h to diagnosis and management

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Disorders of Puberty: An Approach to Diagnosis and Management

PDF PRINT COMMENTS

DAVID A. KLEIN, MD, MPH, Fort Belvoir Community Hospital, Fort Belvoir, Virginia

JILL E. EMERICK, MD, Walter Reed National Military Medical Center, Bethesda, Maryland

JILLIAN E. SYLVESTER, MD, Fort Belvoir Community Hospital, Fort Belvoir, Virginia

KAREN S. VOGT, MD, Walter Reed National Military Medical Center, Bethesda, Maryland

Am Fam Physician. 2017 Nov 1;96(9):590-599.

▶ **Patient information**: See related handout on early and delayed puberty.

Author disclosure: No relevant financial affiliations.

ARTICLE SECTIONS

Disorders of puberty can profoundly impact physical and psychosocial well-being. Precocious puberty is pubertal onset before eight years of age in girls and before nine years of age in boys. Patients with early isolated pubertal changes, prepubertal linear growth, and no worrisome neurologic symptoms typically have a benign pattern of development and should be monitored in the appropriate clinical context. Among patients with true precocious puberty, or full activation of the hypothalamic-pituitary-gonadal axis, most girls have an idiopathic etiology, whereas it is commonly due to identifiable pathology on imaging in boys. History and physical examination should be followed by measurements of serum follicle-stimulating hormone, luteinizing hormone, and testosterone (boys) or estradiol (girls); thyroid function testing; and bone age radiography. Brain magnetic resonance imaging should be performed in girls younger than six years, all boys with precocious puberty, and children with neurologic

symptoms. Delayed puberty is the absence of breast development in girls by 13 years of age and absence of testicular growth to at least 4 mL in volume or 2.5 cm in length in boys by 14 years of age. Constitutional delay of growth and puberty is a common cause of delayed puberty; however, functional or persistent hypogonadism should be excluded. History and physical examination should be followed by measurements of serum follicle-stimulating hormone, luteinizing hormone, and testosterone (boys) or estradiol (girls); and bone age radiography. Abnormal growth velocity necessitates assessment of serum thyroid function, prolactin, and insulinlike growth factor I. Boys 14 years and older and girls 13 years and older may benefit from sex steroid treatment to jump-start puberty. Referral to a pediatric endocrinologist may be warranted after the initial evaluation.

Puberty is a developmental stage characterized by physical and psychosocial maturation. Abnormal pubertal timing can adversely affect a child's physical and psychosocial well-being and may be caused by a range of generally benign or pathologic etiologies. Physicians must identify which findings are suitable for surveillance over time and which suggest treatable underlying pathology.

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SORT: KEY RECOMMENDATIONS FOR PRACTICE

CLINICAL RECOMMENDATION	*EVIDENCE RATING*	*REFI*
Girls with signs of puberty before eight years of age and boys with signs of puberty before nine years of age should be evaluated for precocious puberty.	C	5, 6
Girls without breast development by 13 years of age should be evaluated for delayed puberty, and girls without menarche by 15 years of age should be evaluated for primary amenorrhea.	C	5, 7,
Boys who do not have testicular growth to at least 4 mL in volume	C	5, 7,

Hormonal and Physical Changes of Normal Development

Jump to section +

The physical changes of puberty are a result of gonadal sex hormone production, the start of

which (gonadarche) indicates pubertal onset. Gonadarche is triggered by the pulsatile release of gonadotropin-releasing hormone, which activates the hypothalamic-pituitary-gonadal (HPG) axis.[1–3] Adrenarche (i.e., adrenal androgen production leading to pubic and axillary hair, body odor, and mild acne) is a separate but usually concurrent process and does not in itself indicate true pubertal onset in boys or girls.[4–7]

In girls, increased ovarian estradiol secretion causes breast development at a mean age of 10 years (range: eight to 12 years). Menarche typically follows 2.5 years after the onset of breast development, at an average age of 12.5 years (range: nine to 15 years).[1–5] In boys, testicular enlargement to at least 4 mL in volume or 2.5 cm in length is the first sign of true puberty and occurs at an average age of 11.5 years (range: 9.5 to 14 years).[1–4,8–13] Physical changes are described using sexual maturity ratings *(Table 1*[1–5,9,14] *and Table 2*[1–5,9,14]*)*, such as Tanner stages, and are affected by body habitus and demographic factors.[1–5,12,14]

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Table 1.

