Reviewed By
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Puberty Disorders

Objectives:

- → Describe the endocrinological, Hypothalamus, Pituitary, gonadal axis and target organ in normal Puberty.
- → Describe the different stages of somatic and psychological changes of puberty.
- → Define puberty abnormalities (Precocious and delayed puberty).
- → List types of female precocious puberty.
- → Mention the investigations used to evaluate precocious and delayed puberty.
- → List treatment options of precocious and delayed puberty.
- → Outline the steps in the management of different abnormal puberty.

- → Slides
- → Important
- → Golden notes
- → Extra
- → Doctor's notes
- → Previous Doctor's notes
- → Reference

Editing File

Puberty

What is Puberty?

- → **Puberty:** the transitional period of development during which an individual mature from childhood to sexual & reproductive maturity.
- → **Puberty:** development of the reproductive system & endocrine part HPO Axis).
- → **Puberty:** maturation of the person from childhood to adulthood.
  1. **Maturation of primary sexual characteristic** (internal changes) → hypothalamic pituitary ovarian axis
  2. **Development of secondary sexual characteristic** (external changes):
     - → Sexual hair (pubarche = adrenarche).
     - → Breasts (thelarche).
     - → Genitalia.
  3. **Dramatic growth spurt**
  4. Menarche
  5. **Psychology changes** → mental & emotional maturity.
- → **Onset of pubertal changes is determined primarily by:**
  - → Genetic factors & race.
  - → **Geographic location:**
    - → Metropolitan areas → begin puberty at an earlier age.
    - → Altitudes near sea level → begin puberty at an earlier age.
    - → At latitudes close to the equator → begin puberty at an earlier age.
  - → **Nutritional status:**
    - → Obese children → earlier onset of puberty.
    - → Malnourished → later onset of menses
    - → Chronic illnesses associated with weight loss → later onset of menses.
    - → Excessive exercise relative to the caloric intake → delay onset of puberty.

Age of Onset of Puberty:

Females

8 - 13 years

Males

9 - 14 years

Usual Sequence of Somatic Changes of Puberty:

1. **Onset of growth spurt:** 9.6 Y, before breast development, gradual growth → not visible.
2. **Breast development (thelarche):** 10.6 Y.
3. **Pubic & axillary hair (adrenarche / pubarche):** 11.2 Y.
4. **Maximal[1] growth velocity:** 12 Y.
5. **Menarche:** 12.7 Y.
   - → Improved nutrition + general health + lifestyle → ↓ menarche average age over the last 3 - 4 decades (secular trend).

- → Do not reach full reproductive maturity, the first few cycles are usually anovulatory (menstruation without ovulation), then the number of ovulatory cycles increases.
- → **Estrogen breakthrough bleeding:** at menarche, positive estradiol feedback on the axis is not yet established → ovulation rarely occurs → progesterone is not produced (normally balances estrogen effects) + estrogen-induced endometrial accumulation continues indefinitely → unopposed estrogen → endometrium no longer maintain itself → irregular shedding of thickened endometrium.

1. Be careful between the words MAXIMAL and ONSET.

Endocrinologic Changes of Puberty

Fetal Period:

- → Fetal hypothalamic–pituitary–gonadal axis is capable of producing adult levels of gonadotropins and sex steroids.
- → **20 weeks' gestation:** dramatically ↑ gonadotropins (FSH & LH) in both male and female fetuses.
- → **Early gestation:** fetal adrenal gland produces abundant DHEA-S → precursor for estrogen placental production + convert placental progesterone to cortisol.
- → **Mid-gestation:** ↑ gonadotropin female fetus has lifetime peak number of oocytes (in utero) + brief period of follicular maturation + sex steroid production.
- → **Late in gestation:** surge in glucocorticoids levels in fetal circulation → normal maturation of fetal lungs + fetal thyroid, kidney, brain, and pituitary development.
- → **Before birth:** inhibitory effect of sex steroids on gonadotropin release.
  - → Transient ↑ estradiol (sex steroid) acts on fetal hypothalamic-pituitary unit → ↓ gonadotropin secretion (negative feedback) → ↓ estradiol production.
- → Developing fetus kidney > adult.
- → **First few months of postnatal life:** innermost part of adrenal cortex (fetal zone) largely regresses + rapid ↓ in DHEA-S production.

Newborn Period:

- → **Source of serum estradiol in male and female fetuses:** maternal and placental origin.
- → Birth → acute loss of maternal and placental sex steroids → lost negative feedback action on hypothalamic-pituitary axis → released gonadotropins from the pituitary gland reaching adult or near-adult concentrations in the early neonatal period.
- → **Female infant:**
  - → **Peak gonadotropins serum levels:** 3 months of age.
    - → Slowly decline until they reach the age of 4 years.

Childhood Period:

- → **4 - 10 years old:** hypothalamic–pituitary–gonadal axis is suppressed.
- → **GnRH secretion by the arcuate nucleus is modulated by two inhibitory mechanisms:**
  - → **Intrinsic CNS inhibitory mechanism:** principal inhibitor of gonadotropin secretion from 4 years of age until the peripubertal period.
  - → Negative feedback of circulating sex steroid.
- → **Early childhood:** fetal zone of adrenal gland regression (a few months after birth) → ↓ adrenal androgen precursors → ↓ adrenal androgen production.
- → **8 - 11 years old:** ↑ serum DHEA, DHEA-S, and androstenedione.
  - → ↑ adrenal androgens → growth of axillary and pubic hair (adrenarche / pubarche).
  - → ↑ adrenal androgen production occurs independently of gonadotropin secretion or gonadal steroid levels (initiation mechanism is not understood).

