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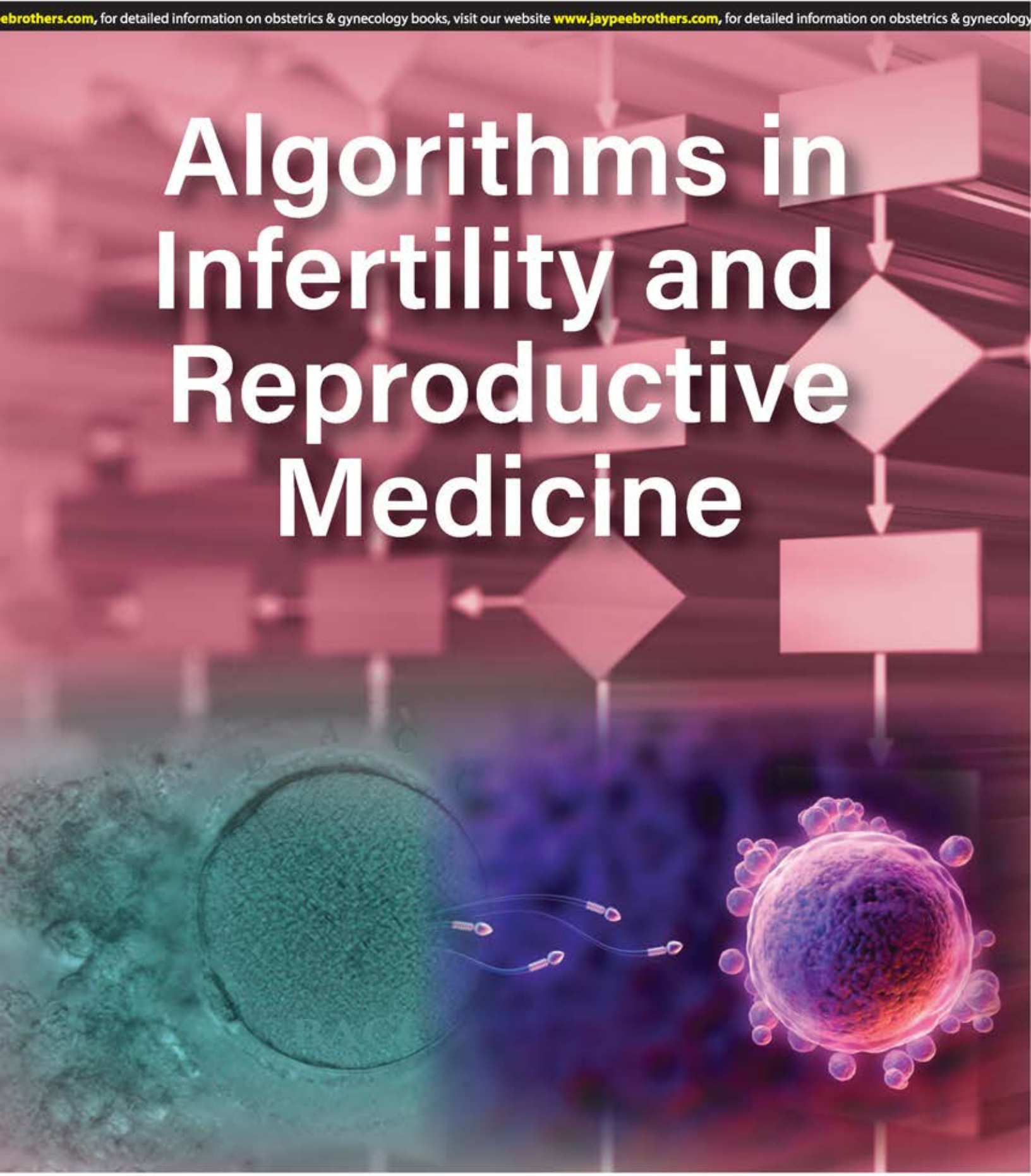
Algorithms in Infertility and Reproductive Medicine



Editors
Kamini A Rao
Harpreet Kaur

JAYPEE

Contents

1. **Work-up of a Case of Infertility** 1
   Snehal Dhobale Kohale
2. **Tubal Evaluation Methods and Assessment of Tubal Factor Infertility** 8
   Vasani Nidhi N
3. **Hysterolaparoscopy: Indications and Usage** 12
   Madhuri, Anshu Dhar
4. **Disorders of Puberty** 21
   Yogita Dogra
5. **Disorders of Sexual Development** 33
   Reeta Mahey, Monika Rajput, Rohitha Cheluvaraju
6. **Thyroid Disorders and Fertility** 50
   Shikha Sardana
7. **Hyperprolactinemia and Infertility: An Algorithm-based Approach** 54
   Sonal Agarwal, Rutvij Dalal
8. **Amenorrhea—Work-up and Management** 61
   Harpreet Kaur
9. **Management of the Hypogonadotropic Hypogonadism Male and Female** 67
   Ruma Satwik
10. **Management of Müllerian Anomalies** 77
    Vanita Suri, Sujata Siwatch
11. **Pelvic TB—Work-up and Management** 86
    JB Sharma, Mansi Deoghare, Sona Dharmendra
12. **Asherman's Syndrome** 89
    Saloni Kamboj, Neena Malhotra
13. **Management of Endometriosis** 99
    Mamta Dighe, Pallavi Kalghatgi
14. **Management of Fibroids and Adenomyosis in Infertility** 108
    Sangita Sharma
15. **Management of PCOS: Infertility and Long-term Management** 118
    Devi R, G Rani Aishwarya
16. **Management of Hirsutism** 131
    Chaitra Nayak
17. **Ovulation Induction Protocols for Intrauterine Insemination** 135
    Shivani Singh Kapoor, Shalu Gupta
18. **Sperm Selection in IUI and IVF** 144
    Mohammed Ashraf C, Ms Lakshmishree BR
19. **Controlled Ovarian Stimulation Protocols for In Vitro Fertilization** 161
    Pratibha S Malik

