

Delayed Puberty

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Author Disclosure
Dr Kaplowitz has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:

1. Define the ages at which puberty is considered delayed in boys and girls.
2. Discuss the typical presentation and natural history of constitutional delayed puberty.
3. Compare the differential diagnosis of delayed puberty for causes other than constitutional delay in girls versus boys.
4. Recognize the psychological consequences of pubertal delay.
5. Describe the evaluation and treatment of delayed puberty in boys and girls.

Introduction

Normal maturation of the hypothalamic-pituitary-gonadal (HPG) axis shows a period of activity in utero and in the first few postnatal months, particularly in boys. The HPG axis then becomes quiescent by 6 months of age and does not resume activity until the time of puberty. Pulsatile secretion of the hypothalamic-releasing factor gonadotropin-releasing hormone (GnRH) results in pulsatile secretion of the pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Increasing LH triggers an increase in production of sex steroids; increasing FSH stimulates the growth and maturation of the seminiferous tubules involved in sperm production and the ovarian follicles involved in oocyte production. However, the changes within the brain that trigger the onset of pulsatile GnRH secretion at the time of puberty still are poorly understood.

In most boys, physical changes of puberty start between the ages of 10 and 13 years, with the first change being enlargement of the testes, followed by pubic hair and penile growth, and subsequent growth at peak height velocity. Most girls start puberty between the ages of 9 and 12 years, with the first visible sign being breast enlargement, followed by growth at peak height velocity and menarche (average age, 12.5 years). Delayed puberty in boys is defined as the failure of pubertal maturation to start by age 14 years, which occurs in about 2.5% of healthy boys; in girls, puberty is considered delayed if there is no evidence of breast development by age 13 years. Pubic and axillary hair development and axillary odor are due to increases in adrenal androgen secretion that are independent of the activity of the HPG axis. Therefore, pubertal delay may be present when pubic hair growth has started if breast development is not present or if a boy has not had any growth of the penis or testes.

Abbreviations

| | |
|---------------|----------------------------------|
| CDP: | constitutional delayed puberty |
| FSH: | follicle-stimulating hormone |
| GH: | growth hormone |
| GnRH: | gonadotropin-releasing hormone |
| HPG: | hypothalamic-pituitary-gonadal |
| IGD: | isolated gonadotropin deficiency |
| IGF-1: | insulin-like growth factor-1 |
| IM: | intramuscular |
| LH: | luteinizing hormone |
| T4: | thyroxine |
| TSH: | thyroid-stimulating hormone |

Delayed Puberty in Boys

When a teenage boy presents with concerns about delayed pubertal development, the most likely diagnosis is constitutional delayed puberty (CDP) (Table 1). In one series of 232 children (including 158 boys) who had delayed puberty seen at Boston Children's Hospital, 63% of the boys had CDP. (1) Such boys generally are healthy but short (below the 10th percentile and often well below the 3rd percentile), with penile length normal for a prepubertal boy (usually 6 to 7 cm stretched) and testes that measure 2.5 cm or less in length (or <4 mL in volume with a Prader orchimeter) (Table 2). Some boys who experience delayed puberty show evidence of early testicular enlargement, but there tends to be a long

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Table 1. Important Causes of Delayed Puberty

Boys

- Constitutional delayed puberty
- Gonadotropin deficiency (hypogonadotropic hypogonadism)
 - Isolated gonadotropin deficiency
 - Kallmann syndrome (with anosmia)
 - Idiopathic
 - Functional gonadotropin deficiency due to chronic illness
 - Multiple pituitary hormone deficiencies
 - Congenital
 - Acquired due to a central nervous system lesion (such as a craniopharyngioma)
- Primary gonadal failure (hypergonadotropic hypogonadism)
 - Radiation to the testes
 - Following surgery for cryptorchidism
 - Vanishing testes syndrome
 - Klinefelter syndrome (small testes but adequate androgen production)