Etiology of Puberty

Hypothalamus:

- GnRH secretion by the arcuate nucleus is modulated by two inhibitory mechanisms:
  - **Intrinsic CNS inhibitory mechanism:** principal inhibitor of gonadotropin secretion from 4 years of age until the peripubertal period.
  - Negative feedback of circulating sex steroid.

Development of HPO Axis:

- **Fifth month gestation:** ovaries become responsive to gonadotropin follicular growth to early antral stage (1 - 2 mm then atresia) → estrogen production → negative feedback.
- Functional HPO axis exists in utero.
- **Primary source of estrogen production in utero:** fetoplacental unit.
  - ↑ estrogens → ↓ FSH & LH levels.

Maturation of HPO Axis:

- **After birth/early infancy:** estrogen ↓ dramatically → ↑ FSH & LH → ↑ ovarian estrogen production.
- **Main mechanism controlling FSH & LH secretion in infants:** sex steroids level.
- **Peak FSH & LH:** 1 - 2 years.
- Intrinsic CNS inhibitory mechanism gradually develops with continued growth & CNS maturation → minimum FSH & LH level for 6 - 8 years .
  - **Principal CNS inhibitor of GnRH:** GABA.

Sequence of Maturation:

01 **Onset of puberty:** GnRH pulses occur during sleep → LH pulses.

02 ↑ frequency of LH pulses with further maturation.

03 LH pulses appear during day time & ↑ in amplitude.

04 Menarche approaches → pulses detected all time (*no diurnal variation*).

05 Similar changes occur in FSH pulses.

06 ↑ LH/FSH ratio.

Normal Pubertal Development

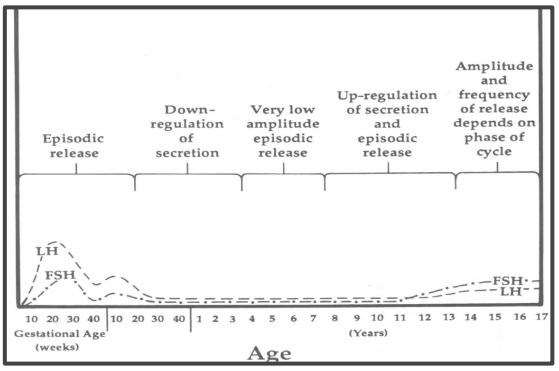
Normal Pubertal Development:

What is the interval between the onset of breast development & menarche?

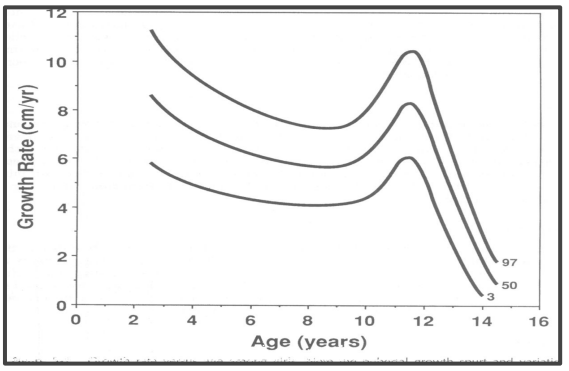
2.3 ± 1 years

Average → 4.2 years
Range → 1.5 - 6 years

What is the time from the onset to the completion of puberty?



Levels of LH & FSH During Fetal Life, Infancy Childhood & Puberty



Growth Rate versus Age in Girls

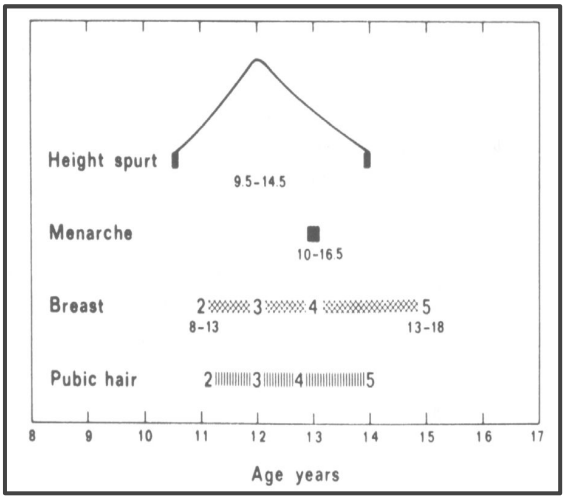
In utero:

- → **10th week:** ↑ FSH and LH.
- → **20th week:** peak FSH and LH.
- → **After 20th week:** gradually ↓ FSH and LH (*suppressed by maternal estrogen*).
- → Maternal estrogen passes through the placenta to the fetus → estrogen acts on the fetal hypothalamus to suppress GnRH release.

After delivery:

- → Maternal estrogen will disappear → ↑ FSH and LH → suppressed FSH and LH through CNS inhibitory mechanism until the age of puberty.

