

Puberty- Normal and delayed

COMPENTENCIES

The resident should be able to:

- Identify the first signs of true puberty
- Know the range of ages for normal pubertal onset
- Define and evaluate delayed puberty
- Know what therapy is available and when treatment is warranted
- Know when referral to an endocrinologist is appropriate.

CASE

A 15-year-old male presents to his pediatrician with concerns regarding growth and development. He complains that he is shorter than all the other males in his class. He does not think that he has started puberty. During the history, you learn that patient's father was 65 inches as a sophomore in high school and reached his current height of 73 inches as a freshman in college. Past medical history is unremarkable; patient has always been healthy. He eats well, exercises, and has never had concerns about his growth in the past.

On physical exam, patient is 62 inches tall (~5th percentile), testicles measure ~2.7cm and he has sparse lightly pigmented pubic hair at the base of the penis. Physical exam is otherwise unremarkable.

QUESTIONS

- 1. What are the first signs of puberty?**
- 2. What are the normal age ranges for pubertal onset?**
- 3. What is the definition of delayed puberty?**
- 4. What is the differential diagnosis for pubertal delay?**
- 5. What is the appropriate evaluation for delayed puberty?**
- 6. How is delayed puberty treated?**
- 7. What are indications for treatment of delayed puberty?**
- 8. What would you do for the patient?**
- 9. When would you refer a patient to an endocrinologist?**

REFERENCES

1. SS Nussey & SA Whitehead. Endocrinology An Integrated Approach. Taylor and Francis Group; 2001.
2. K Ghai & R Rosenfield. Disorders of Pubertal Development: Too Early, Too Much, Too Late, or Too Little. Adolescent Medicine: State of the Art Reviews 1994; 5; 1: 18-35.
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CASE

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1. What are the first signs of puberty?

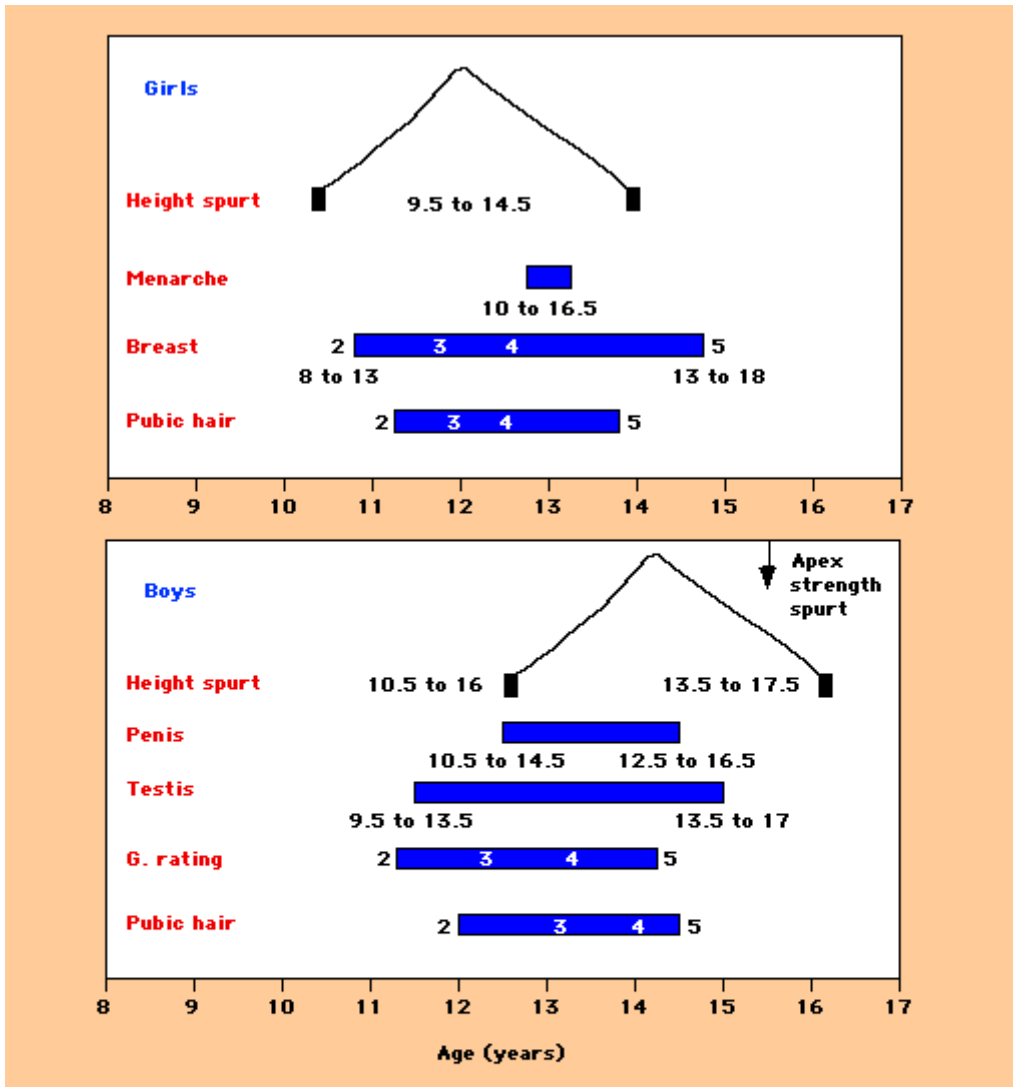
In males, pubertal onset is defined as testicular enlargement to a diameter of 2.5 cm or a volume of 4ml or greater. Breast budding, or thelarche, is the first sign of puberty in females.