Girls

- Constitutional delayed puberty
- Gonadotropin deficiency
 - Functional gonadotropin deficiency
 - Anorexia nervosa
 - Excessive exercise with decreased body fat
 - Chronic illness (eg, Crohn disease, cystic fibrosis, sickle cell anemia)
 - Isolated gonadotropin deficiency
 - Non-X-linked Kallmann syndrome
 - Multiple pituitary deficiencies
- Primary gonadal failure
 - Turner syndrome (gonadal dysgenesis)
 - Total body radiation for treating malignancies
 - Autoimmune ovarian failure

lag (1 to 2 years) between early testicular enlargement and the effects of increased testosterone production (increased penis size, further growth of pubic hair, growth spurt). Most of these boys are slender or of normal weight for height, but a subset of boys who have CDP are overweight and generally are not short.

Review of the growth chart usually shows linear growth slightly below but parallel to the third percentile for many years. Often, boys seem to fall further behind after age 13 years due to delay of the pubertal growth spurt reflected on standard growth charts. Bone age typically is delayed by 2 or more years and usually corresponds better with the height age than the chronologic age.

Delayed puberty has a significant genetic component, and analysis of pedigrees of families of 53 children who had CDP found that the most common pattern of inheritance was autosomal dominant, with or without incomplete penetrance. (2) In this author’s experience, about two thirds of patients have a history of delayed puberty in a parent or an older sibling. For mothers, it is common for menarche to have occurred after age 14 years; for fathers, the typical history is for their growth spurt to have started well after their peers (eg, at age 15 or 16 years versus 13 or 14 years for average-maturing boys). Many fathers recall that they continued to grow in height after they graduated from high school. The natural history in boys who have CDP is for the growth spurt to start sometime between the ages of 15 and 17 years, and because they have a longer period of time to grow, the delayed growth spurt usually results in an adult height within the lower half of the normal range.

Isolated gonadotropin deficiency (IGD) is a relatively rare congenital condition caused by complete or partial deficiency of GnRH, resulting in decreased or absent secretion of LH and FSH. It can be difficult in some cases to differentiate IGD from CDP, although when puberty has not started by age 17 years, CDP becomes less likely. One clue to the diagnosis is that in many cases, affected boys have small penises (≤ 5 cm in length) due to low testosterone production during the prenatal period and

Table 2. Key Findings on Physical Examination

Boys

- Most boys who have constitutional delay are <10th percentile in height
- Testes <2.5 cm in length (<4 mL) are prepubertal; 2.5 to 3.0 cm is early pubertal
- Penis <7 cm stretched is prepubertal
 - Penis <5 cm is small and may suggest congenital gonadotropin deficiency
- Pubic hair may be present in boys who have delayed puberty if penis/testes prepubertal

Girls

- In the sitting position, prepubertal chubby girls often appear to have breasts
 - Very important to distinguish breast from fat by palpation in supine position
- In short girls, look for subtle evidence of Turner syndrome: high-arched palate, cubitus valgus, short fourth metacarpals
- Pubic hair may be present in girls who have delayed puberty (if no breast tissue)

the first 4 postnatal months. The testes often are small and difficult to palpate. Another clue is that some boys who have this condition have Kallmann syndrome, in which IGD is accompanied by hyposmia or anosmia. Therefore, the clinician should ask about the boy's ability to recognize typical smells of foods. The most common genetic defect is a mutation or deletion of the *KALI* gene, which encodes the protein anosmin-1 that plays a key role in neuronal migration, the absence of which results in a migrational arrest of both GnRH and olfactory neurons. Kallmann syndrome due to a *KALI* mutation is X-linked, and a family history of the same disorder sometimes is present in male relatives on the mother's side of the family.