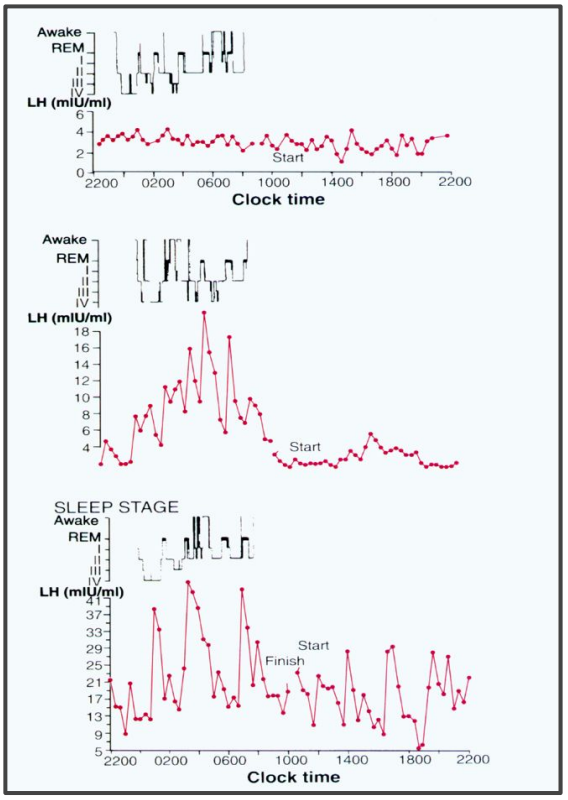
→ Do girls stop growing after menarche?
  → No, growth continues at a decelerating rate for a number of years.



Ages of Girls at Various Stages of Pubertal Development

Normal Pubertal Development

Normal Pubertal Development:



Plasma LH Concentration Measured Every 20 Minutes for 24 Hours

- → **Prepubertal:** LH pulses are low and similar during sleep and wake.
- → **Early pubertal:** LH pulses start to increase during sleep.
- → **Late pubertal:** LH pulses will increase during day and night.

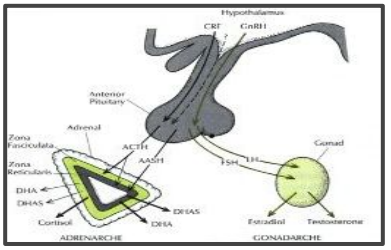
Physical Events of Puberty:

01	02	03	04
Genital organs maturation: uterus - ovaries - vagina external genitalia	**Breast development**	**Pubic hair development**	**Growth spurt:** *mainly dependent on estrogen & growth hormone.*

- → Estrogen has direct anabolic effect → ↑ growth hormone & insulin like growth factors.
- → The onset of growth spurt antedates (**come before**) thelarche & pubarche.
- → ↑ height → onset of growth spurt → cessation of growth = 25 cm.
- → Girls who start the growth spurt early have shorter adult height.
- → **Peak height velocity:** 8.1 cm/yearly.
  - → **Pre-puberty peak height velocity:** 3 -6 cm yearly.

Normal Pubertal Development

Adrenarche:



Adrenarche & Gonadarche Controlled by Different Mechanisms

→ Maturational ↑ in adrenal androgen secretion (*independent of reproductive organ process, occurs at puberty*).
→ **DHEA , DHEAS, androgens (AND) lead to:**
  → Development of pubic & axillary hair.
  → Adult type body odor.
  → Acne.
  → Oily skin & hair.
→ Adrenal androgens ↑ bone age & linear growth, so it has a role in growth spurt.
→ Premature adrenarche ↓ adult height due to early closure of epiphysis.

Gonadarche:

→ reactivation of HPO axis → onset of pubertal gonadal activity → ↑ gonadotropin pulses → sustained follicular development → ↑↑ estrogen production → proliferation of the endometrium → endometrium outgrows the estrogen capacity to maintain it, or the follicle undergo atresia → ↓ estrogen → menarche (does not mean the attainment of reproductive maturity).
→ Anovulatory cycles occur during the first 6 -18 months to 4 years.
  → At the beginning, 90% of the cycles will be anovulatory causing them to be irregular → endometrium is not exposed to progesterone.
→ Ovulatory menstrual cycles requires further maturation of the HPO axis → development of the +ve feedback mechanism.
  → With further maturation of HPO axis 90% of the cycles will be ovulatory and regular.

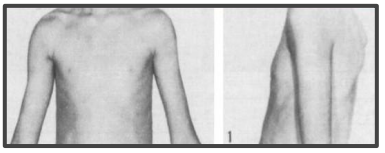
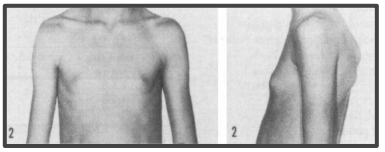
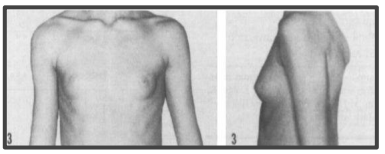
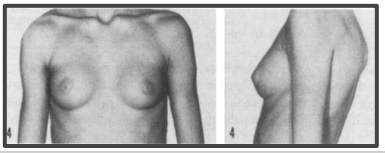
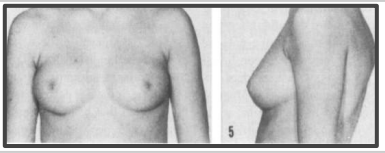
Thelarche (Breast Development):

