

Delayed Puberty

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EDUCATION AND PRACTICE GAPS

- The presence (or reported history) of pubarche (eg, pubic hair) alone in boys and girls is often falsely assumed to indicate onset of true central puberty, thus leading to a missed diagnosis of delayed puberty.
- There is wide variation in the timing of the onset of puberty, yet the genetic factors that underlie this physiologic variation are not well understood.
- Constitutional delay of growth and puberty is one of the most common diagnoses referred to the endocrinology clinic with delayed puberty. Despite being considered a normal variant, it often causes significant concern/anxiety in patients, families, and health care providers due to the stigma associated with short stature and delayed puberty. To this day, there remains a wide sex disparity in referrals for constitutional delay, with boys far overrepresented.
- Girls with mosaic Turner syndrome with minimal or no dysmorphic features may not be identified until they present with delayed menarche.
- Klinefelter syndrome is one of the most common, and yet one of the most underdiagnosed, etiologies of delayed puberty in boys.

OBJECTIVES *After completing this article, the reader should be able to:*

- Provide a brief overview of the developmental biology and genetic components of the hypothalamic-pituitary-gonadal axis and explain how a flaw in the system could lead to delayed or absent puberty.
- Predict constitutional delay of growth and puberty based on review of the patient's history, physical examination, growth chart, and investigations.
- Recognize key clinical features of pathologic or syndromic forms of delayed puberty.
- Plan the initial evaluation for delayed puberty and counsel a patient's family about the anticipated course.

INTRODUCTION

Puberty is defined as the process of gonadal maturation and development of secondary sexual characteristics, which culminates in reproductive competence.

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ABBREVIATIONS

CDGP constitutional delay of growth and puberty
 FSH follicle-stimulating hormone
 GnRH gonadotropin-releasing hormone
 HH hypogonadotropic hypogonadism
 HPG hypothalamic-pituitary-gonadal
 LH luteinizing hormone

Physiologically, puberty is characterized by the concerted activation of the hypothalamus-pituitary-gonadal (HPG) axis.

DEVELOPMENTAL BIOLOGY AND PHYSIOLOGY OF PUBERTY

Around the sixth week of gestation, gonadotropin-releasing hormone (GnRH) neurons begin migration from the olfactory placode to the arcuate nucleus of the hypothalamus, under the guidance of several molecules, including anosmin-1 (*KAL1*), prokineticin 2 (*PROK2*), fibroblast growth factor 8 (*FGF8*), fibroblast growth factor receptor 1 (*FGFR1*), and chromodomain helicase DNA-binding protein 7 (*CHD7*). (1) Normal development of the hypothalamus and gonadotropin-secreting cells (gonadotrophs) of the pituitary depends on genes such as *NR5A1* (*SF1*), *NR0B1* (*DAX1*), *PROP1*, *HESX1*, *LHX*, *LHB*, *LHR* (luteinizing hormone [LH] receptor), *FSHB*, and *FSHR* (follicle-stimulating hormone [FSH] receptor), among others. By week 15 of gestation, the HPG axis is functionally active.

GnRH is secreted in a pulsatile manner from the hypothalamus and carried to the anterior pituitary through the hypophyseal portal system of blood vessels, where it binds to GnRH receptors (encoded by the *GNRH* gene) located on pituitary gonadotrophs. This leads to pituitary secretion of gonadotropins (LH and FSH), which, in turn, stimulate gonadal function, including maturation and function of Sertoli and Leydig cells in the testes in males and granulosa and theca cells in the ovaries in females.

During childhood, there are small but progressive increases in GnRH-induced LH and FSH pulses, which have been detected in healthy children as young as 4 years. (2) The onset of puberty is heralded by the activation of the hypothalamic GnRH pulse generator, which is regulated by a complex interplay of stimulatory and inhibitory factors. Leptin, released by adipose tissue, acts as a metabolic checkpoint for reproductive function by allowing GnRH pulse generation only in the presence of sufficient fat mass. Prolactin produced by pituitary lactotrophs facilitates gonadotropin pulsatility. However, at supraphysiologic levels, it suppresses GnRH and gonadotropin secretion. (3)

With the start of puberty, the amplitude of GnRH pulses increases during sleep and very early in the morning, with levels falling to prepubertal levels later in the day. As puberty progresses, the daytime pulse amplitude increases as well, although nocturnal secretion remains dominant.