Sexual Maturity Ratings in Girls

RATING	*BREAST DEVELOPMENT*	*PU*
1	Prepubertal	No
2	Subareolar breast buds	Sp lor sli pig str sli cu alo me lab
3	Breasts and areolae are further enlarged with a continuous rounded contour	Da co mo cu spr spa ov mo pu
4	Areola and nipple form a secondary mound above the contour of the breast	Ad bu are co sm an is ext

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Table 2.

Sexual Maturity Ratings in Boys

RATING	*GENITAL DEVELOPMENT*	*PU*
1	Prepubertal	N
2	Enlargement of the testes (more than 4 mL in volume and more than 2.5 cm in length) and scrotum, but not the penis	S lo sl p st sl cu th th
3	Continued testicular and scrotal enlargement with penile growth	D co m cu sp sp o' p
4	Continued testicular, scrotal, and penile growth with enlargement of the glans	A bu ar co sr th ex to m

Linear growth velocity is about 5 cm per year from four years of age to puberty with a nadir before the pubertal growth spurt. Girls achieve peak height velocity during sexual maturity ratings 2 and 3 (mean: 8.3 cm per year, age 11 or 12 years) and boys during sexual maturity ratings 3 and 4 (mean: 9.5 cm per year, age 13 or 14 years). On average, girls complete linear growth at 15 years of age and boys at 17 years of age. After menarche, girls grow an average of 7 cm.[1–4,14–18]

When to Suspect a Disorder of Puberty

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PRECOCIOUS PUBERTY

Precocious puberty is diagnosed when secondary sexual characteristics are identified in girls younger than eight years and boys younger than nine years.[5,6] Data suggest a trend toward early pubertal development. Approximately 20% of black girls and 5% to 10% of white girls seven to eight years of age in the United States have glandular breast development, particularly if obese.[19–23] Eight years of age can be considered a reasonable cutoff for evaluation in girls.[5,6] Because of more frequent pathology in boys with precocious puberty than girls, all pubertal boys younger than nine years should be fully evaluated.[5,6,24]

DELAYED PUBERTY

Puberty is considered delayed when there are no signs of breast development by 13 years of age in girls or testicular enlargement by 14 years of age in boys.[5,7,25] Clinicians should suspect pubertal delay if there is halting or regression of pubertal development. In girls with initial pubertal

changes, absence of menarche by 15 years of age is also concerning.

Evaluation of a Suspected Disorder of Puberty

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HISTORY

The clinician should inquire about the onset and progression of body odor, acne, breast or testicular development, and pubic and axillary hair. Current or previous therapies, including chemotherapy, radiation therapy, or exogenous sex steroids, may indicate the underlying etiology. Neurologic symptoms may reveal intracranial pathology. For delayed puberty, a history suggestive of underlying chronic disease (e.g., fatigue, pain, abnormal stools), nutrition and exercise patterns, poor psychosocial functioning, cryptorchidism, anosmia [i.e., in Kallmann syndrome]) is important.

Growth patterns, such as constitutional delay, may be familial. Thus, family history should include pubertal timing, especially the mother's age of menarche and father's age of reaching adult height.[7,9]

Table 3[1–6,9] *and Table 4*[1–5,7,8] summarize history and physical examination findings in the evaluation of early and delayed puberty.

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Table 3.
Early Pubertal Development: History and Physical Examination Findings

FINDINGS	*POSSIBLE DIAGNOSES*
Abdominal pain	Gonadal malignancy
Asymmetric testes	Gonadal tumor
Body mass index and weight (growth charts)	High: may be associated with precocious puberty
Café au lait spots	McCune-Albright syndrome, neurofibromatosis
Dull pink (vs. red) vaginal mucosa	Estrogen exposure (unspecified)
Enlarged thyroid	Hyper- or hypothyroidism
Exposure to exogenous sex steroids	Peripheral precocious puberty

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Table 4.