Delayed puberty in boys due to primary gonadal failure (also referred to as hypergonadotropic hypogonadism) is uncommon (only 7% in a Boston series) (1) and generally can be suspected based on the history and physical examination findings. A history of radiation to the testes for malignancy, surgery for bilateral cryptorchidism or testicular torsion, or mumps orchitis may suggest the diagnosis. On physical examination, the testes are either unusually small or nonpalpable. If the testes cannot be palpated and no history suggests a specific cause of gonadal failure, the diagnosis of "vanishing testes syndrome" should be considered; such boys, who have normal external genitalia (suggesting normal testicular production prenatally), subsequently develop testicular atrophy or destruction of unknown cause. The finding of elevated gonadotropin concentrations confirms the diagnosis of primary gonadal failure.

Klinefelter syndrome (47, XXY karyotype or XY/XXY mosaicism) is a relatively common cause of gonadal failure (incidence of 1 in 500 to 1 in 1,000), but it rarely presents as simple pubertal delay. Penile enlargement occurs at the usual age along with increased pubic hair, but the diagnosis typically is suspected when the testes are unusually small (≤ 3.0 cm or ≤ 6 mL) for the degree of androgenization. Such poor growth results from seminiferous tubule dysgenesis due to the extra X chromosome, which becomes apparent after testosterone production has started to increase. Affected boys usually are tall and may have a variety of behavioral problems and learning difficulties.

Delayed Puberty in Girls

CDP is less common in girls than in boys (30% of 74 girls in the Boston series), (1) but should be suspected in healthy 13- to 15-year-old girls who have a family history of pubertal delay in at least one parent (Table 1).

Functional gonadotropin deficiency is a common di-

agnosis in girls who experience delayed puberty and are unusually thin for various reasons. The clinician should consider the diagnosis of anorexia nervosa if there is a history of poor caloric intake associated with an unreasonable fear of becoming fat. Girls who exercise excessively without enough caloric intake to maintain normal weight also are at risk for pubertal delay or very slow progression through puberty, with delayed menarche. The three types of exercise most associated with this scenario are competitive swimming, ballet dancing, and gymnastics. (3) Excessive exercise with weight loss is seen less often with team sports and running, perhaps because most sports (other than swimming) have an off-season when training is less intense. The likely explanation for the delay in puberty and menarche is that decreased body fat results in decreased leptin concentrations and a reversible gonadotropin deficiency; the same explanation is likely for girls who are very thin due to chronic illness. One of the concerns for these girls is that chronic low estrogen concentrations may impair bone accretion, resulting in lower peak bone mass and an increased risk of fractures.

Isolated gonadotropin deficiency due to Kallmann syndrome is uncommon in females, probably because the most common form, due to a defective *KALI* gene, is X-linked.

Primary ovarian failure (hypergonadotropic hypogonadism) was found in 26% of the 74 girls referred for delayed puberty. In very short girls who have delayed puberty, the diagnosis of Turner syndrome always should be considered. This condition occurs in about 1 in 2,500 girls and most often is diagnosed either in infancy (due to congenital lymphedema or associated coarctation of the aorta) or in childhood, based on short stature and characteristic physical findings, such as webbed neck (present in 40%), high-arched palate, cubitus valgus, and short fourth metacarpals. Girls in whom the condition is not diagnosed until their teen years often have fewer physical findings and are more likely to have chromosomal mosaicism (eg, 45,X/46,XX) than the more common 45,X karyotype. Estrogen production is low to absent due to gonadal dysgenesis, but there usually is pubic hair development because adrenal androgen secretion is not affected.

A less common cause of primary ovarian failure is autoimmune destruction of the ovaries, which is more likely if there are other autoimmune conditions such as type 1 diabetes mellitus or the multiple autoimmune endocrinopathy syndrome, which can include hypothyroidism, Addison disease, and hypoparathyroidism. Girls who have had total body irradiation or chemotherapy as

part of their treatment for various malignancies also are at high risk for ovarian failure.

Conditions Affecting Either Sex

Functional gonadotropin deficiency frequently is due to chronic illnesses, but in nearly all cases, the illness is diagnosed at a much earlier age. The most common causes are sickle cell disease, chronic renal failure, Crohn disease, cystic fibrosis, celiac disease, rheumatoid arthritis, and severe asthma. In these cases, poor weight gain usually is a contributing factor, and strategies to enhance weight gain may result in the progression of puberty.