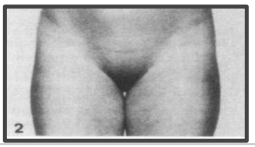
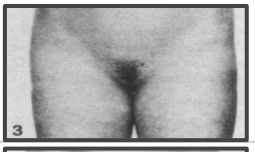
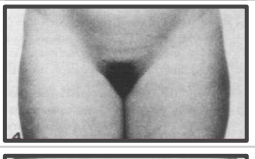
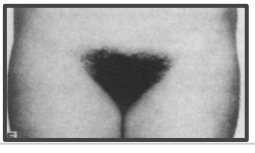
→ The first visible change of puberty
→ Thelarche is induced by estrogen
→ Starts at 10.6 completed in ~ 3 years
→ Effects of estrogen on the breast:
  1. Ductal proliferation
  2. Site specific adipose deposition
  3. Enlargement of the areola & nipple
→ Breast development may be unilateral for several months
→ Other hormones that play a role in breast development: prolactin, glucocorticoids & insulin.
→ In normal girls the stage of breast development is consonant with the stage of pubic hair development.

Normal Pubertal Development

Tanner Staging:

→ Usually both breast and pubic hair staging go together.

Tanner Staging of Breast Development Mnemonic: ABCDE - Extra Pictures		
Stage 1	**Prepubertal** → Elevation of papilla only (Absent development of the breast).	
Stage 2	**Breast bud** → Elevation of breast & papilla as a small mound with enlargement of the areolar region.	
Stage 3	**Enlargement of breast & areola** → Further enlargement of breast and areola without separation of their contours.	
Stage 4	**Areola (more prominent) & nipple form a double mound atop breast tissue**	
Stage 5	**Adult configuration areola & beast having smooth contour, with projecting central papilla (End stage)**	

Tanner Staging of Pubic Hair Development Mnemonic: A Small CAT - Extra Pictures		
Stage 1	**No pubic hair (Absent) prepubertal**	
Stage 2	**Sparse downy hair on the medial aspect of the labia majora**	
Stage 3	**Darkening, coarsening & curling of hair which extends upwards and laterally**	
Stage 4	**Hair of adult consistency limited to the mons (Adult type)**	
Stage 5	**Hair spreads to medial aspect of thighs**	

Precocious Puberty

Abnormalities in the Process of Sexual Maturation:

1. Precocious Puberty	→ Fusion of the growth plates signifies the maturation of the HPO axis and termination of growth. → **Types of precocious puberty:** **A. Complete Isosexual** → Involves **all** changes of puberty. → **Primary concern:** premature closure of distal epiphysis of long bones → short stature. → Fertility and sexual response are **not** impaired. → **Includes/Types:** i. **Central** / true / / GnRH dependent precocious puberty. ii. **Peripheral** / GnRH independent precocious puberty. **B. Incomplete Precocious Puberty (Incomplete Isosexual)** → Partial (often transient) pubertal development in the absence of other stigmata of puberty. → Involves only **one** change. → Slow progression. → No change or waning of physical finding may occur. → **Causes:** transient hormone ↑ or unusual end-organ sensitivity. → **Includes/Types:** i. Premature **thelarche**. ii. Premature **adrenarche**. iii. Premature **menarche**.
2. Delayed Puberty	→ Absence of secondary sex characteristics by age 13 or the absence of menses by 15 (*more information can be found in the last page*).
3. Isolated Puberty (Dyssynchronous)	→ Physical changes are not followed by menarche after an appropriate interval. → **Example:** reaches 16 years old with no menarche, sometimes it is due to simple problem like imperforate hymen.
4. Heterosexal Changes	→ **Example:** A female who develops virilization like hirsutism and enlargement of clitoris due to excess androgen amounts → investigate the reason.
5. Timing of Progression of Pubertal Changes	→ Starts at normal age (8 years old) but within 6 months menarche starts.

What is Precocious Puberty?

→ **Early onset of puberty before:**

 **8 years of age in girls**

 9 years of age in boys

→ Precocious puberty is more common in girls than boys.

→ **Difficult to ascertain the early age limit because[1]:**

→ 15% of black girls, 5% of white girls have breast development at 7 years of age without associated early menarche.

→ 17.7% of black girls, 2.8 % of white girls have pubic hair development at 7 years of age.

→ Mostly secondary to **idiopathic premature maturation** of HPO axis with GnRH release.

→ **Diagnostic criteria:**

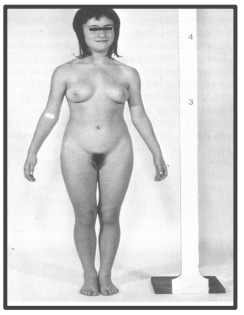
→ Accelerated growth before age 8 in girls and age 9 in boys.

→ Development of female secondary sexual characteristics.

1. It's normal to some extent but if the other signs develop fast then we have to investigate e.g. if a 7 year old comes with breast buds we just have to keep an eye on her and observe if the other signs develop fast then we can call it PP..

1. A. i. Central Precocious Puberty (CPP)

Introduction:



7 years old child with CPP

→ **CPP:** physiologically **normal pubertal development** that occur at an early age.
→ **GnRH dependent:**

↑ GnRH pulses → ↑ gonadotropins (FSH - LH) → ↑↑ ovarian estrogen production & eventual ovulation.

→ Follows the pattern of pubertal changes that occur in normal puberty.
→ More common in girls than boys.