DELAYED PUBERTY

Puberty is considered delayed when there is failure of pubertal maturation at an age that is 2 SD or more above the

population mean (traditionally, breast development by 13 years in girls and testicular enlargement by 14 years in boys). (4) Even if puberty begins at a normal age, a delay should be suspected when maturation halts or regresses. Lack of menarche by 15 years of age, or within 3 years of thelarche, is considered delayed in girls. (5) A gap of more than 5 years from onset of testicular enlargement to completion of puberty in boys is indicative of arrested maturation. (6) Because pubarche is independent of HPG axis activation, the presence of pubic hair, axillary hair, and/or apocrine odor alone (ie, without gonadal activity) does not rule out delayed puberty.

The key role of the primary care provider when evaluating delayed/absent puberty is to distinguish between normal variations and pathologic abnormalities that warrant a detailed investigation/referral to a pediatric endocrinologist.

Etiologies can be broadly classified as 1) constitutional delay, 2) secondary or functional hypogonadotropic hypogonadism (HH) caused by chronic illness or malnutrition, 3) HH due to a genetic and/or anatomical defect in the hypothalamic and/or pituitary portion of the HPG axis, and 4) primary gonadal insufficiency. (7)

CONSTITUTIONAL DELAY OF GROWTH AND PUBERTY

Constitutional delay of growth and puberty (CDGP) is a normal variant that occurs in otherwise healthy children wherein puberty begins spontaneously at a later-than-typical age and progresses normally thereafter (Fig 1). Children with constitutionally delayed puberty have a younger bone age relative to their actual age and a height that is more appropriate for their delayed bone age than their actual age, thus giving rise to the term constitutional delay of *growth* and puberty. As peers embark on their pubertal growth spurts, the height discrepancy is further accentuated.

CDGP is the most frequent cause of delayed puberty. In a retrospective review of 232 individuals with delayed puberty referred to a tertiary care center, 65% of boys and 30% of girls were found to have CDGP. (8) An autosomal dominant inheritance pattern is likely, with a history of a similar growth/pubertal pattern noted in 50% of parents of children with CDGP. (9) Theoretically, the prevalence should be similar in boys and girls; however, twice as many boys with CDGP are seen, (8) which likely reflects referral bias.

CDGP is a diagnosis of exclusion because it may be clinically and biochemically indistinguishable from pathologic causes of delayed puberty. Near-normal height velocity and a family history of "late bloomers" in an otherwise healthy child point toward a diagnosis of CDGP. Onset of adrenarche is also