Pubic hair in isolation can be secondary to adrenarche rather than gonadarche and thus is not necessarily a sign of true puberty onset.

2. What are the normal age ranges for pubertal onset?

Normal ages for puberty are 8-13 years in girls, with the mean age being 11 years and 9-14 years in boys, with a mean age of 11.5 years.

The table below shows the different age ranges for pubertal milestones in girls and boys.



Timing of pubertal milestones In girls, the first sign of puberty is the onset of breast development (thelarche) which occurs at a mean age of approximately 11 years; this is followed by pubic hair growth and menarche. In boys, the first sign is testicular enlargement which occurs at a mean age of approximately 11.5 years; this is followed by penile and pubic hair growth. In The diagrams above demonstrate the sequence of events at puberty. An average boy and girl are represented in relation to the scale of ages. The range of ages within which some of the changes occur is indicated by the figures below them. (Data from Marshall, WA, Tanner, JM. Arch Dis Child 1969; 44:291.)

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3. What is the definition of delayed puberty?

Delayed puberty is failure to develop secondary sexual characteristics by a certain age, usually set as two standard deviations from the mean. By this definition, 2.5% of the population will be considered to have pubertal delay. Pubertal arrest, which is defined as no progress in puberty over two years, is also included in the definition of pubertal delay.

In girls, delayed puberty is defined as lack of breast development by age 13 years (some authors use a cut-off of 12 years), lack of pubic hair by age 14 years, lack of menarche by age 16 years, or greater than five years between thelarche and menarche.

In boys, puberty is considered delayed if testicular enlargement does not occur by 14 years of age, there is lack of pubic hair by age 15 years, or more than five years are required to complete genital enlargement.

4. What is the differential diagnosis for pubertal delay?

The differential diagnosis of delayed puberty includes constitutional delay of puberty (CDP); growth retarding or attenuating disorders, i.e., undernutrition, endocrinopathies, metabolic disorders, and chronic disease; primary gonadal failure (hypergonadotropic hypogonadism); and gonadotropin deficiency (hypogonadotropic hypogonadism).

The vast majority of those children who experience delayed puberty will have CDP.

5. What is the appropriate evaluation for delayed puberty?

Evaluation of delayed puberty begins with a thorough history and physical. History should address any signs that would suggest endocrinopathy, syndromic diseases, or chronic disease, and should also address constitutional problems such as undernourishment. Family history should assess for delayed puberty in parents or siblings that would suggest/support a diagnosis of CDP.

Work-up includes a physical exam where height and Tanner stages of development are carefully examined. If breast or testicular development is present, normal spontaneous puberty will occur in greater than 95% of patients and reassurance and follow-up are the appropriate course.

If there are no signs of puberty, gonadotropins are assessed initially. If gonadotropins are elevated, a diagnosis of primary gonadal failure is made. Causes for primary hypogonadism include chromosomal abnormalities (Turner syndrome, Klinefelter syndrome) and autoimmune, post infectious, or traumatic destruction of the gonads.

Iatrogenic damage to the gonads, such as from surgery, chemotherapy or radiation therapy can also lead to primary hypogonadism.

If gonadotropins are low or normal, then further testing is warranted and may include a CBC, ESR, chemistry panel, thyroxine, cortisol, and plasma somatomedin C to exclude other causes for delayed puberty. Bone age is often assessed by obtaining a radiograph of the left hand and wrist. This is helpful in the evaluation of delayed puberty because bone age correlates better with the stage of sexual maturation than ~~to~~ **does** chronological age.

Onset of puberty usually corresponds to a bone age of 11-12 years. If the bone age is prepubertal, normal levels of gonadotropins do not rule out primary hypogonadism, but once bone age reaches an early pubertal stage, normal levels of FSH and LH exclude primary hypogonadism.