20. Management of Ovarian Hyperstimulation Syndrome 170
Deepika Krishna

21. Pregnancy of Unknown Location 180
Veronica Irene Yuel

22. Diagnosis and Management of Ovarian Torsion 185
Divya Sardana, Aashna Arora

23. Work-up and Management of Thin Endometrium 190
Runa Acharya

24. Endometrial Preparation for Frozen Embryo Transfer 196
Manishi Mittal, Umesh Nandani Jindal

25. Work-up of Azoospermia 207
Divyashree PS

26. Ejaculatory/Erectile Dysfunction—Work-up and Management 215
Vivek Kakkad, Harsh Nihlani

27. Dyspareunia—Work-up and Management 220
Sudha Prasad, Saumya Prasad, Shrinkhla Khandelwal, Priyanka Kar

28. Work-up and Management of Premature Ovarian Insufficiency 226
Nivedita Shetty, Prakash B Savanur

29. Recurrent Pregnancy Loss: Work-up and Management 231
Shalini Gainder, Plabani Sarkar

30. Recurrent Implantation Failure—Work-up and Management 239
Mandeep Kaur, Ajitabh Shukla

31. Lifestyle Factors in Infertility 250
T Shilpa Reddy

32. Luteal Phase Support—What and Till When 256
Sandhya Krishnan

33. Fertility Preservation Techniques 260
Jasneet Kaur

34. Third Party Reproduction 269
Sowmya Dinesh HR

35. PGT: When and Where to Offer 279
Abha Majumdar, Bhawani Shekhar

36. Viral Infections and IVF—Hepatitis B, Hepatitis C, and HIV 285
Sweta Gupta, Sapna Yadav, Rahul Kumar Gupta

Index 293

CHAPTER

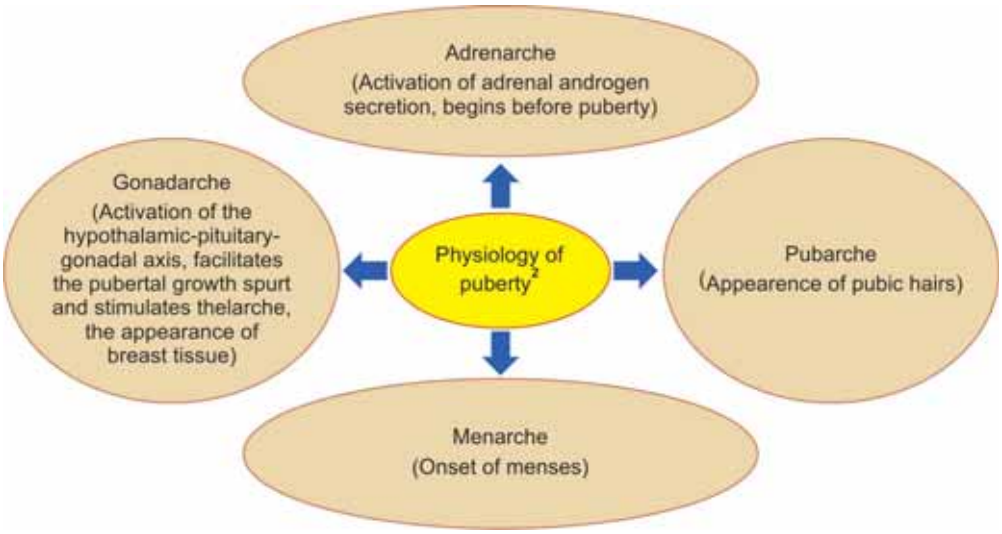
4

Disorders of Puberty

Yogita Dogra

INTRODUCTION

Puberty is a stage of cognitive, psychological, and biological development. Although growth and the appearance of secondary sexual characteristics are the most obvious markers of the onset of puberty, changes in body composition and cognitive development are also significant.[1] Although puberty occurs naturally, it may be a difficult changeover for many teenagers, and it offers even more obstacles when it occurs prematurely or late.



Puberty is characterized by a set of predictable occurrences that differ in time, chronology, and pace. In most teenage females, the first symptom of puberty is an increase in development, followed by breast development (thelarche), the formation of pubic hair (pubarche), and, lastly, commencement of menstruation (menarche).[2]

Marshall and Tanner described the most commonly used staging methods for describing puberty's physical changes in 1969 (for girls)[3] **(Fig. 1)** and 1970 (for boys).[4]

Breast development (thelarche) follows a well-defined timeline.[2]

- *Tanner stage I:* No glandular breast tissue palpable.
- *Tanner stage II:* Breast budding seen as expansion and spreading of the areolae.
- *Tanner stage III:* The breast expands and rises above the areolae.
- *Tanner stage IV:* Areolae and nipple produce secondary mounds.
- *Tanner stage V:* The breast attains an adult shape.

Pubarche follows thelarche in the majority of teenagers. In a considerable proportion of individuals, however, pubarche precedes thelarche. In every situation, the two are interdependent and advance simultaneously.[2]

- *Tanner stage I:* No hairs
- *Tanner stage II:* Tiny quantity of long, generally straight hair
- *Tanner stage III:* The hair subsequently becomes curlier and coarser as it grows outward
- *Tanner stage IV:* Hair expands farther to cover the entire triangle over the pubic region
- *Tanner stage V:* Adult pattern with expansion across the medial thigh.

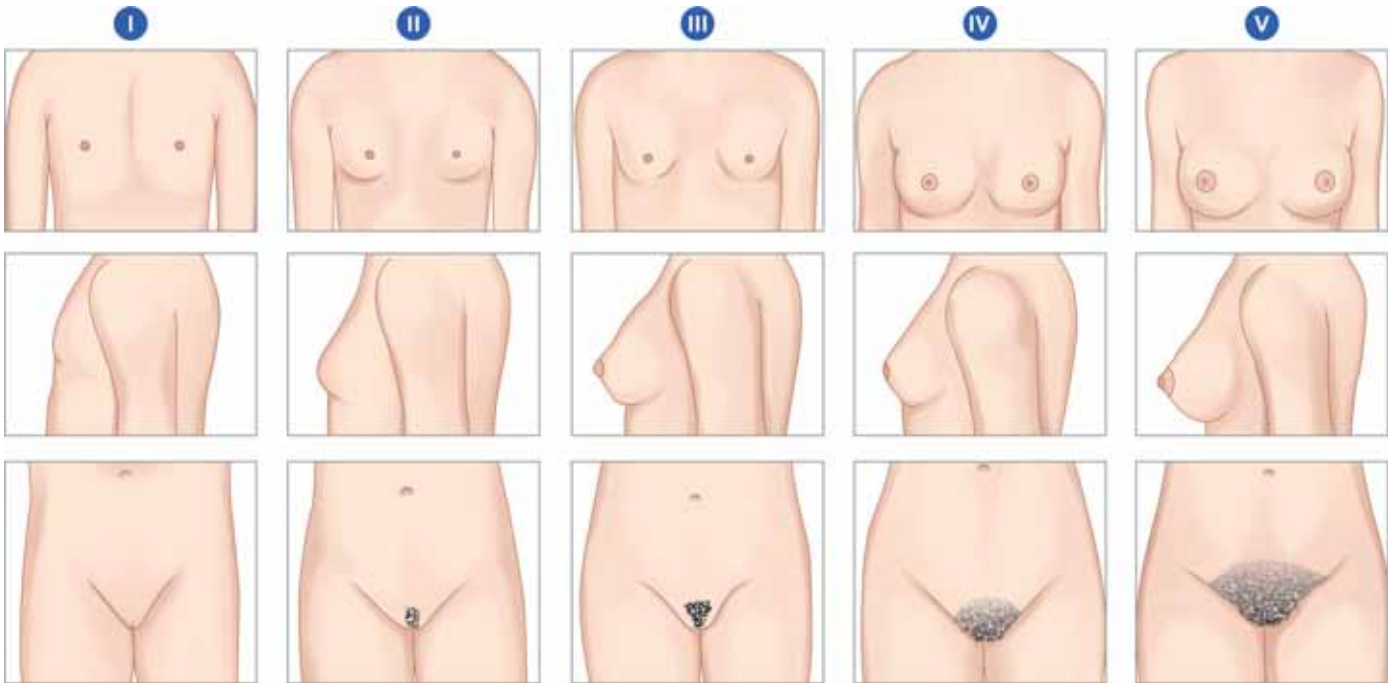
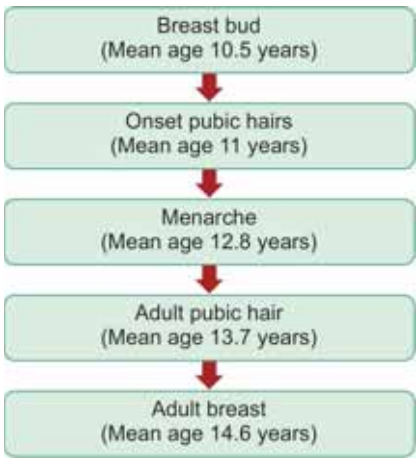