Longstanding primary hypothyroidism is a rare cause of delayed puberty, and typically the patient manifests other signs and symptoms, such as goiter, slow growth, fatigue, and cold intolerance.

Delayed puberty seldom is the presenting manifestation of panhypopituitarism because growth hormone (GH) deficiency generally is congenital and results in severe short stature, which would prompt an endocrine evaluation at a much earlier age. However, in rare cases, delayed puberty can be part of the presenting picture of acquired hypopituitarism, which can result from a craniopharyngioma or other mass in the region of the pituitary or hypothalamus. It is common for affected patients to have a history of increasingly severe headaches as well as diabetes insipidus. Pituitary adenomas are a rare cause of either pubertal delay (more often in boys) or secondary amenorrhea in girls. The most common of these tumors is the prolactin-secreting adenoma, which often presents with galactorrhea but not gynecomastia. Headaches are present in more than 50% of the cases.

Diagnostic Evaluation

In the healthy child manifesting pubertal delay for whom undiagnosed chronic illness is not a major concern, it is best to start with a limited number of studies rather than ordering a large number of tests of limited diagnostic value. The key tests are LH and FSH assessment, with measurement of total (not free) testosterone in boys and estradiol (not total estrogens) in girls. Boys who have delayed puberty usually have a testosterone concentration less than 40 ng/dL (1.4 nmol/L). A testosterone value of more than 50 ng/dL (1.7 nmol/L) indicates that puberty is underway and that genital enlargement and a growth spurt should become apparent soon. An LH value of greater than 0.3 mIU/mL (0.3 IU/L) and estradiol concentration of greater than 20 pg/mL (73.4 pmol/L) in girls usually suggests the onset of puberty.

Any child who has primary gonadal failure will, by age

10 to 12 years, have strikingly elevated LH and FSH values due to failure of the normal increase in gonadal steroids and a gonadal protein called inhibin to exert negative feedback on the HPG axis. If the LH and FSH concentrations are not elevated, the child has either CDP or permanent or functional gonadotropin deficiency. Although very low LH and FSH (<0.3 mIU/L [0.3 IU/L]) values suggest gonadotropin deficiency, much overlap exists between basal LH and FSH in CDP and IGD. Endocrinologists sometimes measure LH and FSH after stimulation with GnRH. Although peak LH and FSH values are, on average, significantly lower in IGD, there is overlap between values reached in IGD and CDP. (4) Measuring testosterone concentrations in boys after a 3-day series of human chorionic gonadotropin hormone injections (which has LH-like actions on the testes) also has been used. Concentrations achieved in boys who have CDP are higher than in those who have IGD, with overlap.

For a girl whose LH and FSH concentrations are elevated, a karyotype is needed to rule out Turner syndrome, unless there is another explanation, such as a history of radiation to the ovaries. The karyotype can be obtained at the first endocrine consultation. For a boy who has elevated LH and FSH concentrations and abnormally small testes, a karyotype should be ordered if the clinical presentation is compatible with Klinefelter syndrome. If ovarian failure is idiopathic, an autoimmune cause should be considered, but antiovarian antibodies are not a reliable method of testing for this condition.

For healthy children who have typical histories for CDP but have no goiter, thyroid testing (ie, free thyroxine [T4] and thyroid-stimulating hormone [TSH]) generally is not necessary. If short stature is so severe that hypopituitarism is a concern, measuring insulin-like growth factor 1 (IGF-1) may be helpful if it is very low when adjusted for bone age. In addition, the free T4 concentration may be low, with a nonelevated TSH concentration.