If all above tests are normal and the history is unremarkable, the diagnosis may be CDP or gonadotropin deficiency (secondary hypogonadism), as random LH and FSH are low in both. The most common diagnostic challenge in the assessment of delayed puberty is distinguishing CDP from idiopathic gonadotropin deficiency. GnRH testing, which measures the response of LH and FSH to exogenous GnRH administration, can be helpful in distinguishing the two entities; however, there is considerable overlap among prepubertal, early pubertal, and hypogonadotropic responses. Bone age can also be

useful in distinguishing idiopathic gonadotropin deficiency from CDP. In patients with CDP, bone age will be delayed but puberty will begin at a pubertal bone age. If bone age reaches 13 years in females or 14 years in males without clinical or hormonal signs of puberty, then the diagnosis is most likely to be gonadotropin deficiency even in the presence of normal levels of gonadotropins. However, there are currently no available lab tests to definitively distinguish between these two entities. Eventual onset and normal progression of puberty is the only way to positively distinguish CDP from hypogonadotropic hypogonadism. Therefore, patients carrying a diagnosis of CDP must be followed closely.

The pathogenesis of CDP is unclear but it is thought that extreme variations in normal result in prolonged persistence of the hypogonadotropic state of childhood. Frequently, there is a positive family history of delayed puberty in parents and siblings.

Gonadotropin deficiency can be congenital or acquired. Congenital causes include isolated GnRH deficiency, Kallmann syndrome, and syndromic causes of GnRH deficiency, such as Prader-Willi syndrome. Acquired causes of hypogonadotropic hypogonadism include tumors such as craniopharyngiomas, infiltrative diseases, e.g., hemochromatosis and histiocytosis, head trauma and pituitary apoplexy. Chronic illness, malnutrition and eating disorders and endocrinopathies (hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's disease) can all cause secondary hypogonadism by impairing secretion of GnRH and should be assessed for in the initial patient history and by the above described laboratory evaluation.

** See Figure 2.

6. How is delayed puberty treated?

Any underlying cause of pubertal delay should be identified and treated. For pubertal delay caused by hypogonadism and in some cases of CDP, treatment with hormonal therapy is appropriate. For CDP, often reassurance that puberty will progress at a normal tempo once it begins and final adult height and development will be unaffected is sufficient. Watchful waiting is often more acceptable to the patient and family if early signs of puberty that were not obvious to the patient are pointed out. However, some patients with CDP experience a significant amount of psychosocial distress secondary to their delay and therefore warrant treatment.

Exogenous hormones are used to treat delayed puberty. The goals of therapy are to induce age-appropriate secondary sexual characteristics and to induce a growth spurt without inducing premature epiphyseal closure and thereby compromising final adult height. Patients receiving therapy require frequent monitoring, usually every 3-6 months; therapy should be under the guidance of an endocrinologist. In patients with CDP, treatment is discontinued when endogenous hormone production is established.

Patients with gonadotropin deficiency or hypogonadism require lifelong therapy.

In males, testosterone is administered intramuscularly once per month in relatively low doses, typically 50-100 mg of testosterone enanthate or testosterone cypionate.

Transdermal testosterone gel and patches are also available for treatment. Oral testosterone preparations are potentially hepatotoxic and therefore should not be used. In those males suspected of having CDP, therapy is usually continued for 6 months. After that time, hormone replacement is held and endogenous gonadal function is reassessed.

In females with an inability to progress through puberty autonomously or those with CDP causing psychosocial dysfunction, hormone replacement therapy is timed to correlate with puberty onset in their peers. Estrogen is given orally or transdermally. Initial doses are quite low, typically 5 ug of ethinyl estradiol or 12.5-25 ug of transdermal estradiol daily, and are slowly increased. Progesterin is not added until full contour breast development has occurred. Once regular menstruation is established, therapy should be withdrawn to assess for spontaneous menstruation, which would confirm a diagnosis of CDP. Persistent hypogonadism beyond 18 years of age is highly suggestive of congenital GnRH deficiency and adult hormone replacement therapy with estrogen and progesterone is required.

7. What are the indications for treatment of delayed puberty?

Delayed puberty should be treated in those patients who cannot progress through puberty autonomously and in those who are experiencing stress and embarrassment due to their delay. Boys more often than girls experience significant distress from pubertal delay and therefore present more often than females for evaluation. Patients who require treatment for delayed puberty should be referred to an endocrinologist and monitored serially.

8. What would you do for the patient?

This patient shows signs of pubertal development, including testicular enlargement and Tanner stage 2 pubic hair. Additionally, family history seems to be consistent with CDP in patient's father, making constitutionally delayed puberty more likely in this patient. Pointing out the signs of pubertal onset to the patient and reassurance with follow-up would be appropriate in this case.

