. Constant exposure paradoxically desensitizes pituitary gonadotropes to pulses of GnRH and thus suppresses secretion of gonadotropin. Progestins arrest progression of secondary sexual characteristics and menses but do not retard progression of bone age maturation and therefore do not preserve height potential. GnRH agonists are not useful in treating patients with incomplete (peripheral) precocious puberty because their precocity is not mediated by early activation of the pituitary-gonadal axis. Depending on the exact diagnosis, treatment for these patients may include thyroxine, glucocorticoids, enzyme inhibitors, antiandrogen, surgery, or radiotherapy.

REFERENCES:

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