Delayed Puberty: History and Physical Examination Findings

FINDINGS	*POSSIBLE DIAGNOSES*
Abdominal pain	Gastrointestinal disease
Anosmia	Kallmann syndrome
Asymmetric testes	Oophoritis or orchitis
Body mass index and weight (on growth charts)	Low: eating disorder, caloric insufficiency, gastrointestinal or other systemic disease
Chemotherapy, radiation treatment, brain tumor	Hypogonadism
Cryptorchidism or orchidopexy	Hypogonadism
Dysmorphic features (webbed neck, short stature,	Turner syndrome

PHYSICAL EXAMINATION

Height, weight, and body mass index should be plotted on growth curves, and the height velocity should be calculated.[3,23] Target height (midparental height) can be determined using the following equation: [mother's height + father's height + 13 cm in boys or − 13 cm in girls] ÷ 2.[18,26] A target height differing from the projected height, as established by extending the growth curve to adulthood or bone age radiography, by approximately more than 10 cm may suggest a pathologic condition.[26] Because of the effects of sex steroids on epiphyseal maturation, patients with precocious puberty may present with relatively tall stature (leading to shorter adult height), and those with delayed puberty may present with short stature.[26]

The patient's sexual maturity rating should be noted, as well as the amounts of acne and axillary and facial hair. In boys, determining the location, consistency, and size of the testes can evaluate for cryptorchidism, malignancy, or Klinefelter syndrome (firm testes), and help determine pubertal staging. In girls, dull pink vaginal mucosa suggests estrogen exposure; virilization (e.g., clitoromegaly) should be excluded.[4–7,9,27]

The thyroid, abdomen, and neurologic system should be examined for evidence of thyroid or gastrointestinal disease or intracranial pathology. Any dysmorphic features or café au lait spots may suggest Turner or McCune-Albright syndrome.[4–7,9,27]

Early Pubertal Development

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eTable A includes the differential diagnosis of isolated pubertal changes and true precocious

puberty.

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eTable A.
Differential Diagnosis of Early Pubertal Development

*DIAGNOSIS**	*CHARACTERISTICS*
Generally benign variants	
Lipomastia	Fat tissue but no glandular breast tissue on palpation; associated with obesity
Nonprogressive precocious puberty	Early but normal sequence of pubertal events that does not progress prematurely
Premature adrenarche	Pubic and axillary hair growth, body odor, sweating, and/or mild acne; may have mildly elevated dehydroepiandrosterone sulfate, but normal levels of FSH, LH, 17-hydroxyprogesterone, estradiol, and testosterone; no change in linear growth velocity or enlargement of the testes, penis, breasts, ovaries, or

ISOLATED PUBERTAL CHANGES

Premature thelarche, defined by isolated glandular breast tissue on palpation, should be differentiated from lipomastia (isolated fatty breast tissue), which is common in obese children.[21] To differentiate these conditions, clinicians may examine the patient in the supine position, thereby making the breasts less prominent, to determine presence or absence of glandular tissue under the areolae. Isolated prepubertal vaginal bleeding not caused by trauma, abuse, a foreign body, infection, or an exceedingly rare tumor is usually benign.[6,28]

Premature adrenarche, driven by adrenal androgens rather than activation of the HPG axis, leads to slowly progressive appearance of pubic and axillary hair, body odor, sweating, and/or mild acne without change in linear growth velocity or enlargement of the testes, penis, breasts, ovaries, or clitoris. Dehydroepiandrosterone sulfate may be at a pubertal level (i.e., slightly elevated for the patient's chronologic age), whereas estradiol, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) remain at prepubertal levels.[5,6,9] Less than 5% of patients have an elevated 17-hydroxyprogesterone level, suggesting mild nonclassic congenital adrenal hyperplasia, which does not usually require treatment. Thus, laboratory evaluation for such isolated findings may be delayed.[6] Deferring laboratory tests also applies in cases of fine, sparse pubic hair growth that sometimes occurs in infancy.[6]