Causes:

Idiopathic
→ 80 - 90% → Diagnosis of exclusion after CNS imaging (usually). → **Common age group:** 6 - 7 years old. → **Management**: GnRH agonist suppression (leuprolide or Lupron) of gonadotropins until appropriate maturity or height has been reached.
CNS Tumors
→ **Hypothalamic hamartomas (***we should rule it out by brain MRI***):** → Congenital malformation. → **Most common** type of CNS tumor that cause CPP. → Size & shape do not change significantly over time. → Intrahypothalamic type → may be associated with seizures. → **Rapidly progressing** CPP in a child **< 2 years** of age suggest this diagnosis. → **Treatment:** GnRH is satisfactory & safe. → **Other examples of CNS tumors:** → Optic gliomas. → Craniopharyngioma. → Dysgerminoma. → Ependymoma. → Ganglioneuroma. → You do not have to memorize the names.
CNS Dysfunction
→ Any CNS pathologic process stimulates hypothalamic release of GnRH, which leads to FSH release and ovarian follicle stimulation of estrogen production. → **Common age group:** < 6 years of age. → **Examples:** → Space occupying lesion (e.g. Arachnoid cyst). → Hydrocephalus. → Irradiation. → Trauma. → Infection. → Septo-Optic dysplasia (congenital). → Excessive exposure to sex steroids (congenital adrenal hyperplasia).

1. A. i. Central Precocious Puberty (CPP)

Treatment:

Purpose of Treatment:

→ Gain normal adult height, as a CPP patient will have an ultimately shortened adult height due to the premature fusion of the long bone epiphyses.

→ Amelioration of the psychosocial consequences of ↑ size → unrealistic adult expectations.

Who Should be Treated:

→ Patients with early puberty (< 6 years old), accelerated growth & advanced skeletal age (bone age > 2 years of the chronologic age, menarche < 8 years old).

→ Patients with early onset but without indication that puberty is advancing should be followed up.

Medications:

GnRH analogues	→ **Treatment of choice** for central precocious puberty. → stop the whole process → best treatment available. → GnRH agonists[1] (zoladex) bind to GnRH receptors (*competitive inhibition*) → down regulation of receptor function → ↓ gonadotropin secretion → ⃠HPO axis → ↓ estrogen secretion → puberty manifestation regression. → **Goal of therapy:** complete suppression of gonadotropin secretion → prepubertal GnRH stimulation test result. → **Adult height:** treated patient > untreated patient → Related to skeletal age at the onset of treatment (the sooner the better). → **Adult height:** treated patient < target / predicted height for normal. → Treatment is continued until the progress of puberty is age appropriate. → Best statural outcome when the patient is treated until bone age 12 - 12.5 years. → Growth hormone may be added to the treatment. → After discontinuation of treatment, resumption of puberty occurs & precedes at a normal pace. → **Side effects:** local injection reaction - sterile abscess.
Medroxyprogesterone acetate	→ Used in the past. → Suppress the progression of puberty & menses. → **No** effect on skeletal maturation & adult height .

1. it will be in steady level which suppress LH+FSH and estrogen, normal GnRH release in plusital pattern.

1. A. ii. Peripheral Precocious Puberty (PPP)

Introduction:

- → **GnRH independent.**
- → **Due to:**
  - → Inappropriate sex hormone secretion.
  - → Exposure to exogenous sex steroids.
  - → Peripheral estrogen not to hypothalamic development.
- → **Prepubertal levels:** ↓ LH & FSH + ↑↑ estrogen.
- → May present with some or all of the physical changes of puberty.

Causes:

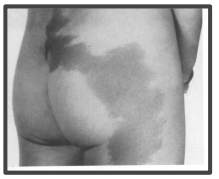
A. Exogenous Sex Steroids or Gonadotropins
B. Abnormal Secretion of Gonadotropins
→ Rare. → **Example:** tumors secreting hCG (teratoma). → hCG is similar to FSH, stimulates follicle development and estrogen release.
C. Functioning Ovarian Tumors
Check Next Slide
D. Functional Ovarian Cysts
→ Secrete estrogen → breast development. → Rupture or resolution → ↓ estrogen → vaginal bleed. → Surgery should be avoided due to complications like adhesions. → Usually resolves spontaneously. → If large (> 5 cm) → remove it, if left it will rotate around blood vessels → prevent blood supply + pain.
E. Adrenal Tumors
→ Rare. → **Lead to:** pubic hair - acne - hirsutism - ↑ height.
F. Congenital Adrenal Hyperplasia
→ Usually presents in babies soon after birth however, there's a late onset of CAH → which presents as heterosexual changes with puberty like hirsutism and voice thickening (deepening) due to increased secretion of adrenal androgens. → **Baby was born with ambiguous genitalia and karyotyping showed 46XX**
G. Chronic Primary Hypothyroidism
→ Primary hypothyroidism → ↑ TSH →TSH acts on FSH receptors → PPP. → **Treatment:** thyroxine → resolution of PPP.

1. A. ii. Peripheral Precocious Puberty (PPP)

Introduction:

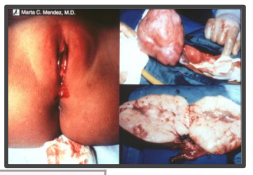
Causes:

H .McCune-Albright Syndrome (Polyostotic Fibrous Dysplasia)
→ Congenital condition. → Café-au-lait skin spots. → Multiple cystic bone lesions. → GnRH independent PP. → **Endocrine disorders:** hyperthyroidism - hyperparathyroidism - Cushing Syndrome. → Autonomous functioning ovaries with 1 or 2 ovarian cysts → ↑ estradiol. → ovaries secrete estrogen by themselves without needing any estrogen. → **Treatment:** testolactone (🚫 aromatase activity → ↓ estrogen synthesis).