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

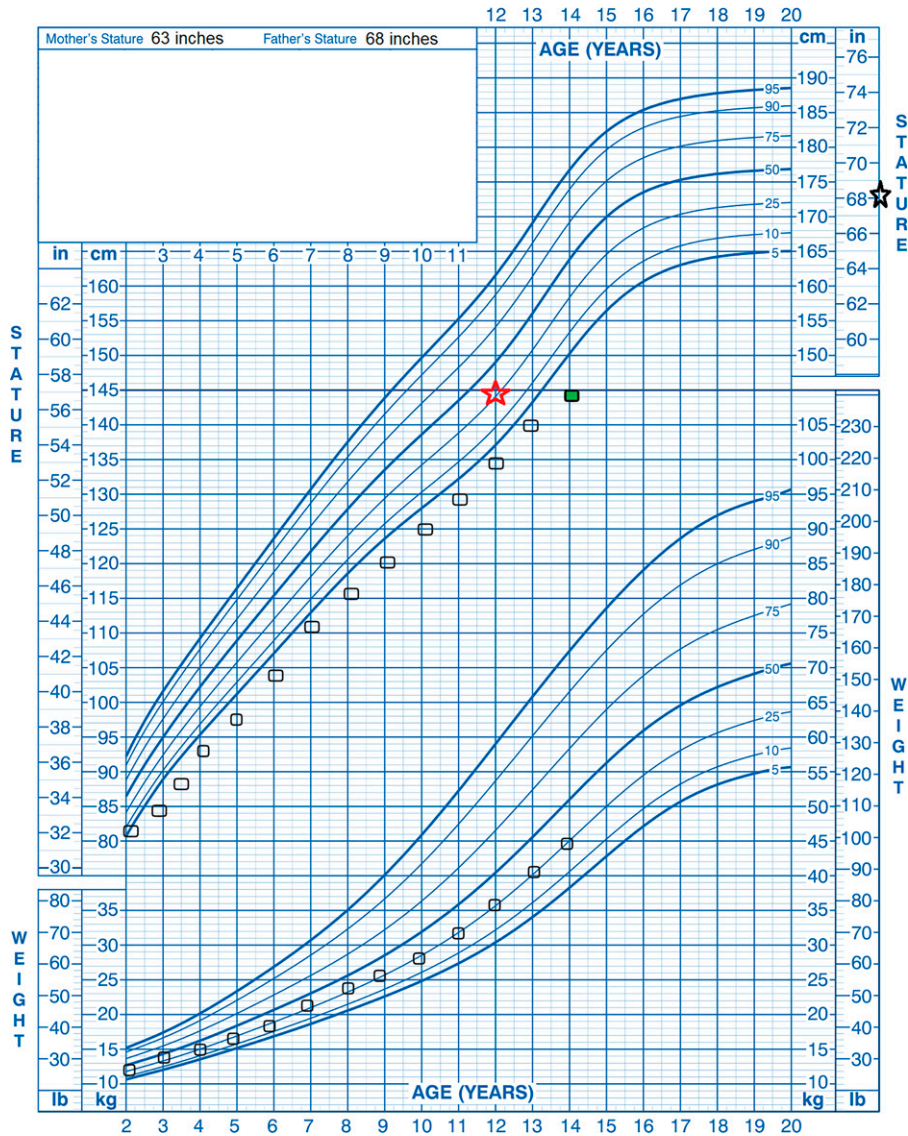


Figure 1. Constitutional delay of growth and puberty. A 14-year-old boy presents with concerns of short stature and minimal signs of puberty. His height and weight values since 2 years of age are plotted on the growth chart (white boxes). A normal growth velocity is apparent on review of previous height measurements. At the time of evaluation, his height is found to be significantly short at less than the third percentile for his age (green box), and his mid-parental height (black star) is at the 29th percentile, based on Centers for Disease Control and Prevention growth charts. At a chronological age of 14 years, his bone age is delayed at 12 years (red star). His height is at the 25th percentile for his bone age, which is consistent with his genetic potential. The discrepancy in height is exaggerated as the patient undergoes prepubertal physiologic growth deceleration while his 14-year-old peers are undergoing their pubertal growth spurts. This can result in psychosocial distress even though his final predicted height may be within the normal range for his genetic potential. Treatment may be considered under guidance of a pediatric endocrinologist to minimize the risk of adverse effects. Of note, in this case, the patient's height trajectory is parallel (albeit lower) to the reference growth charts, demonstrating a normal growth velocity. Decreasing height percentiles over time (height getting farther away from the mean) would be indicative of poor growth velocity, suggestive of associated pathologies such as growth hormone deficiency, hypothyroidism, etc. Growth velocity is calculated by annualizing the difference in heights over 2 or more separate visits, at least 4 months apart. Age-appropriate references for growth velocity should be used. (31) (Adapted from CDC growth charts (2000), developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion: <http://www.cdc.gov/growthcharts>.)

typically delayed in CDGP, whereas it is usually normal in pathologic hypogonadism. (10) If pubertal onset has not occurred by 17 years of age in boys, it is unlikely to be CDGP. (11)

Ultimately, CDGP can be diagnosed with certainty only retrospectively if the child eventually enters and progresses through puberty spontaneously.

Pubertal delay can lead to significant psychosocial distress in teens and their families, more so in boys, but also in girls. (12)(13) A delay in the timing of a pubertal growth spurt and, thus, relative short stature compared with peers can be perceived as a barrier to scholastic, employment, and social success. (14) The pubertal growth spurt may be blunted in children with CDGP, leading to a slight deficit in adult height compared with the genetic target. (15)(16)(17)(18) Although most patients do not require medical intervention, a short course of low-dose testosterone has been used in boys with psychosocial distress. This should be directed by a pediatric endocrinologist to avoid adverse effects such as accelerated bone age advancement (which is rare with proper dosing and short duration of therapy). Pharmacologic treatment of CDGP in girls is infrequent, partly because of higher risk of precipitous bone age advancement from exogenous estrogen, and likely some treatment bias.

FUNCTIONAL HH

Functional HH is a homeostatic hypothalamic response to intense physical or emotional stress, caloric deficit, and/or chronic systemic illness. In this situation, the HPG axis is capable of normal function, but puberty is either delayed or stalled until the underlying condition is addressed.