Patients with early isolated pubertal changes, prepubertal linear growth, and no worrisome neurologic symptoms typically have a benign pattern of development, necessitating only surveillance over three to six months to evaluate for progression.[3–6,9,29] Laboratory or bone age assessment may be deferred initially. Notably, bone age advancement by two standard deviations has low predictive value in differentiating benign pubertal variants from concerning causes of precocious puberty.[6,30]

Gynecomastia, or estrogen-mediated glandular breast tissue, is common in pubertal boys. Evaluation for chronic disease; hyperprolactinemia; testicular or adrenal neoplasm; use of prescription, recreational, or performance-enhancing drugs; or hypogonadism (e.g., Klinefelter syndrome) should be initiated if symptoms persist for 18 to 24 months or the patient has no pubertal changes.[31]

CENTRAL AND PERIPHERAL PRECOCIOUS PUBERTY

Precocious puberty can be characterized by the pathologic location. In central precocious puberty, the HPG axis is activated, resulting in early but normal development, symmetric progression of secondary sexual characteristics, and increasing growth velocity.[6,9,32] Central precocious puberty is approximately 10-fold more common in girls than in boys.[33] Although usually idiopathic in girls, it can be incited by head trauma, neoplasm, radiation, or genetic conditions.[5,6,9] Pathologic causes of central precocious puberty are more common in boys.[5,6,9]

Peripheral precocious puberty occurs when hormonal influences originating outside of the HPG axis produce incomplete, atypically sequenced or rapid pubertal progression.[5,6,9] Quickly progressing or significant hyperandrogenic findings may warrant workup for congenital adrenal hyperplasia or an androgen-secreting tumor. Elevated estradiol levels in the setting of low LH may suggest an estrogen-secreting tumor.[6] Hypothyroidism and exogenous steroid use should be excluded. Multiple café au lait spots and fibrous dysplasia of bones are concerning for McCune-Albright syndrome or neurofibromatosis.[5,6,9]

The initial workup should include measurement of serum FSH, LH, and testosterone in boys or estradiol in girls; thyroid function testing; and bone age radiography (*eTable B*, *Figure 1*[5,6,9]). In cases of hyperandrogenic findings, measuring serum dehydroepiandrosterone sulfate and 17-hydroxyprogesterone is indicated. An LH level of more than 0.3 mIU per mL (0.3 IU per L) is the most reliable laboratory finding for central precocious puberty; however, in patients with lower values and high clinical suspicion, a gonadotropin-releasing hormone analogue stimulation test may be warranted.[6,34] In cases of diagnostic uncertainty, pelvic ultrasonography can evaluate for increased uterine and ovarian volume expected for age, which may indicate central precocious puberty or a tumor.[6]

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eTable B.

Diagnostic Testing in the Evaluation of Pubertal Disorders

TEST	CON… PREC… PUBI…
Laboratory testing (refer to local reference value	
First-line	
Serum estradiol	Eleva… (girls… estro… expo… mark… eleva… 100 p… mL [… per L… evalu… ovari… tumo… espec… lutein… horm… suppr…
Serum testosterone	Eleva… testic… (boys… adren… exog…

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Diagnostic Approach to Early Pubertal Development

Figure 1.

A diagnostic approach to early pubertal development (i.e., in girls younger than eight years and boys younger than nine years). (DHEA-S = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging.)

Information from references 5, 6, and 9.

The appropriate timing for neuroimaging to identify central nervous system lesions (e.g., hypothalamic hamartoma, malignancy) in children with precocious puberty is controversial. Girls younger than six years, all boys with precocious puberty, and children with neurologic symptoms such as headache, vision changes, or seizures should be screened with magnetic resonance imaging.[5,6,9] Some experts discourage routine neuro-imaging for asymptomatic girls six to eight years of age because pathology requiring treatment is exceedingly rare. With shared decision making, parents can weigh the risks of sedation, intravenous contrast media, and follow-up imaging (leading to anxiety and high cost) against the low likelihood that imaging will show a new central nervous system malignancy (at most 1%).[5,6,35]