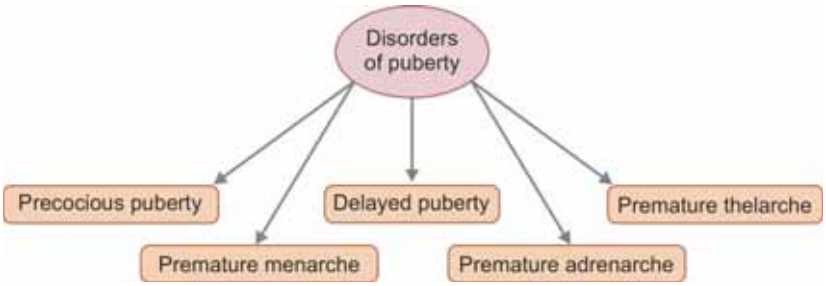
Fig. 1: Illustration of the Tanner scale for females.
(*Courtesy:* Michał Komorniczak, Poland)

SEQUENCE OF PUBERTAL MILESTONES[2]



SUMMARY OF PUBERTAL EVENTS[2]

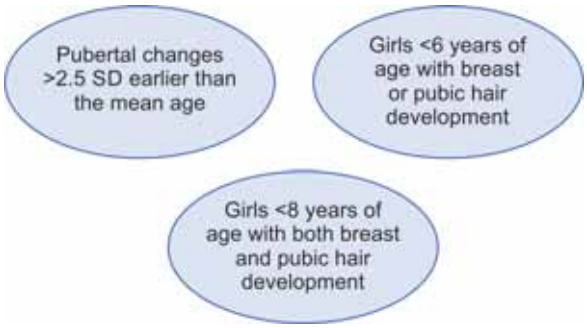
- During fetal life, the hypothalamic-pituitary-gonadal axis differentiates and develops, becoming completely functioning prior to birth.
- Pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH) is greatly reduced to extremely low levels of activity starting in late infancy and continuing through childhood as a result of central inhibitory mechanisms and, to a lesser extent, a considerable sensitivity to low levels of gonadal steroid feedback.
- Adrenal androgen production increases (adrenarche) in late childhood, continues to rise consistently thereafter, and eventually encourages pubarche.
- After a decade of inactivity, pulsatile GnRH production escalates and the hypothalamic-pituitary-gonadal axis (gonadarche) is revived.
- Before 10 years of age, gonadotropin [follicle-stimulating hormone (FSH) and luteinizing hormone (LH)] levels escalate gradually, followed by a steady rise in estradiol levels, which promote thelarche.
- Gonadal estrogen production increases significantly at midpuberty to drive endometrial development, resulting in the commencement of menstruation (menarche).



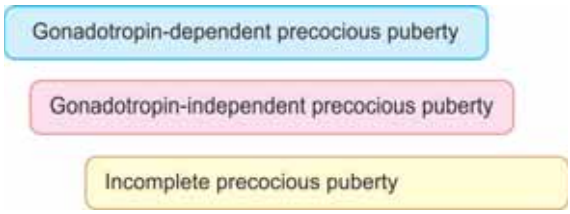
PRECOCIOUS PUBERTY

Precocious puberty refers to pubertal development that occurs at a younger age than would be predicted based on recognized standard norms, i.e., before 8 years in girls and before 9 years in boys. Its causes are numerous, ranging from typical developmental deviations such as early adrenarche to major disease such as malignant brain neoplasms. Precocious puberty in children requires rigorous investigation to determine the reason and, if necessary, prompt intervention to dodge the psychological and developmental repercussions of unusually early sexual maturity.[2]

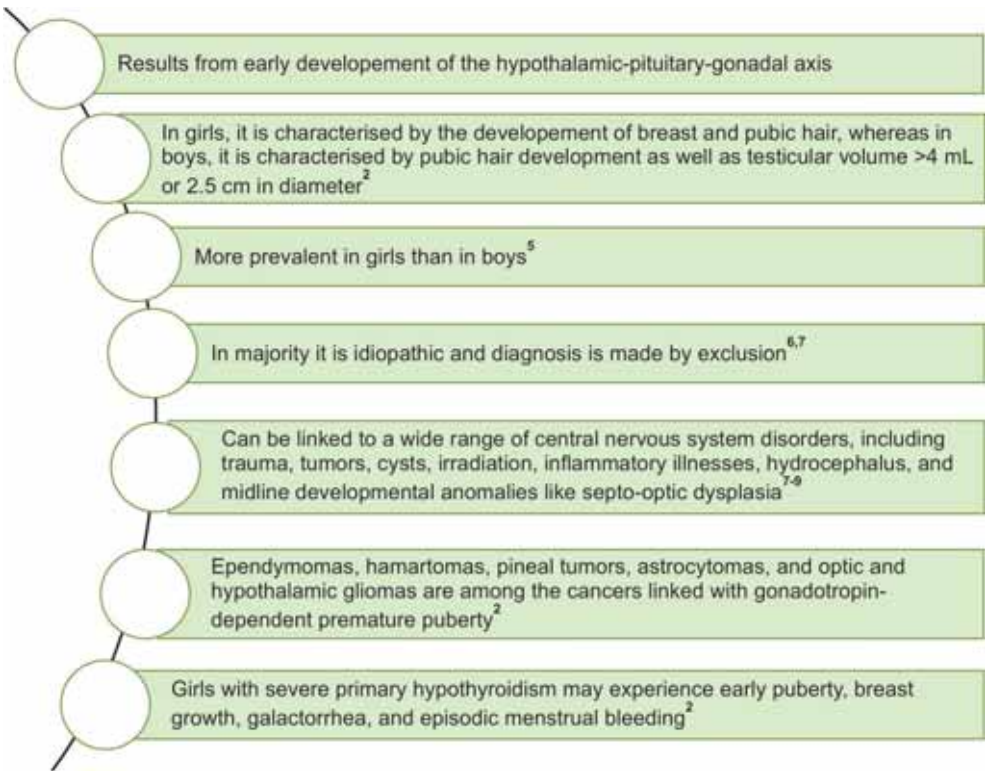
Indications for Evaluation[2]