A caloric deficit may occur due to decreased consumption (eg, anorexia nervosa), intense physical activity (eg, competitive gymnastics, ballerina syndrome, etc), malabsorption (eg, celiac or inflammatory bowel disease), or increased caloric requirement (eg, chronic systemic illnesses such as cystic fibrosis). Decreased body fat leads to a deficiency of leptin, a critical level of which plays a permissive role in activation of the GnRH pulse generator. Elevated circulating levels of cytokines (as seen in inflammatory conditions) inhibit the HPG axis. Exogenous or endogenous exposure to elevated glucocorticoids (chronic stress) can also suppress the HPG axis. Elevated prolactin levels, due to prolactinoma, medication adverse effects (eg, older antipsychotic agents), or severe primary hypothyroidism, inhibit gonadotropin release. Iron deposits can impair pituitary function in children receiving long-term transfusions. Thus, it is important to obtain a thorough assessment directed at timely identification and management of the underlying etiology. In most cases, normal growth and puberty patterns are possible with prompt intervention.

PATHOLOGIC HH

HH refers to failure of activation of the hypothalamic GnRH pulse generator, leading to an impairment of gonadotropin production. This results in low serum sex steroid

levels with absent/minimal secondary sexual characteristics, along with failure of germ cell development.

Congenital

Congenital isolated HH can occur due to variants in any of the multiple genes involved in the development of the hypothalamic or pituitary components of the reproductive axis as described previously herein, most notably *ANOS1*, *FGFR1*, *FGF8*, *PROK2*, *CHD7*, *KISS1*, *KISS1R*, *GNRH*, and *GNRHR*. More than 50 genes related to the condition are known, explaining approximately 50% of cases. (19)

Given the developmental origins of GnRH neurons in the olfactory placode, congenital HH can be associated with anosmia (absent sense of smell) or hyposmia (reduced sense of smell), referred to as Kallmann syndrome, which, in its classic form, is inherited in an X-linked manner in conjunction with variants in the *ANOS1* gene (previously called *KAL1*), which encodes the protein anosmin-1, the absence of which prevents GnRH neuronal migration to the hypothalamus. Other features of Kallmann syndrome may include unilateral renal agenesis, sensorineural hearing loss, and synkinesia (alternating mirror movements). Interestingly, the HH of Kallmann syndrome may, in some cases, be reversible.

Genes associated with isolated HH in the backdrop of obesity include those encoding leptin (*LEP*) and the leptin receptor (*LEPR*). Reduced lean mass (including muscle), delayed puberty with reduced linear growth, and low circulating levels of insulinlike growth factor 1 have recently been found in patients with loss-of-function variants of the *MC3R* gene, which encodes the melanocortin 3 receptor in the hypothalamus. (20)

Congenital HH can also be a part of global hypopituitarism due to genetic variants (including *PROP1*, *HESX1*, *LHX*, *LHB*, and *FSHB*) involved in pituitary gland development or with optic nerve hypoplasia. It may also be a feature of some genetic syndromes, such as congenital adrenal hypoplasia and Prader-Willi, Noonan, CHARGE, and Bardet-Biedl syndromes.

Acquired

Central nervous system tumors (eg, craniopharyngiomas, the most common suprasellar tumor in adolescents) can disrupt the hypothalamic-pituitary stalk (infundibulum) or directly impact pituitary function to inhibit gonadotropin production. A concurrent history of headaches and/or visual disturbances mandates urgent imaging. Intracranial surgeries and/or cranial radiation therapy greater than 30 Gy are known risk factors for HH. Moderate to severe

trauma to the brain can be associated with disrupting injuries to the hypothalamus, stalk (infundibulum), and/or pituitary. Inflammatory, autoimmune, and infiltrative diseases of the pituitary gland are other rare causes of acquired HH.

HYPERGONADOTROPIC HYPOGONADISM

Hypergonadotropic hypogonadism, also called primary gonadal failure, is always pathologic. Elevated circulating gonadotropin levels result from the absence of sex steroid-induced negative feedback. The broad etiologic categories include genetic defects and acquired causes.

Genetic Defects

With an incidence of 1 in every 2,000 to 2,500 live female births, Turner syndrome is the most common cause of primary ovarian failure in girls. The deficient X chromosomal dosage leads to universal short stature (thought to be due to loss of a copy of the *SHOX* gene on the X chromosome) and, to varying degrees, other classic phenotypic features, including congenital heart disease (up to 50%, including tortuosity of the transverse aortic arch, bicuspid aortic valve, and coarctation of the aorta), cubitus valgus (45%), low posterior hairline (40%), high-arched palate (35%), short fourth metacarpals (35%), renal anomalies (35%), and webbed neck (25%). Girls with fewer physical findings, as in the case of chromosomal mosaicism (45,X/46,XX), frequently are not diagnosed during early childhood, with delayed puberty being their presenting feature. Girls with Turner syndrome have gonadal dysgenesis or “streak ovaries” in 85% of cases at birth. However, because adrenal androgen secretion is not impaired, onset of pubarche usually occurs at a normal time.