If started early in the course of central precocious puberty, gonadotropin-releasing hormone

analogues (e.g., leuprolide [Lupron]) appear to safely prevent premature fusion of growth plates, thereby preserving height potential.[36] Because of high annual costs, treatment may be most appropriate if bone age suggests impending short stature or if the patient exhibits aggression (boys) or profound emotionality in response to menses (girls).[10,37]

Delayed Puberty

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Delayed puberty is the absence of breast development by 13 years of age in girls or the absence of testicular growth to at least 4 mL in volume or 2.5 cm in length by 14 years of age in boys.[7–9,25,38] Constitutional delay of growth and puberty is the most common cause of delayed puberty in boys (60%) and girls (30%).[39,40] It represents an extreme of the normal spectrum of pubertal timing and is a diagnosis of exclusion.[39,40] For more than 75% of patients with constitutional delay of growth and puberty, family history may reveal parental pubertal delay.[41,42]

Other etiologies of delayed puberty are categorized based on gonadotropin levels. In hypergonadotropic hypogonadism, gonadal insufficiency delays puberty and results in elevated levels of FSH and LH. Conditions causing hypergonadotropic hypogonadism can be congenital or acquired and are collectively more common in girls (26%) than in boys (7%) with delayed puberty.[7,39]

Hypogonadotropic hypogonadism is characterized by low levels of FSH and LH and further classified by the pathology. Functional hypogonadotropic hypogonadism is caused by chronic disease, stress, or inadequate nutrition, and the condition may be transient or reversed. Persistent hypogonadotropic hypogonadism is caused by a congenital abnormality in the HPG axis or an acquired etiology such as a central nervous system tumor, trauma, surgery, or radiation.[7,43] Patients with persistent hypogonadotropic hypogonadism require treatment to induce puberty, maintain normal adult levels of sex steroids, and optimize fertility.[44] *eTable C* includes the differential diagnosis of delayed or absent puberty.

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eTable C.

Differential Diagnosis of Delayed or Absent Puberty

DIAGNOSIS	*CHARAC*
Generally benign variant	
Constitutional delay of growth and puberty	Normal gr velocity, hi of delayed puberty in parents, de bone age
Functional hypogonadotropic hypogonadism*	
Celiac disease	Abdominal malabsorpt anemia, po weight gai stature may the only symptom; positive se results, cor with endos biopsy
Diabetes mellitus	Polyuria, polydipsia, polyphagia weight loss known but controlled disease;

Initial workup should include measurements of serum FSH, LH, testosterone in boys or estradiol in girls, and bone age radiography (*eTable B*, *Figure 2* [7,8,25,44,45]). If abnormal growth velocity is a concern, serum thyroid function, prolactin, and insulinlike growth factor I should be assessed.[7] Constitutional delay of growth and puberty can be difficult to distinguish from persistent hypogonadotropic hypogonadism; the latter may be diagnosed at 18 years of age if there is inadequate response to jump-start therapy (which is defined later in this section), and sex steroid replacement is still required.[7,45]

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Diagnostic Approach to Late or Absent Pubertal Development

Figure 2.

A diagnostic approach to late or absent pubertal development. (FSH = follicle-stimulating hormone; LH = luteinizing hormone.)

Information from references 7, 8, 25, 44, and 45.

Bone age indicates the degree of sex steroid effect on bone maturation and future growth potential.[7,9] For example, patients with constitutional delay of growth and puberty generally have a delay of more than two years, but this finding is nonspecific.[8]

Delayed puberty can cause significant psychological distress and low self-esteem.[46,47] Girls older than 13 years and boys older than 14 years with possible constitutional delay of growth and puberty or gonadotropin-releasing hormone

deficiency may be offered jump-start therapy to induce puberty.[5,7,8,25,45] For example, treating boys with testosterone cypionate or enanthate (e.g., 50 to 100 mg intramuscularly per month) and girls with overnight transdermal estradiol (e.g., 6.2 mcg, one-fourth of the 25-mcg 24-hour patch) for three to six months may accelerate attainment of final adult height and generally does not lead to premature epiphysis closure.[7,25] If pubertal progression does not occur within four to six months after completing therapy, further evaluation for persistent hypogonadotropic hypogonadism and long-term hormone therapy should be initiated.[5,7] Indications for referral to a pediatric endocrinologist are listed in *eTable D*.