A single radiograph of the hand and wrist for a bone age determination often is obtained in short children experiencing delayed puberty because, as noted previously, the bone age typically is delayed by at least 2 years in children who have CDP. This finding may allow the endocrinologist to predict an adult height that is in the low-normal range (5 ft 5 in to 5 ft 8 in in boys), even when the child's height is below the third percentile, which is reassuring to the child and the parents. Ordering a computed tomography scan of the head or magnetic resonance imaging is unnecessary unless the endocrinol-

ogist finds evidence of hypopituitarism, which may include a very low IGF-1 concentration, low GH values after provocative testing, and a low free T4 concentration or diabetes insipidus.

The primary care clinician is best suited to identify children whose puberty is delayed, and it is reasonable for that clinician to obtain basic testing: measurement of LH, FSH, and either testosterone or estradiol as well as a bone age radiograph, which the endocrinologist will wish to review. After that initial evaluation is accomplished, referral to an endocrinologist is a logical next step.

Psychological Consequences of Delayed Puberty

In late-maturing 14- to 16-year-old boys, there often is concern about how short and underdeveloped they are relative to their peers, and teasing and low-self esteem frequently are reported. Many boys are aware that they probably do not have an underlying medical problem (particularly when there is a family history of late growth) but still are impatient to start growing. This concern is highest in boys who are participating in team sports, where being short and less muscular than peers is perceived to be a major disadvantage. Although many such boys continue to participate, others drop out and feel more isolated socially. Declining academic performance and school avoidance are occasional problems. One study of 43 boys whose CDP was untreated and who were evaluated at a mean age of 21 years found that 25 of them felt that their growth delay had affected their success either at school, work, or socially, and 20 of them would have preferred to have had treatment to advance their growth spurt. (5)

Girls who experience pubertal delay have fewer psychological concerns than boys, although some report feeling different because of their lack of physical development and that by age 13 to 14 years, most of their peers have reached menarche. One study that followed 15 untreated girls who had CDP until a mean of 19 years found that although there was no difference between patients and controls in self-esteem or marital or employment status, 80% felt their growth delay had affected their success either at school, work, or socially. (6)

Management

Referral to an endocrinologist for boys who have reached or are approaching age 14 years and girls who have reached 13 years without showing significant physical changes of puberty is appropriate because even when there is no underlying medical condition, therapy that is

effective, safe, and inexpensive often can be offered. It is not necessary to refer boys or girls who clearly are delayed but finally are showing true evidence of pubertal progression on physical examination.

For boys who have CDP and are impatient to start growing and developing without waiting 1 to 2 years until their own puberty starts, a brief course of testosterone therapy can be offered if their testosterone values still are prepubertal or at a very early pubertal concentration (<50 ng/dL [1.7 nmol/L]); about 80% of boys to whom this therapy is offered agree to it. Several studies have shown that on average, androgen therapy in boys ages 14 years and older has no effect on the adult height, which is predicted on the basis of bone age. Oral testosterone seldom is used because of concerns about liver toxicity. The simplest and safest form of therapy is monthly injections of testosterone in oil (eg, testosterone enanthate), which is absorbed slowly over several weeks. Although many dosing regimens have been reported, I have had excellent success with 100 mg administered intramuscularly (IM) for 4 months, usually given in the office of the referring physician. When assessed 1 month after the last injection, the average increase in height is 3.8 cm, which is as much as many of these boys have grown in the previous 12 months, and increase in weight is 4.4 kg. (7) There also is an increase in penile length and in pubic hair, although testicular size changes little.

The injections are stopped, and when the child is re-examined 4 to 5 months later, linear growth continues, but the most important change is an increase in the size of the testes. Because this change depends on increased secretion of gonadotropins, it confirms that endogenous puberty is underway and that no additional treatment is needed. The Figure shows the growth chart of a boy who has CDP before and after a brief course of testosterone. The dotted line shows the likely growth pattern without treatment; the final height is the same but is achieved significantly earlier when testosterone is administered.

Although it is rare for boys to complain about the pain of injections, low-dose oral androgens are an option for the needle-adverse 14-year-old boy or for a 12- to 13-year-old boy in whom a slower effect on growth and puberty is desired. The drug of choice is the anabolic steroid oxandrolone (2.5 mg/day), which has been used since the 1970s in short boys who do and do not have pubertal delay and has a long record of safety. After 8 to 12 months, treatment usually can be stopped with the onset of endogenous puberty.