Klinefelter syndrome (47,XXY) is estimated to occur in 1 in 667 males based on prenatal cytogenetic analysis. (21) However, it remains remarkably underdiagnosed, with less than 10% of patients diagnosed before puberty. Males with Klinefelter syndrome typically present with incomplete puberty and gynecomastia rather than with delayed onset of puberty. The extra X chromosomal material leads to Sertoli cell dysgenesis, causing impaired spermatogenesis, along with variable degrees of testosterone deficiency, together yielding small-sized, firm testes. The extra copy of the *SHOX* gene on the extra X chromosome is likely the cause of frequently associated tall stature. There is also a significant risk of learning disabilities, language and visuospatial processing defects, and neuropsychiatric conditions such as attention-deficit/hyperactivity disorder and depression.

A male phenotype with a 46,XX karyotype attributed to *SRY* gene translocation can present with delayed puberty, gynecomastia, micropenis, and/or infertility. Patients with pure gonadal dysgenesis in conjunction with a 46,XY karyotype (Swyer syndrome) present with a female phenotypic appearance, but no spontaneous thelarche or menarche. A variant in any of the genes involved in gonadal differentiation and development (“sex determination genes”), such as *FOXL2* and *WT1*, manifest with primary hypogonadism. Inactivating variants of the FSH and LH receptor genes can cause resistance to gonadotropins and, thus, gonadal failure.

Most individuals with *NROB1* (encoding *DAX1*) and *NR5A1* (encoding *SF1*) variants have a spectrum of sex development and reproductive phenotypes, including HH, impaired spermatogenesis, primary ovarian insufficiency, hypospadias, and adrenal insufficiency (in those with *NROB1* variants). (22)

Acquired Causes

Primary ovarian failure can be seen in patients with autoimmune polyglandular syndromes in association with Addison disease (primary adrenal insufficiency), hypoparathyroidism, type 1 diabetes mellitus, and/or Hashimoto thyroiditis. It is caused by dysregulated, tissue-specific T-lymphocytic destruction of ovarian cells, with the resultant antibodies serving as markers of the autoimmune process.

Antineoplastic chemotherapy with alkylating agents, as well as localized ionizing radiation, may permanently damage germ cells. In males, Sertoli cells (involved in spermatogenesis) are more susceptible to such toxicity, resulting in small testes. Leydig cells are relatively resilient so that testosterone production may remain intact even in the absence of testicular enlargement. Risk of infertility can be as high as 66.4%, (23) and 23% of male childhood cancer survivors will eventually develop Leydig cell dysfunction. (24) This functional dichotomy between endocrine and reproductive compartments is not seen in ovaries, where estrogen deficiency is synchronous with decline of oocyte reserve. Because anti-Müllerian hormone is produced by oocytes, a declining serum level can be indicative of primary ovarian insufficiency. One in every 6 female cancer survivors has primary ovarian failure. (25)

Perinatal injury to the testes due to thrombosis or torsion is a presumed cause for “vanishing testes” syndrome, which is seen in less than 5% of patients with cryptorchidism. The presence of otherwise normal male genitalia indicates that the testes were present and functioning at least early in gestation.

Mumps orchitis should be considered, especially in unvaccinated males.