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eTable D.

Indications for Referral to a Pediatric Endocrinologist in Children with Suspected Abnormalities of Puberty

Concern for early puberty*
Any pubertal changes before 6 years of age in girls and 9 years of age in boys
Pubertal changes with associated headaches, vision changes, new-onset seizures
Rapid pubertal progression
Confirmed central or peripheral precocious puberty (not a generally benign variant)
Known predisposing conditions (e.g., neurofibromatosis, previous irradiation, known neoplasm)
Concern for delayed puberty†
Boys without testicular growth to at least 4 mL in volume or 2.5 cm in length by 14 years of age
Girls without breast development by 13 years of

This article updates a previous article on this topic by Blondell, et al.[48]

Data Sources: A PubMed search was completed using the MeSH function with the key term puberty and at least one of the following qualifiers: early, precocious, delayed, absent, or disorder. The search included meta-analyses, randomized controlled trials, observational studies, and reviews. Nonhuman studies and studies older than 10 years were excluded. The reference lists of included reviews were searched for additional studies of interest. Other searches included Essential Evidence Plus, the Cochrane Database of Systematic Reviews, and the U.S. Preventive Services Task Force website. Search dates: October 1, 2016, to May 21, 2017.

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Defense; or the U.S. government.

The Authors show all author info

DAVID A. KLEIN, MD, MPH, is an associate program director of the National Capitol Consortium Family Medicine Residency, Fort Belvoir, Va. He is also an assistant professor of family medicine and pediatrics at the Uniformed Services University of the Health Sciences, Bethesda, Md....

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Objective: Lipodystrophy syndromes are extremely rare disorders of deficient body fat associated with potentially serious metabolic complications, including diabetes, hypertriglyceridemia, and steatohepatitis. Due to their rarity, most clinicians are not familiar with their diagnosis and management. phy syndromes, many clinicians are. unfamiliar with their diagnosis and. management. In December 2015, an expert panel including represen Patients with AGL may develop type 1. Figure 2. Diagnostic approach to lipodystrophy syndromes. Lipodystrophy should be suspected in patients with regional or generalized lack of adipose tissue. Early adrenarche, true precocious puberty, or central hypogonadism may occur in children with generalized li-podystrophy. Disorders of puberty can profoundly impact physical and psychosocial well-being. Precocious puberty is pubertal onset before eight years of age in girls and before nine years of age in boys. Patients with early isolated pubertal changes, prepubertal linear growth, and no worrisome neurologic symptoms typically have a benign pattern of development and should be monitored in the appropriate clinical context. This review provides a summary of the psychological aspects of CHH/KS and outlines an approach to comprehensive care that spans medical management as well as appropriate attention, care and referrals to peer-to-peer support and mental health services to ameliorate the psychological aspects of CHH/KS. Disorders of puberty can profoundly impact physical and psychosocial well-being. Precocious puberty is pubertal onset before eight years of age in girls and before nine years of age in boys. Patients with early isolated pubertal changes, prepubertal linear growth, and no worrisome neurologic symptoms typically have a benign pattern of development and should be monitored in the appropriate clinical context. Among patients with true precocious

puberty, or full activation of the hypothalamic-pituitary-gonadal axis, most girls have an idiopathic etiology, whereas it is commonly due to identifiable 8. Normal puberty Normal puberty is initiated by the onset of pulsatile secretion of gonadotropin- releasing hormone (GnRH) from the hypothalamus These pulses cause release of luteinizing hormone (LH) and follicular stimulating hormone (FSH) from the pituitary gland These pituitary gonadotropins then circulate to the gonads and stimulate production of sex steroids. CDGP is a diagnosis of exclusion. Children with constitutional delay are more likely to be short for age. with a history of relatively normal growth rate. Delays in bone maturation . Delay in adrenarche. Disorder Of Puberty. davinpratama. approach to short stature.