For boys who have permanent hypogonadism (either due to primary gonadal failure or gonadotropin defi-

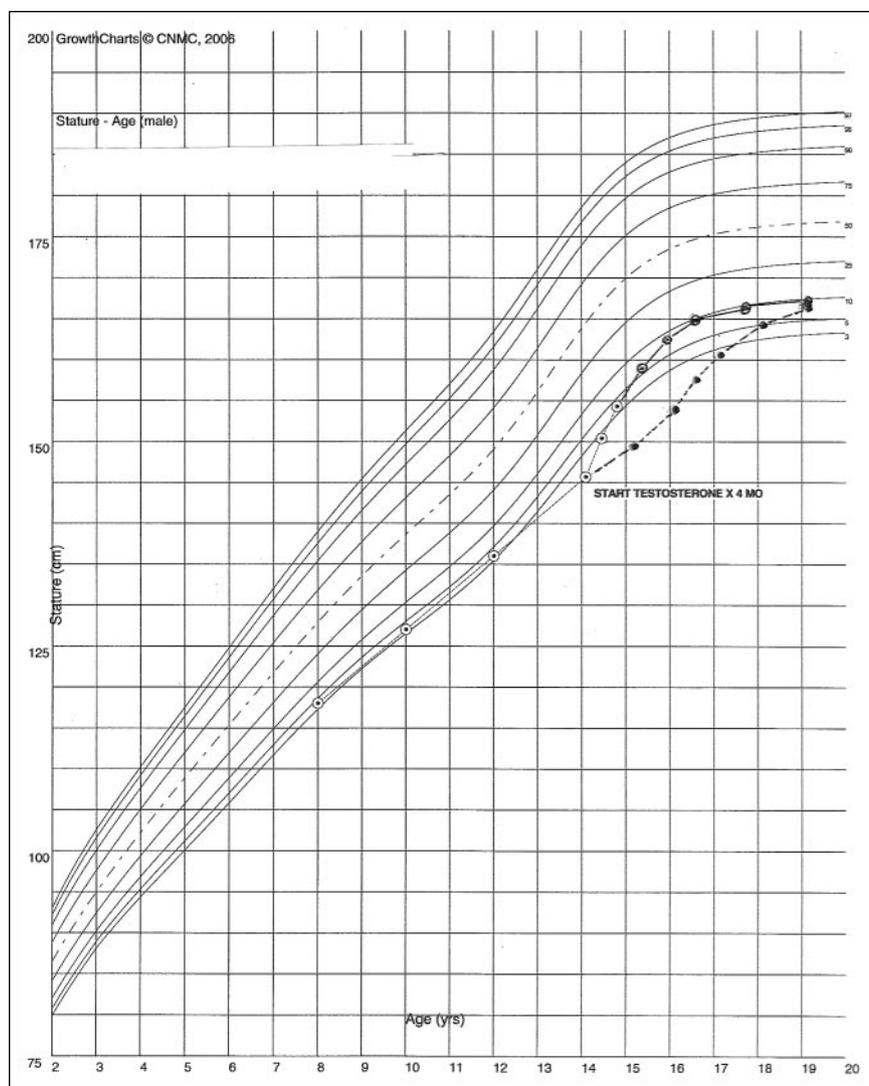


Figure. Growth chart for a boy who experienced constitutional delayed puberty, showing growth at the low end of the normal range, with an apparent fall-off at the time of normal puberty and a dramatic growth spurt during and immediately after a 4-month course of monthly 100-mg testosterone in oil injections. The dotted line shows the likely growth trajectory had the boy not received testosterone, with the adult height being the same in both cases but achieved significantly earlier in the treated boy.

ciency), IM testosterone is the initial treatment of choice, usually starting at a lower dose of 50 mg/month and increasing by about 50% every 6 months until a full adult replacement dose of 200 mg every 2 to 4 weeks is reached. Testosterone also can be administered transcutaneously with daily placement of a patch, which is available in two strengths (2.5 and 5 mg) and does not allow a gradual increase in dose as with IM testosterone. However, many boys complain about itching where the patch is placed, and others like the monthly injections

simply because they prefer not to bother with daily patch placement. Another treatment option is testosterone gel, which is used widely in adult men who have hypogonadism, but dosing, as for the patch, is not child-friendly.