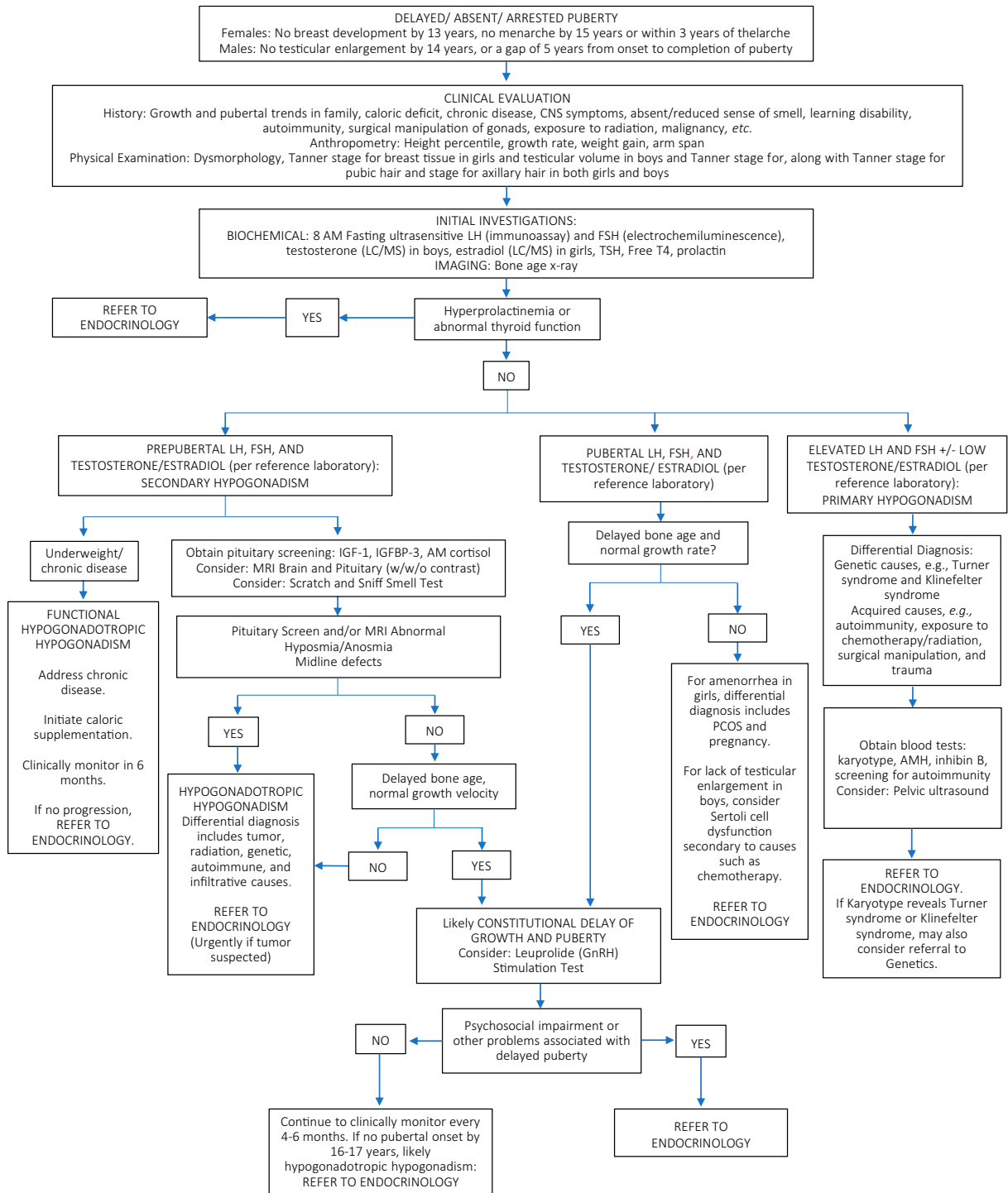


Figure 2. Algorithm for the evaluation of delayed puberty. AMH=anti-Müllerian hormone, CNS=central nervous system, FSH=follicle-stimulating hormone, IGF-1=insulinlike growth factor 1, IGFBP-3=insulinlike growth factor binding protein-3, LC/MS=liquid chromatography–mass spectrometry, LH=luteinizing hormone, MRI=magnetic resonance imaging, PCOS=polycystic ovary syndrome, TSH=thyrotropin, T4=thyroxine.

Decreased blood flow to the gonads from surgical injury (eg, orchiopexy in males), torsion, or trauma can lead to ischemia and atrophy, with resultant primary testicular or ovarian failure.

EVALUATION

The importance of a thorough history and physical examination is illustrated by the unique features of many of the causes of hypogonadism listed previously herein. When available, parents' heights and pubertal history can help set the expectation for the child's course. An objective evaluation of the sexual maturity rating (Tanner stage) and review of growth patterns can be extremely insightful (Fig 2). As mentioned previously herein, adrenarche is typically not delayed with pathologic forms of hypogonadism. Conversely, a remarkable number of boys referred to the endocrinologist for delayed puberty may already have the beginning of testicular enlargement, which can go unnoticed when the focus is on absence of penile enlargement and pubic hair growth.