9. When would you refer a patient to an endocrinologist?

A patient should be referred to a subspecialist when the patient/parents feel anxious regarding lack of pubertal development and reassurance is not adequate. Additionally, if evaluation of the hypothalamic-pituitary-gonadal axis is being considered, referral is necessary as interpretation of hormone tests can be difficult. Referral ensures that the appropriate tests are ordered and carried out and interpreted correctly. As mentioned above, any patient requiring treatment for pubertal delay should be under the care of an endocrinologist.

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1. SS Nussey & SA Whitehead. Endocrinology An Integrated Approach. Taylor and Francis Group; 2001.
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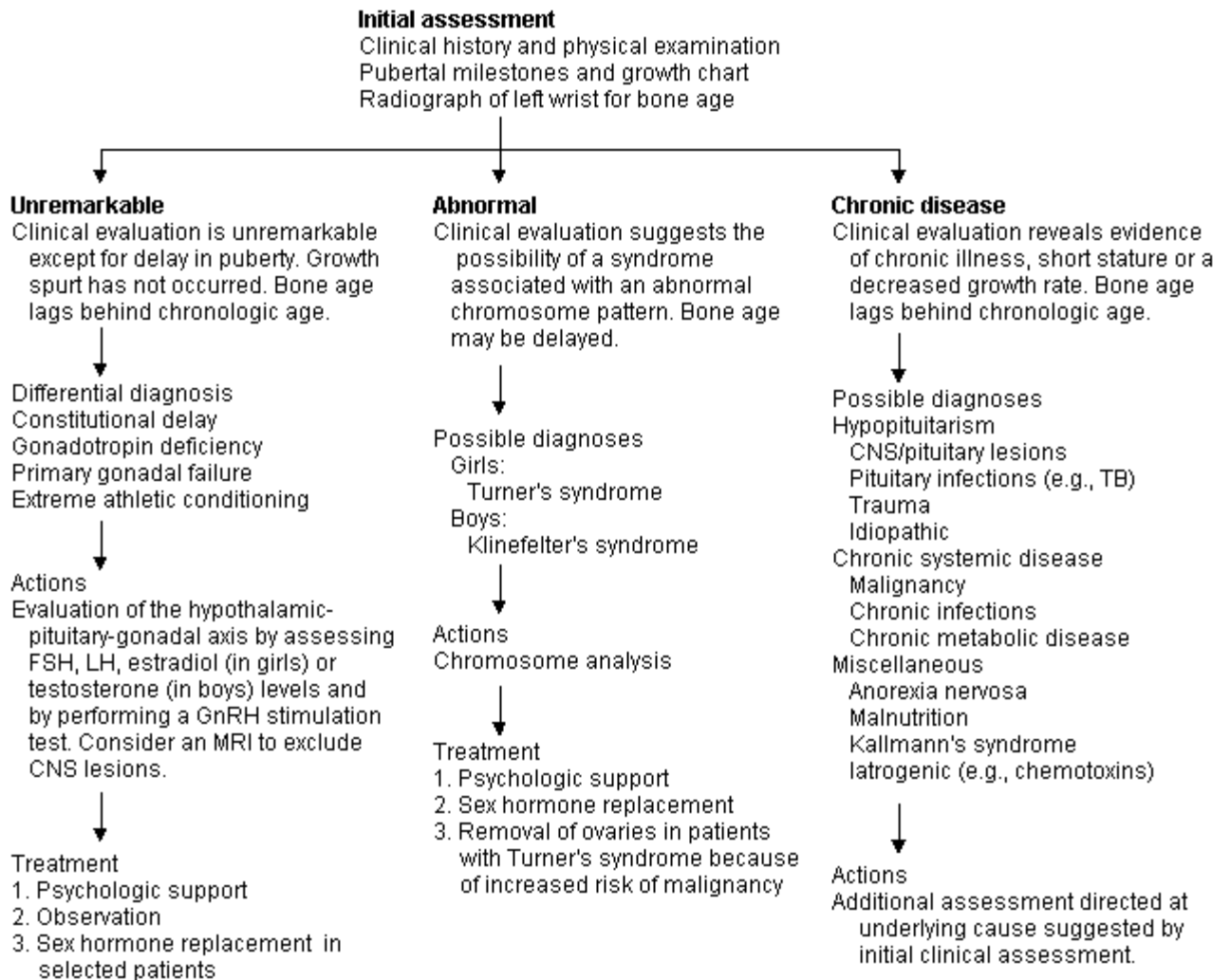


FIGURE 2. An approach to the child presenting with delayed puberty. (FSH=follicle-stimulating hormone; LH=luteinizing hormone; GnRH=gonadotropin-releasing hormone; MRI=magnetic resonance imaging; CNS=central nervous system; TB=tuberculosis)
Disorders of Puberty. RICHARD D. BLONDELL, M.D., MICHAEL B. FOSTER, M.D., and KAMLESH C. DAVE, M.B.B.S. American Family Physician July 1999 Vol 60 No 1

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