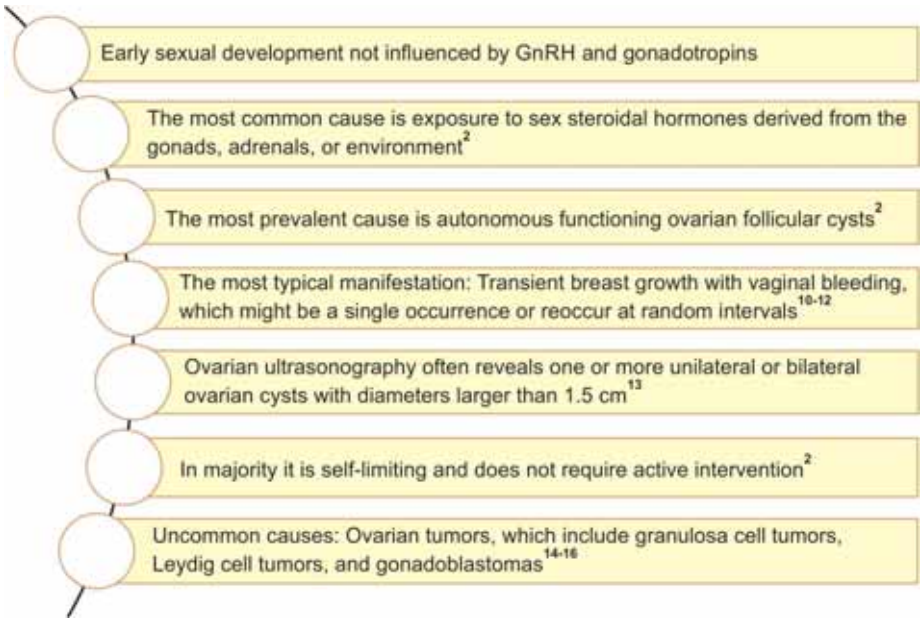
Classification of Precocious Puberty[2]



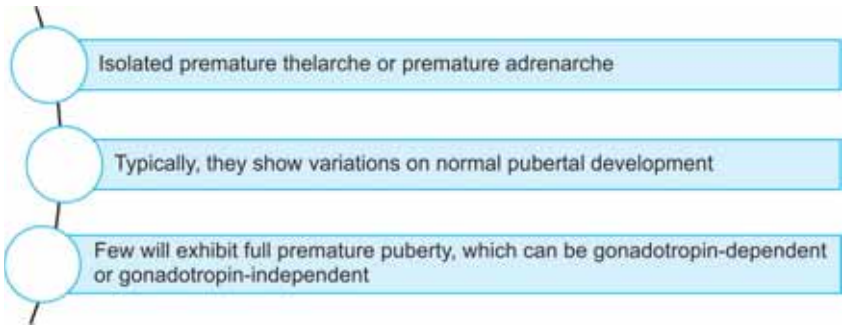
Gonadotropin-dependent or True Precocious or Central Precocious Puberty



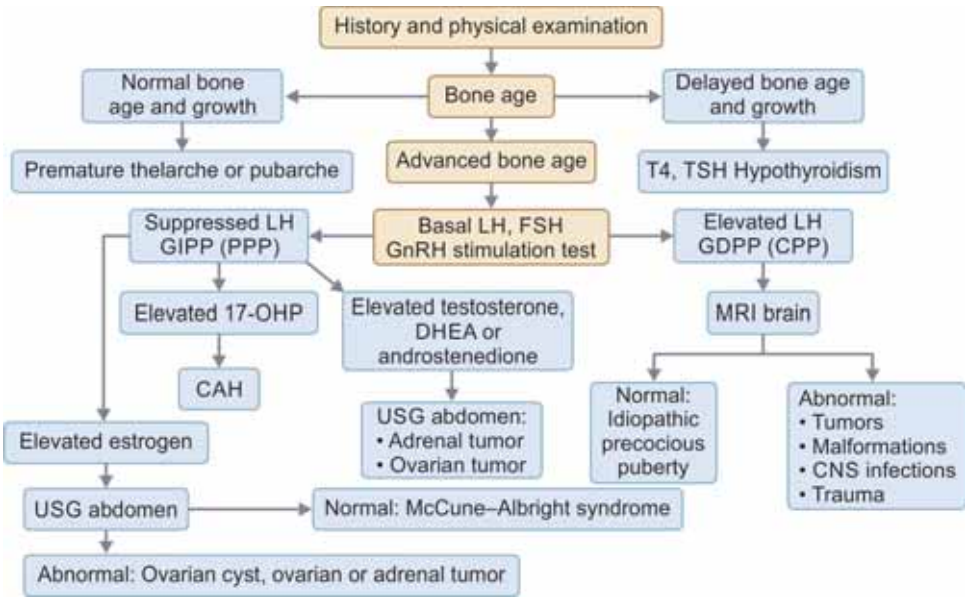
Gonadotropin-independent or Pseudoprecocious or Peripheral Precocious Puberty



Incomplete Precocious Puberty[2]

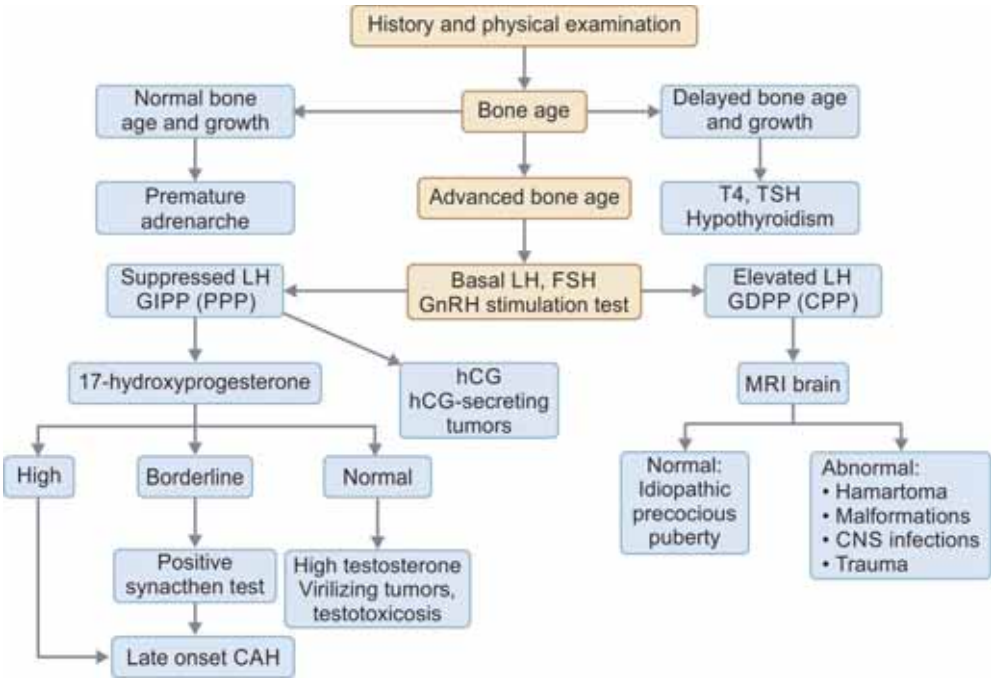


Evaluation of Precocious Puberty in Girls[17]