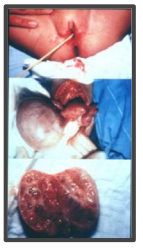


Functioning Ovarian Tumors:

→ Uncommon.
→ Malignant ovarian tumors are responsible for 2 - 3% of all precocious pseudopuberty cases in girls.
→ **Most common:** granulosa cell tumors[1].
→ **Present with:** rapid progression of breast development - vaginal bleeding - abdominal pain.
→ Palpable mass & dulling of vaginal mucosa.
→ Excessively ↑↑ estradiol level.
→ **Confirming the diagnosis:** US - CT - MRI.
→ **Treatment:** excision → regression of secondary sexual characteristic.



Granulosa cell & Granulosa-Theca Cell Tumors	Mixed Germ Cell	Cystadenoma - Gonadoblastoma - Lipoid
→ 70% present with PP. → **Present with:** vaginal bleeding - breast development.	→ Usually benign.	→ May produce estrogen or androgen or both. → Rare.
Ovarian Tumor (Sertoli-Leydig) Triad	**Adrenal Tumor Triad**	**Congenital Adrenal Hyperplasia 21-OH Deficiency (CAH) Triad**
→ Abrupt-onset virilization. → Pelvic mass. → ↑↑ testosterone levels.	→ Abrupt-onset virilization. → Abdominal/flank mass. → ↑↑ DHEAS levels.	→ Gradual-onset hirsutism. → Normal exam. → ↑ 17-OH progesterone.



1. Gonadal-stromal cell ovarian tumor that autonomously produces estrogen. Management: Surgical removal.

1. A. ii. Peripheral Precocious Puberty (PPP)

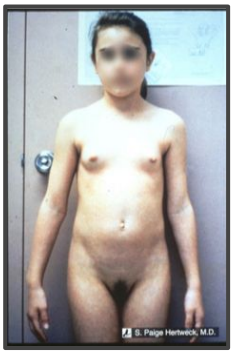
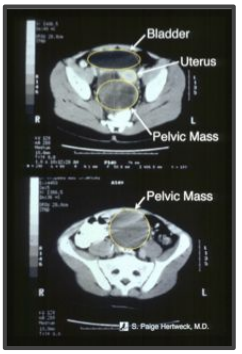
Treatment:

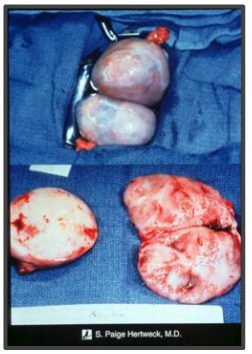
→ Treat the cause if possible.
→ Girls with prolonged PPP → prolonged CNS exposure to estrogen → central precocious puberty.
→ Use medications if we can't reverse the cause (congenital conditions).

Testolactone	→ **Aromatase inhibitor:** 🚫 conversion of testosterone to estrogen. → **Dose:** 35 mg/kg/D → 3 divided doses.
Ketoconazole	→ 🚫 steroid biosynthesis. → **Dose:** 200mg tds.
Cyproterone acetate	→ **Potent progestin, antiandrogen & antigonadotropic:** 🚫 androgens at receptor level + suppress gonadal & adrenal steroidogenesis. → **Dose:** 100 mg/m^2 → 2 divided doses.
Spironolactone	→ **MOA:** → 🚫 androgens at the receptor level. → ↓ ovarian androgen production. → antimineralocorticoid → **Dose:** 50 - 100 mg bd. → Widely used for hirsutism.
Medroxyprogesterone acetate	→ Injections given every 3 months to suppress the physical signs of puberty.

Case Reports

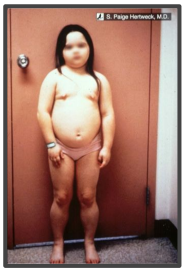
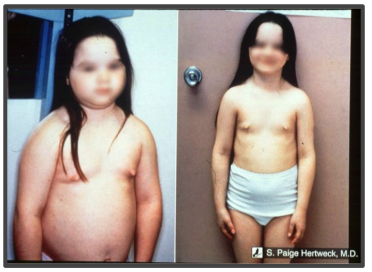
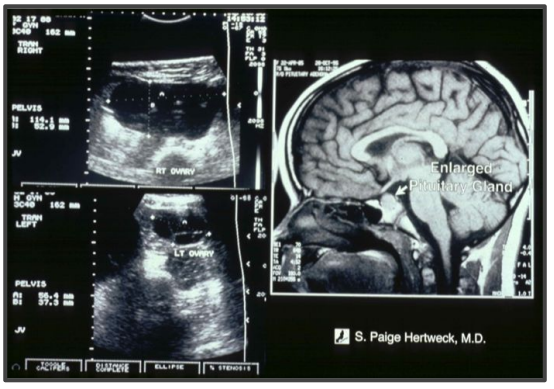
Case 1



→ **8** years old, **3 month** history of **vaginal bleeding**, **breast &pubic hair Tanner III**, height 70th % weight 95th %, **pelvic mass**.
→ **Labs:** FSH 4.1 - LH 3.2 - TSH 2.3 - Prolactin 21 - LDH 192 - hCG 103 - AFP 5.
→ **Procedures:** laparotomy BSO - appendectomy - omentectomy.
→ **Diagnosis:** ***Bilateral Dysgerminoma*** arising in a **Gonadoblastoma**, karyotype XY
→ **Treatment (Rx):** 8 courses of chemotherapy, no recurrence at 20 months.