A slow growth rate may point toward a previously undiagnosed chronic disease or a genetic syndrome (eg, Turner syndrome in girls).

A delayed bone age may help identify constitutional delay, although it should not be interpreted in isolation. The first step in biochemical assessment includes pediatric-specific assays of LH and FSH along with ultrasensitive assays of estradiol or testosterone samples collected early in the morning to detect subtle rises that occur at the beginning of puberty.

Low serum gonadotropin levels with low estradiol or testosterone levels can be due to CDGP or HH. In case of clinical and basal biochemical ambiguity, a positive response to a GnRH stimulation test may help identify CDGP. (26) When HH is suspected, a comprehensive assessment of pituitary function, including insulinlike growth factor 1, prolactin, free thyroxine, and cortisol levels, is critical and should be

performed between 7 and 9 AM. A magnetic resonance image of the sella may reveal anatomical pituitary or hypothalamic anomalies. A smell test is used to screen for odor identification deficits associated with Kallmann syndrome. With increased accessibility and reduced cost, molecular genetic analysis may soon become the norm for determining the etiology of HH.

When serum levels of gonadotropins are significantly elevated, in the presence of low or low-normal estradiol or testosterone, a karyotype is crucial because the most common cause of primary gonadal failure is a chromosomal abnormality in both sexes. Anti-ovarian antibodies in girls, an adrenal steroid panel in boys, and abdominal and pelvic ultrasonography can also be revelatory.

TREATMENT

Regardless of the cause, once pathologic hypogonadism is identified, initial treatment is generally focused on sex steroid replacement beginning during the adolescent years. The overarching goal is to simulate normal pubertal progression while supporting bone mineral accrual, promoting psychosocial health, and attaining genetic potential for height. (27)

In girls, estrogen replacement is typically started at one-eighth the dose used for adults and is gradually increased over 2 to 3 years to an adult dose. Although many formulations of estrogen are available, transdermal patches are largely preferred to avoid variability associated with first-pass hepatic metabolism and potential hepatic complications of oral formulations. After 2 to 3 years of estrogen therapy, medroxyprogesterone or micronized progesterone is added for 12 to 14 days per month to allow for cyclical menstrual bleeding and provide endometrial protection (against cancer) from prolonged unopposed estrogen exposure.

Testosterone replacement for boys typically starts at 15% to 25% of the full adult dose and is also gradually increased

Table. Delayed Puberty: When to Refer to Endocrinology

Statistically significant pubertal delay	No signs of puberty in girls aged ≥ 13 y No menstrual period by age ≥ 15 y in girls No signs of puberty in boys aged ≥ 14 y
Pubertal arrest	>4 y between the first signs of puberty and menarche in girls >4 y between the onset and completion of genital growth in boys
Psychosocial impairment attributed to delayed puberty	Children with constitutional delay and psychological compromise who might benefit from sex steroid therapy
High-risk for pubertal impairment	Children with significant predisposition to pubertal delay or arrest (eg, Turner syndrome, Klinefelter syndrome, history of gonadal irradiation)
Girls with secondary amenorrhea	Cessation of regular menses for 3 mo or the cessation of irregular menses for 6 mo

Adapted from Nakamoto J, Chan Y, Allen D, Geffner M. Puberty. In: *Principles and Practice of Pediatric Endocrinology*. Springfield, IL: Charles C Thomas; 2005.

over several years. Historically, intramuscular testosterone has been the mainstay in adolescents for pubertal induction. However, various other routes, including transdermal and subcutaneous, can be used based on patient and provider preference.

Alternative treatment regimens, including use of human chorionic gonadotropin to induce endogenous testosterone production, human menopausal gonadotropin administration to promote egg development, and pulsatile infusion of GnRH analogues by subcutaneous pumps, are strategies being used to improve fertility outcomes. (28)(29)(30) However, further research is required to support the use of any of these approaches in adolescents.

We do recommend that sex steroid replacement be performed under oversight of an endocrinologist because the dose and modality of administration need to be carefully titrated to clinical, radiologic, and biochemical effects.

Last, it is important to involve a mental health professional if indicated based on individual assessment given that delayed puberty can profoundly impact psychosocial well-being.

See the Table for guidance for primary care providers on when to refer the patient to endocrinology.