(CAH: congenital adrenal hyperplasia; CNS: central nervous system; CPP: central precocious puberty; DHEA: dehydroepiandrosterone; FSH: follicle-stimulating hormone; GDPP: gonadotropin-dependent precocious puberty; GIPP: gonadotropin-independent precocious puberty; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; PPP: peripheral precocious puberty; T4: thyroxine; TSH: thyroid-stimulating hormone; USG: ultrasonography; 17-OHP: 17-hydroxyprogesterone)

Evaluation of Precocious Puberty in Boys[17]



(CAH: congenital adrenal hyperplasia; CPP: central precocious puberty; DHEA: dehydroepiandrosterone; FSH: follicle-stimulating hormone; GDPP: gonadotropin-dependent precocious puberty; GIPP: gonadotropin-independent precocious puberty; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; LH: luteinizing hormone; MRI: magnetic resonance imaging; PPP: peripheral precocious puberty; T4: thyroxine; TSH: thyroid-stimulating hormone; 17-OHP: 17-hydroxyprogesterone)

- A complete history and physical examination, as well as bone age evaluation, to see whether there is a corresponding increase in linear growth.
- The medical history to determine when the physical change(s) were first observed in the patient's siblings and parents. Look for evidence of growth acceleration, rule out any previous history of neurologic disease or trauma, or exposure to sex steroids, and identify any associated symptoms of headache, seizures, or abdominal pain.[2]
- Height, weight, and growth velocity (cm/year) should also be measured during the physical examination, as this is typically an early indicator of developing premature puberty.[18]
- To identify papilledema, a symptom of elevated intracranial pressure, a fundoscopic examination should be conducted.[2]
- Look out for any café au lait spots, which raise the suspicion of McCune–Albright syndrome.[2]
- Tanner staging of pubic hair and/or breast development should be undertaken.
- The glandular breast tissue's diameter should be assessed and to exclude the adipose tissue from glandular tissue.

Imaging and Endocrine Evaluation

- Basal and GnRH-stimulated serum gonadotropin levels to distinguish gonadotropin-dependent from gonadotropin-independent precocious puberty.
- The GnRH stimulation test is carried out by taking blood samples before and 30–40 minutes after a single intravenous dose of GnRH (100 g).[2]
- The most effective diagnostic measure is the stimulated serum LH levels.
- A head MRI is recommended in children with gonadotropin-dependent precocious puberty (as shown by high baseline or stimulated serum LH levels) to rule out a cerebral mass lesion.[19,20]
- Thyroid function tests (TSH and free T4) should be conducted in case of suspicion of hypothyroidism.
- Serum concentrations of estradiol, testosterone, and hCG (functional ovarian cysts and tumors, functional adrenal tumors), late afternoon cortisol (Cushing syndrome), DHEA-S (premature adrenarche), and 17-OHP (CAH) should be evaluated in children with gonadotropin-independent precocious puberty (as identified by normal basal and stimulated serum LH levels), and 17-OHP (CAH).[2]
- Abdominal and pelvic ultrasonography is recommended in all precocious puberty females to diagnose functioning ovarian cysts or tumors.[2]

Treatment of Precocious Puberty[2]

The primary aims of therapy are to halt or restrict growth until normal pubertal age, optimize adult height, and lower the risk of psychological difficulties associated with early sexual maturation.

Indications for Medical Management

- When sexual maturity advances to next stage in a span of 3–6 months.
- Accelerated growth, >6 cm in a year.
- Bone age is advanced by a year or more.
- When estimated adult height falls below the specified range or decreases with repeated measurements.[20]

Treatment of Gonadotropin-dependent Precocious Puberty[2]

- The management of gonadotropin-dependent precocious puberty is planned by the underlying disease as well as the rate of sexual development.
- If an intracranial lesion has been diagnosed, therapy should be tailored to the lesion, if feasible.
- The decision to treat patients with no intracranial lesion should primarily be based on the pace of progression and the estimated adult height.

Growth spurt should be observed for minimum of 3–6 months before opting for treatment[21]

Long-acting GnRH agonists (depot preprations) are effacacious for the treatment[19]

- Buserelin 6.3 mg every 2 months
- Goserelin 3.6 mg every month or 9.8 mg every 3 months
- Histrelin 50 mg implant every year
- Leuprolide 3.75–7.5 mg monthly or 11.25 mg every 3 months
- Triptorelin 3.0–3.75 mg monthly or 11.25 mg every 3 months[22-24]

- The efficacy of GnRH agonist therapy may be easily determined by measuring serum LH concentrations every 30–60 minutes following repeated injections of the agonist. Following acute GnRH agonist stimulation, the LH level should be <3,0 IU/L, which is comparable with prepubertal norms.[25]
- GnRH agonist treatment should be monitored at 3–6 month intervals with serial physical examinations to identify any progressing pubertal development; bone age should also be checked routinely.[19]
- Breast development should cease, and growth pace and bone age progression should decelerate.[26]
- Treatment with GnRH agonists appears to have no deleterious long-term effects on hypothalamic-pituitary-gonadal axis function.[27]

Treatment of Gonadotropin-independent Precocious Puberty[2]

Based on underlying disease

Girls having functioning tumors of the ovaries or adrenals are surgically managed

Depending on the nature and location of the tumor, hCG-secreting tumors may additionally require adjuvant radiation or chemotherapy

Solitary unilateral functioning ovarian cysts can also be surgically removed

Treatment of McCune–Albright Syndrome in Girls

Intended to prevent aromatization and estrogen production

As an alternative, antiestrogens like tamoxifen have been used successfully to treat the vaginal bleeding that often accompanies excess estrogen[28]

Bone pain and fractures can be alleviated with bisphosphonate medication for patients with fibrous dysplasia[29]

Supplemental treatment with a GnRH agonist may be useful for those who, like individuals with idiopathic gonadotropin-dependent precocious puberty, develop a gonadotropin-dependent component to their precocious development as a result of persistent early exposure to sex steroids[29]

PREMATURE ADRENARCHE[2]

Increased adrenal androgens have been linked to the unexpected appearance of vaginal hair at a young age.

- A serum DHEA-S concentration >40 ug/dL is the strongest predictor of adrenarche.

Bone age and growth rate are often above normal, although they are not excessive.

- When describing the clinical extremity of premature adrenarche, the term "exaggerated adrenarche" is sometimes used.

Benign condition and requires no specific treatment.

PREMATURE PUBARCHE[2]

Generally the outcome of an early adrenarche.