Case 2

→ **Height:** 20th %.
→ **Wight:** 95th %.
→ **Thyroid:** slightly prominent.
→ **Breasts:** Tanner III.
→ **Pubic hair:** Tanner II.
→ **Hymen:** well estrogenized.
→ **P/R:** pelvic mass 5 cm.
→ **FSH:** 5.4 IU/L.
→ **LH:** 0.3.
→ **Estradiol:** 94 pg/ml.
→ **TSH:** 50 mIU/ml.

1. B. Incomplete Precocious Puberty (Precocity)

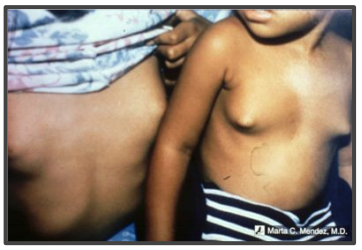
Introduction:

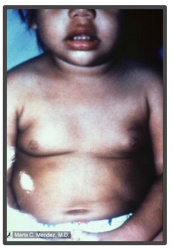
→ Partial (often transient) pubertal development in the absence of other stigmata of puberty.
→ Involves only **one** change.
→ Slow progression.
→ No change or waning of physical finding may occur.
→ **Causes:** transient hormone ↑ or unusual end-organ sensitivity.

Types:

1. Premature Thelarche

→ **Premature thelarche:** premature breast development in the absence of other signs of sexual maturation.





→ ↑↑ estradiol level.
→ Unilateral or bilateral.
→ Without areolar development.
→ < 2 years of age.
→ Non progressive.
→ **Diagnosis:** by exclusion of CPP and PPP.
  → Follow up → distinguish cases of slow progressing CPP.
→ **Treatment:** not indicated, subsequent normal puberty occur but keep under observation.

2. Premature Pubarche (Adrenarche)

→ **Premature pubarche:** the appearance of pubic hair before 8 years of age in girls.
→ **Adrenarche:** early maturation of normal pubertal adrenal androgen production.
→ Evidence of premature adrenarche without activation of the HPO axis.
→ No breast development.
→ Slightly ↑ growth velocity & advanced skeletal maturation → early closure of epiphysis → short adult height.
→ Puberty occur normally at the appropriate age.
→ Late onset CAH may have a similar presentation.
→ **Diagnosis:**
  → By exclusion of CAH, androgen secreting tumors & CPP.
  → ACTH stimulation test → marked ↑ 17-OH progesterone.
  → ↑ plasma level of 17-OH progesterone, AND, DHEA.
→ **Treatment:** depends on cause, late onset CAH is treated with glucocorticoids.
→ **Complications:**
  → **CPP:** due to late diagnosis or inadequate CAH treatment.
  → PCOS in 50% (**characteristics:** hyperandrogenism + insulin resistance).

1. B. Incomplete Precocious Puberty (Precocity)

Introduction:

Types:

3. Premature Menarche (Isolated)
→ Uncommon. → **Rule out serious causes of bleeding:** → **Neonatal period:** due to withdrawal of maternal estrogen produced by the fetoplacental unit. → Shedding of the endometrium. → Slight bleeding (normal). → Spontaneous regression of ovarian cysts. → Hypothyroidism. → McCune Albright Syndrome. → **Differential diagnosis:** → Vulvovaginitis. → Foreign body in the vagina. → Trauma. → Sexual abuse. → Vaginal tumors.
4. Androgen Secreting Tumors
A. Adrenal Tumors
→ Rare. → Function autonomously. → ↑ DHEA - DHEAS - testosterone. → ↑ Cortisol. → Could be benign or malignant with poor prognosis. → ↑ **DHEAS** is consistent with an adrenal tumor.
B. Ovarian Tumors
→ **Most common:** arrhenoblastoma then lipoid cell tumors. → ↑ testosterone & AND. → Normal DHEA & DHEAS. → ↑ **testosterone** is consistent with an ovarian tumor.

Evaluation of Patients with Sexual Precocity

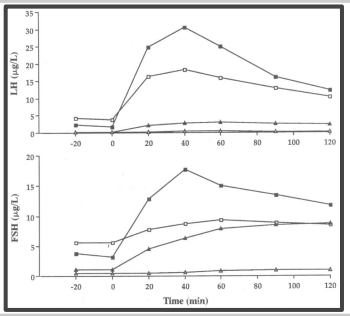
Evaluation of Patients with Sexual Precocity:

→ We have to differentiate between CPP & PPP.