SUMMARY

- Based on strong research evidence (8)(9)(10)(11), constitutional delay is a normal variant of delayed puberty. No mandatory treatment is needed. However, in the presence of significant psychosocial concerns around stature and puberty, short-term, low-dose treatment with sex steroids may be

considered under the guidance of a pediatric endocrinologist. This is based on moderate research evidence. (32)(33)

- Bone age radiography is usually the first step in investigation of delayed puberty. Based on strong research evidence, biochemical assessment for a central etiology involves early-morning measurement of luteinizing hormone, follicle-stimulating hormone, and estradiol/testosterone levels (ultrasensitive assays), (34)(35) followed by gonadotropin-releasing hormone stimulation testing and imaging, as indicated. A human chorionic gonadotropin stimulation test can be used to assess defects in androgen synthesis and action. (36)
- Based on strong research evidence as well as consensus, pathologically delayed or absent puberty may be categorized as functional (due to caloric deprivation and/or ongoing chronic disease), congenital (due to genetic variants causing hypogonadotropic or hypergonadotropic hypogonadism), or acquired (due to tumors, trauma, iatrogenic, infections, etc). (7)(8)(9)(10)(11)(12)(13)(14)(15)(16)(17)(18)(19)(20)(21)(22)(23)(24)(25)
- Based on strong research evidence, treatment of delayed or arrested puberty involves replacement of the appropriate sex steroid. (27)(28)(29)(30)

References for this article can be found at <https://doi.org/10.1542/pir.2020-005291>.



1. A 13-year-old boy is shorter than his peers in school and his parents ask for your guidance. Upon review of the growth chart, you see he has been consistently at the third percentile for height. You obtain a bone age film that is consistent with 11 years. The father went through puberty later than his peers and his height is now 5 ft 11 in (180 cm). The parents are asking if a referral to pediatric endocrinology is necessary. Which of the following is the most appropriate next step in management?
 - A. Assess for traumatic brain injury.
 - B. Evaluate the patient for cystic fibrosis.
 - C. Perform renal ultrasonography to check for renal agenesis.
 - D. Perform audiology assessment for sensorineural hearing impairment.
 - E. Reassure the family that this is a normal pubertal and growth variant.

2. A 14-year-old girl is a talented ballerina. She dances 15 hours per week in addition to participating in an honors program in high school. Her parents bring her to the clinic for evaluation because of concerns related to delayed puberty and short stature. On physical examination, her BMI is at the third percentile. She has some coarse pubic hairs and small breast buds. Her mother relates that she was also very thin as a child and continues to have a very low BMI as an adult. The family stresses that it is important that she remain thin for her possible dancing career. Which of the following is the most likely cause of this patient's delayed puberty and short stature?
 - A. Congenital adrenal hyperplasia.
 - B. Hyperthyroidism.
 - C. Decreased body fat.
 - D. Pituitary tumor.
 - E. Turner syndrome.

3. A 3-year-old-boy is brought to the clinic because of concerns for poor growth. His height and weight have plateaued, and he has not grown for the past 12 months. He is in foster care due to a history of abusive head trauma at 14 months of age. He is a picky eater and is inattentive at mealtimes. He has disrupted sleep patterns and wakes several times each night. You discuss the situation with the foster family. Among the following, which is the most appropriate immediate next step in management?
 - A. Bone age determination.
 - B. Endocrinology referral.
 - C. Nutrition evaluation.
 - D. Trial of melatonin for sleep.
 - E. Ultrasonography of the thyroid.

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4. A 15-year-old, 6-ft tall boy with attention-deficit/hyperactivity disorder is struggling in school. On physical examination he has gynecomastia and small, firm testes. You discuss further evaluation with the family, including genetic testing. Results of genetic testing are most likely to confirm which of the following diagnoses?
- A. 46, XO.
 - B. 47, XXY.
 - C. Kallmann syndrome.
 - D. Prader-Willi syndrome.
 - E. SRY translocation.
5. A 16-year-old boy, who is a cancer survivor from acute lymphocytic leukemia is brought to the clinic for a routine examination. He is growing well and has a sexual maturity rating of III to IV. He does not want to talk about his treatment history, and he is more focused on clearance to participate in high school sports. He is receiving average grades in school and has friends. His mother has questions about the long-term effects of his therapy. In counseling the patient and his mother, which of the following is the most appropriate information to discuss with them about the long-term effects of his therapy?
- A. He is at risk for antisocial behavior and poor social peer relationships.
 - B. He is at risk for infertility.
 - C. He is restricted from playing any sports in high school due to his cancer history.
 - D. He requires monitoring with yearly brain magnetic resonance imaging.
 - E. There are no long-term effects of his chemotherapy.