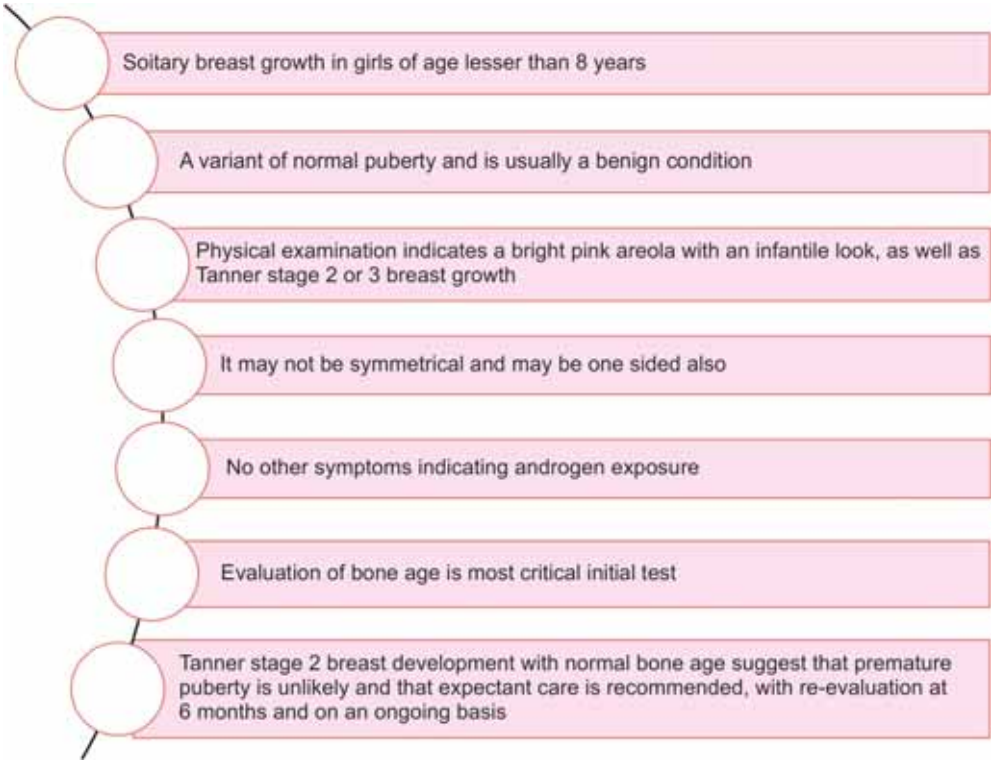
- Without an accompanying rise in adrenal androgen production, idiopathic premature pubarche is likely caused by an increased sensitivity of hair follicles to baseline androgen levels.

Premature puberty is unlikely if the sexual hair is sparse and slow-growing and the bone age is normal, thus expectant care with regular re-evaluation at 6 months is advised.

- Serum testing for testosterone and DHEA-S can be performed as part of a limited endocrine evaluation and compared to age-adjusted norms.

Benign condition and requires no specific treatment.

PREMATURE THELARCHE[2,30,31]

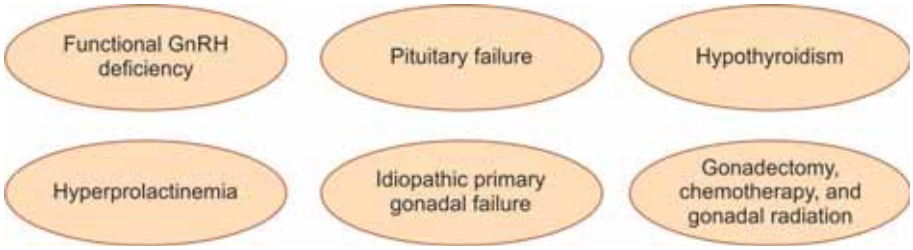


- Premature thelarche is followed by gonadotropin-dependent precocious puberty in around 15–20% of females, with a mean bone age of 9.0 ± 1.1 years and a mean age of 7.1 ± 0.7 years.

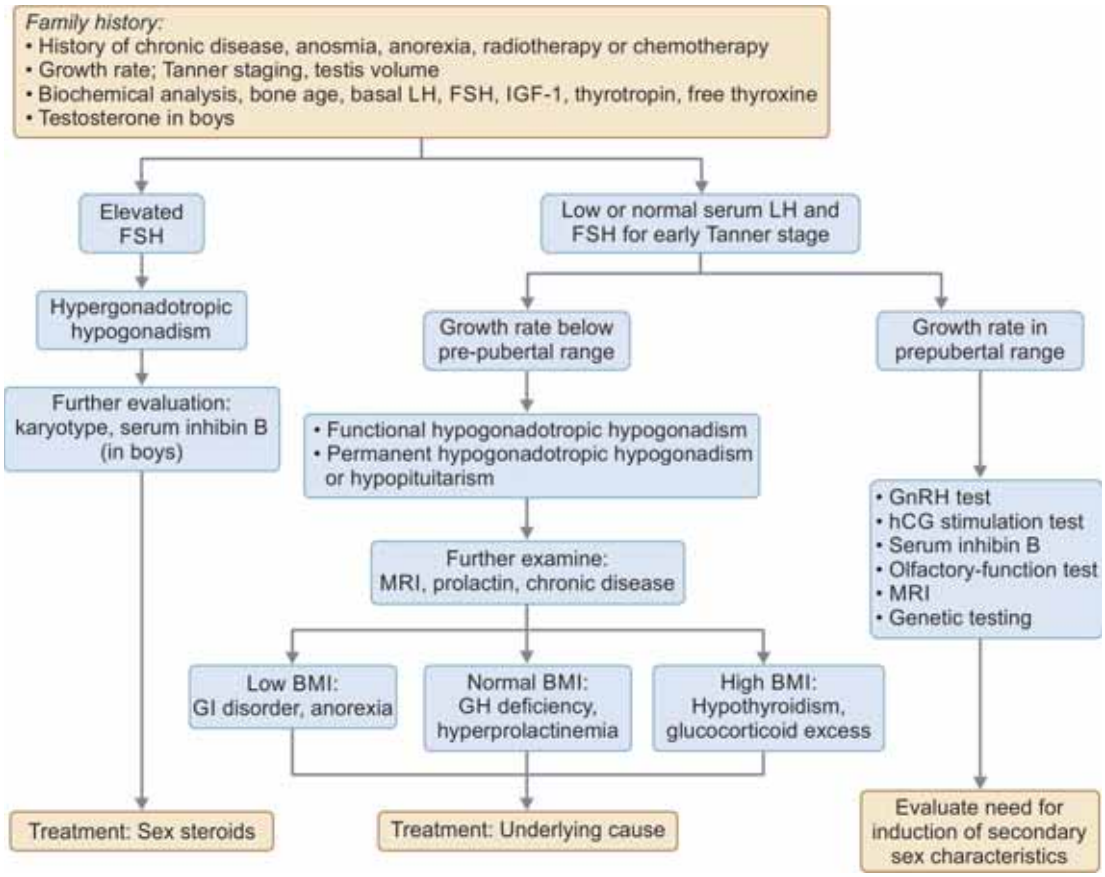
DELAYED PUBERTY

- When sexual development has not begun by the age at which 95% of children of the same sex begin pubertal development, we say that puberty has been delayed.[2]
- Delay in breast development by 13 years, a delay of over 4 years between thelarche and the completion of puberty, or the lack of menarche by 16 years are all indicative of delayed puberty in females. For males, this condition manifests itself when testicular development is delayed past the age of 14 years or when there is an interval of >5 years between the beginning of testicular development and the end of puberty.[32,33]
- Hypogonadism, the medical term for delayed puberty, can result from either an inactive hypothalamic-pituitary axis (hypogonadotropic hypogonadism) or an intrinsic failure of the testes (hypergonadotropic hypogonadism).[2]