Although IM depot forms of estradiol are available, most girls who experience pubertal delay and need estrogen therapy are started on the lowest available doses of oral estrogens, either conjugated estrogens 0.3 mg/day or micronized estradiol 0.5 mg/day. For girls who have constitutional delay or functional gonadotropin deficiency, it is reasonable to treat for 4 to 6 months and then stop treatment to determine if there is any progression of pubertal development off treatment, although few data have been reported on outcomes of a brief course of sex steroid therapy in girls, as there have been in boys.

For girls who have Turner syndrome and other permanent causes of hypogonadism, the dose of estrogens typically is doubled every 6 to 12 months until doses of 1.25 mg conjugated estrogens or 2 mg estradiol are reached. When breakthrough vaginal bleeding is noted or after 12 to 24 months of estrogen therapy without any vaginal bleeding, it is recommended that regular menses be established with the addition of oral medroxyprogesterone (5 mg for 10 days each month), which is successful for most patients after a few

months. A simpler alternative is to switch patients to oral contraceptives, although even the lowest-estrogen agents contain higher estrogen doses than are needed to induce good breast and uterine development.

In recent years, the use of transdermal estrogen therapy has increased because estrogen patches are believed to be more physiologic than oral estrogens and estrogen absorbed transdermally does not pass through the liver. Initial doses to induce puberty are in the range of 0.025 to 0.05 mg applied twice weekly. One recent study

Summary

- Constitutional delayed puberty is the most common cause of delayed puberty in boys but is less common in girls. In most cases, there is short stature, a normal rate of growth, and a delay of 2 years or more in bone maturation.
- In girls, delayed puberty often is due to functional gonadotropin deficiency associated with excessive thinness or to primary ovarian failure, particularly due to Turner syndrome.
- Laboratory evaluation should start with measuring LH, FSH, and testosterone or estradiol. Elevated gonadotropin values are a reliable indicator of primary gonadal failure. Differentiation of constitutional delay from the much less common isolated gonadotropin deficiency often is difficult, even with laboratory tests.
- Boys, and to a lesser extent girls, who experience delayed puberty often are concerned about their lack of development and short stature and may experience poor self-esteem.
- Strong evidence suggests that a brief course of testosterone therapy in boys via monthly IM injection causes a prompt growth spurt as well as physical changes without affecting the ultimate adult height negatively.
- Current evidence suggests that girls who have pubertal delay can be treated with either oral or transdermal estrogens with equal efficacy and safety.

compared three doses of oral and transdermal estradiol in girls who had Turner syndrome and also were receiving GH and found that their metabolic effects were nearly

identical. There were no differences in concentrations of IGF-1, as earlier studies with postmenopausal women had suggested. (8)

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PIR Quiz

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Match the clinical scenario with the *most* likely diagnosis.

6. 13–11/12-year-old girl who has secondary amenorrhea and a body mass index of 13 kg/m².
7. 14–10/12-year-old girl who has primary amenorrhea and is a competitive gymnast.
8. 15–1/12-year-old tall boy who has small testes and Sexual Maturity Rating 5 pubic hair.
9. 16–9/12-year-old short girl who has primary amenorrhea and a webbed neck.
10. 17–5/12-year-old boy who has small testes and anosmia.
 - A. Constitutional delayed puberty.
 - B. Functional gonadotropin deficiency.
 - C. Kallman syndrome.
 - D. Klinefelter syndrome.
 - E. Turner syndrome.

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