Causes of Hypogonadotropic Hypogonadism[2]



Evaluation of Delayed Pubertal Development[2,3]



(BMI: body mass index; CDGP: constitutional delay of growth and puberty; FSH: follicle-stimulating hormone; GH: growth hormone; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; IGF-1: insulin-like growth factor-1; LH: luteinizing hormone; MRI: magnetic resonance imaging)

- The medical history should reveal if pubertal development has not yet begun or has begun and then stopped.
- This may be determined by a combination of a physical examination, a history of any relevant illnesses, and a measurement of the patient's bone age.
- In addition to dietary and activity patterns, significant diseases and medications that might delay or slow the onset of puberty are also important contextual variables.
- Delayed puberty may be an early indicator of a metabolic disorder such inflammatory bowel disease or hypothyroidism.
- Most people with constitutional delay have a similar history in other family members, so it is important to have a full family history, paying special attention to the ages at which older siblings and parents reached important developmental milestones.
- It is important to measure more than just height and weight during a physical examination; the Tanner staging of breast and pubic hair development should also be taken into account.

Imaging and Laboratory Evaluation[2]

- Measurements of blood FSH, LH, and estradiol concentrations are commonly used to make this distinction between primary (hypergonadotropic) and secondary (hypogonadotropic) hypogonadism.
- Once this difference has been identified, additional laboratory assessment can focus on identifying the underlying etiology of hypogonadotropic or hypergonadotropic hypogonadism.

Hypergonadotropic Hypogonadism[2]

- To rule out chromosomal abnormalities, a karyotype should be performed on all women with hypergonadotropic hypogonadism unless there is a good reason not to, such as a history of chemotherapy or gonadal radiation.
- Turner syndrome (45,X) is the template for the most prevalent condition of this sort, gonadal dysgenesis.
- Those with a Y chromosome (e.g., 46,XY, Swyer syndrome) who have a high risk of malignant transformation in occult testicular elements (20–30%) will be identified by

karyotype in addition to those with other structural X chromosomal abnormalities (e.g., deletions, rings, and isochromosomes).
- Individuals with hypergonadotropic hypogonadism with a normal (46,XX) karyotype may be tested for 17-hydroxylase deficiency, an uncommon steroidogenic enzyme defect associated with sexual infantilism and hypertension, and other odd causes of primary ovarian failure.

Hypogonadotropic Hypogonadism[2]

- In females with hypogonadotropic hypogonadism, serum prolactin levels should be measured to identify those with hyperprolactinemia.
- Hyperprolactinemia is a reason for MRI imaging, unless it is clearly ascribed to medicines.
- Other laboratory tests, such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), and liver function test (LFT) to identify patients who may have an undetected chronic disease.
- Although pelvic ultrasonography can be used to determine whether or not a uterus is present in a female who is a virgin, this procedure should be performed with caution.
- An MRI of the head to detect mass lesions.
- The presence or absence of olfactory bulbs and tracts can also be determined by imaging, as they are absent in Kallmann syndrome.

Treatment of Delayed Puberty[2]

- When possible, treating the underlying cause is the best course of action, such as in the cases of hypothyroidism (with thyroid hormone treatment), hyperprolactinemia (with dopamine agonist therapy), and the removal of a craniopharyngioma or other operable central lesion.
- Those with unexplained delays in puberty should be evaluated for congenital GnRH insufficiency apart from those with constitutional puberty delay.
- Both hormone replacement therapy and expectant care, including reassurance and psychological support, are options for patients with congenital GnRH deficiency or constitutional puberty delay.
- Management with sex hormones to be reserved for females above the age of 12 years who show no or few indicators of sexual maturity that cause substantial anguish or worry.
- Long-term goals for individuals with isolated GnRH insufficiency include maintaining sex hormone levels within the normal physiologic range and, if and when fertility is a concern, stimulating ovulation with exogenous gonadotropin therapy.
- Complete sexual maturation is targeted to occur within 2–3 years after starting oral or transdermal estrogen medication (0.25–0.5 mg oral micronized estradiol or its equivalent) and increasing gradually dependent on response (Tanner stage and bone age).
- Addition of a progestin to the treatment plan is not recommended since it may have an unfavorable impact on breast growth and/or appearance.
- After menstruation has begun or after 12–24 months of estrogen therapy, progestin medication can be started safely.
- Hormone medication can be discontinued for periods of 1–3 months once breast development is complete and menstruation has begun to assess the likelihood of spontaneous menstruation, which is typical in females with constitutional puberty delay.
- Persistent hypogonadism after the age of 18 strongly indicates congenital GnRH insufficiency.
- Only patients with a confirmed GH deficiency should get GH medication. It is common for patients with constitutional delayed puberty to have low serum GH and IGF-I levels; however, these levels often increase with estrogen treatment and are typically normal in those with congenital GnRH impairment.

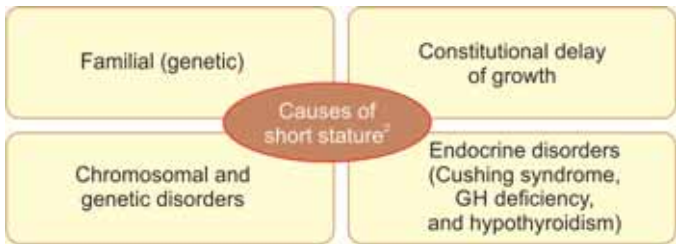
GROWTH DISORDERS IN ADOLESCENT AGE

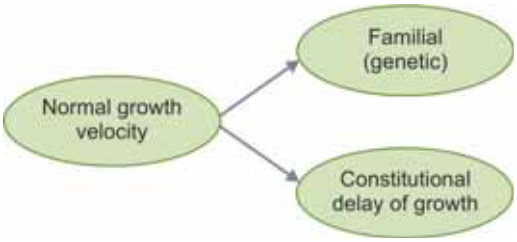
One of the worst aspects of teenage development issues is the way it may make a young person feel "strange". The adolescent probably hates being different more than anybody else. Height gain occurs constantly, although in an atypically nonlinear fashion.[2] There are three distinct phases of maturation.

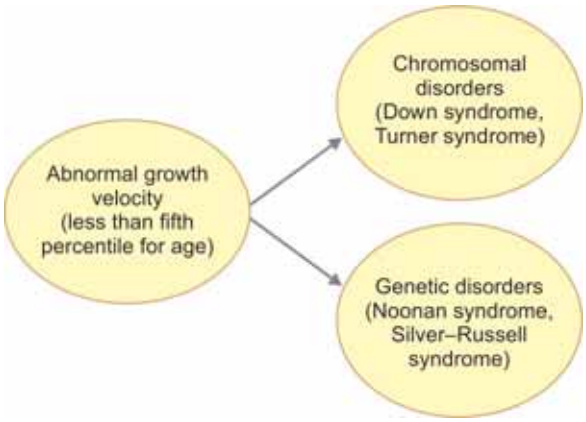
1. The first is the newborn stage, when a child's height increases by 30–35 cm in just 2 years.
2. The second stage, childhood, sees growth remain relatively constant around 5–7 cm/year; however, it usually slows in late childhood.
3. The third and final phase, puberty, is characterized by a growth spurt of 8–14 cm each year due to elevated levels of both GH and sex steroid hormones.[23,34]

Short Stature

A kid is considered to be of short stature if they are two or more standard deviations below the mean height for children of the same gender and chronological age on a standard growth chart. The direction of progress is more important than any specific value. The most important finding is the mitigation of irregular increases in size (percentile). Children should average at least 5 cm of growth every year from the age of 4 years until the onset of puberty.[2]



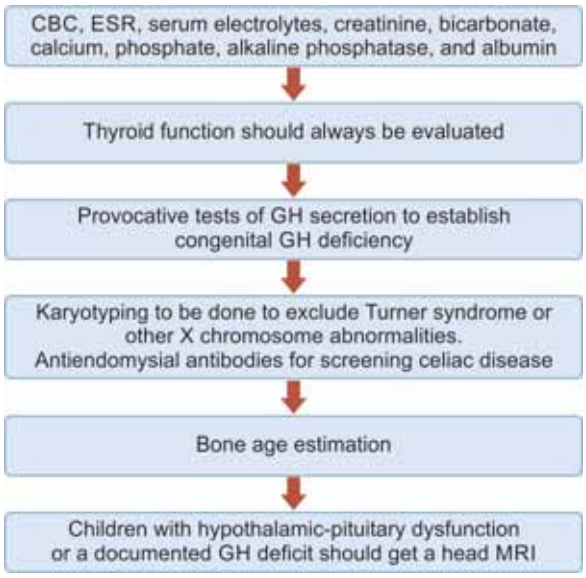




Children with short stature due to endocrine problems are typically overweight for their height.

Idiopathic short stature is defined as when a kid is underweight for his or her age and has a height that is more than two standard deviations below the mean for that age. The growth rates of these kids are often below average, yet their blood levels of IGF-I are normal. People with constitutional growth delay have a delayed bone age than those with hereditary or familial short stature but nonetheless have a predicted adult height within the normal range.[2]

Evaluation[2]



- Serum TSH and free T4 levels should be checked since both primary and secondary hypothyroidism can cause growth failure.
- Hypercortisolism (Cushing syndrome) in children is unusual unless brought on by an overdose of glucocorticoids.
- Severe growth failure, a delayed bone age, and extremely low blood concentrations of IGF-I and its primary binding protein, IGFBP-3, are classic symptoms of congenital GH insufficiency in young children.

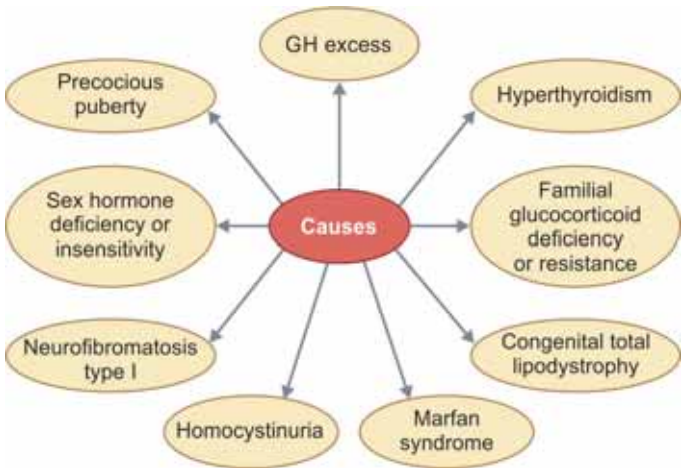
Treatment

- If a female patient's height is >2.25 standard deviations below the mean for her age, her epiphyses are not closed, and her projected adult height is <59 inches, then GH medication is indicated for the treatment of idiopathic short stature.[2]
- Most kids with idiopathic short stature, especially those who have a constitutional growth delay, make up for lost time throughout the teen years even without treatment.[35]
- The best time to begin therapy is between the ages of 5 and early adolescence.[36]
- Although GH treatment appears promising, it should be reserved for children whose short stature is a significant disability and whose confidence and social skills are expected to considerably benefit from a significant increase in height.[37]
- A long-acting GnRH agonist may be used as an alternate therapy to postpone pubertal growth and epiphyseal fusion.[2]

Tall Stature[2]

Tall stature is defined as two or more standard deviations above the mean height for children of the same gender and chronological age.

Height over average that is tall stature is more socially acceptable and less often recognized as a problem than height below average (short stature).



- Family history and the lack of dysmorphic characteristics separate familial or constitutional long height from problems of excessive development.

- A comprehensive physical examination along with family history and bone age are usually enough to establish the diagnosis and give reassurance in most tall but otherwise normal youngsters.

Treatment

- Treatment should be restricted to people whose tall height is causing serious psychological concerns.
- For decades, sex steroids are being prescribed to kids who are particularly tall in the hopes that their bones will fuse sooner.[38,39]
- The puberty growth surge happens before menarche, thus therapy needs to start before menarche to be effective, making the stage of secondary sexual development crucial.[40]
- The average age for starting therapy is between 10 and 12 years.
- Even if treatment is initiated after menarche, it is possible to achieve a reduction of 1 inch in height.[41,42]
- A low-dosage oral contraceptive tablet with 15–30 g of ethinylestradiol is a common starting dose.[43]
- Taking serial measurements of bone age every 6–12 months throughout therapy can demonstrate that treatment has been successful in closing the epiphyses.[43]
- A recent study including adult women with inherited tall height indicated that those treated with estrogen as teenagers had a considerably greater risk of future infertility and cycle fecundity was lowered by around 40% compared to those who were not treated.[44]

Key Learning Points

- Central precocious puberty typically starts before 8 years of age.
- It is important to differentiate between the central precocious puberty and peripheral precocious puberty.
- The gold standard for management of central precocious puberty is GnRH analogs.
- Management of peripheral precocious puberty is directed at its etiology.
- Delayed puberty is characterized by the absence of breast development by 13 years in females and by a lack of testicular enlargement by 14 years.
- When feasible, treating the underlying cause of delayed puberty should be the primary focus of treatment.

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