History	→ Onset & progression of symptoms. → → Normal tempo → CPP. → → Abrupt & rapid → estrogen secreting tumor. → History of CNS trauma or infection. → Symptoms associated with neurological or endocrine dysfunction. → Exposure to exogenous steroids. → History of abdominal pain or swelling. → Family history → early puberty or short stature.
Physical Examination	→ Tall stature for age or changes in height velocity. → Secondary sexual characteristics (Tanner staging) → synchronous → CPP. → Neurological examination. → Fundoscopy & gross visual field evaluation. → Virilization. → Evidence of hypothyroidism or hyperadrenalism. → **Examine skin for:** acne - odor - café-au-lait spots - hirsutism. → **Abdomen & PR:** masses.
Investigations	**Lab Studies:** → ↑ DHEA & DHEAS → adrenarche or adrenal origin of PPP. → TSH, T4 & hCG → **LH, FSH & estradiol:** → → ↓ **LH:** LH:FSH < 1 → prepubertal gonadotropin secretion. → → ↑ **LH:** LH:FSH > 1 → pubertal gonadotropin response - CPP. → **GnRH stimulation test (100 ugm of GnRH IV):** → → Check FSH & LH levels at baseline (*before injection*) 20, 40, 60 minutes. → → **Prepubertal (PPP):** → → → FSH > LH → → → Minimal ↑ LH, <10 IU/ml. → → → FSH & LH levels are similar to prepubertal girls. → → **Pubertal (CPP):** → → → ↑ LH > FSH. → → → LH peak above upper limit for prepubertal. → → → FSH & LH levels are similar to normal puberty.

GnRH Stimulation Test

→ ■ → 6 years old with CPP.
→ □ → 14 years old with normal puberty.
→ ▲ → 16 years old with H-P destruction secondary to craniopharyngioma.
→ △ → 5 years old prepubertal.



Evaluation of Patients with Sexual Precocity

Evaluation of Patients with Sexual Precocity:

Investigations	**Bone Age Radiography:** → **CPP & PPP:** advanced. → **Premature adrenarche:** slightly ↑. → **Premature thelarche:** normal. **CT / MRI of the Hypothalamic Pituitary Region:** → Important in all patients with suspected CPP or with neurological symptoms & signs. **US:** → We usually start with it. → Adrenal. → **Ovaries:** rule out ovarian cysts or tumors + assess size. → **Uterus:** assess size. **Vaginal Smear for Pyknotic Index:** → We don't usually do it. → A simple method of assessing the level of estrogen stimulation. → Result is expressed in the form of % of basal, parabasal & superficial cells. → Greater % of superficial cells = greater the estrogen effect.

Psychosocial Consequences of Precocity

Psychosocial Consequences of Precocity:

01 Children with PP are taller & appear older than their peers' unrealistic expectations from parents, teachers & others child will be under stress.

02 They perceive themselves as different however this does not have any long term effect & they do well psychologically.

03 Sexual maturity at an immature age make them vulnerable to be victims of sexual abuse.

Delayed Puberty

Introduction:

→ **Delayed puberty:** absence of pubertal development /No breast development by age 13.
→ **Delayed puberty:** no menarche by age 15.
→ **Delayed puberty:** no menarche by 3 years after the onset of breast development.
→ **Delayed puberty:** lack of progression to next Tanner stage in a year.
→ Sexual hair onset does not mean the onset of puberty / it is due to adrenal androgen secretion.

Classification:

<table>
<tr><th colspan="2">1. Hypergonadotropic Hypogonadism</th></tr>
<tr><td colspan="2">→ Autoimmune ovarian failure.
→ Turner's syndrome.
→ Previous radiation or chemotherapy.
→ Galactosemia.
→ Gonadal dysgenesis (XX, XY).</td></tr>
<tr><th colspan="2">2. Hypogonadotropic Hypogonadism</th></tr>
<tr><th>Reversible Causes</th><th>Irreversible Causes</th></tr>
<tr><td>→ Constitutional delay: most common (30%).
→ Systemic disease: hypothyroidism - prolactinoma - excessive exercise - anorexia nervosa - brain tumor - CAH - chronic diseases.</td><td>→ Kallmann's syndrome: most common.
→ Hypopituitarism.
→ Congenital CNS lesion.
→ GnRH receptor defects.</td></tr>
<tr><th colspan="2">3. Eugonadotropic Eugonadism</th></tr>
<tr><td colspan="2">→ Eugonadotropic eugonadism: normal pubertal onset but lack of menarche.
→ Mullerian agenesis: most common.
→ Vaginal septum / imperforate hymen.
→ Androgen insensitivity.
→ Hypothalamic amenorrhea with onset after puberty (excessive exercise - extreme weight loss - psychogenic stress).</td></tr>
</table>

Evaluation:

1. History
2. Physical examination
3. **Investigations:**
    → **Hormonal profile:** FSH - LH - prolactin - TFT.
    → **Imaging:** pelvic US - MRI - bone age - brain MRI.

Management:

→ Treat the underlying cause:
    → Turner syndrome → HRT.
    → ↑ FSH - normal karyotype → HRT.
    → ↑ FSH - XY karyotype → HRT + gonadectomy.
    → ↓ or normal FSH.
→ Exclude systemic disease, if no systemic disease:
    → Brain MRI.
    → GnRH stimulation test.

Delayed Puberty

Introduction:

- **Delayed puberty:** failure to undergo thelarche by age of 14 (requires evaluation).

Causes:

- Constitutional (idiopathic) delay and it's the majority of cases.
- Hypergonadotropic hypogonadism (the axis is active and is producing FSH and LH but the ovaries aren't listening)
- Hypogonadotropic hypogonadism (the pituitary hasn't turned on the Axis, so the ovaries are just waiting for the signal).

Workup:

- **Begin with:** bone age + assessment of biochemical state (FSH and LH).
  - ↑ FSH and LH → ovaries problem (primary ovarian failure - Turner syndrome - resistant ovarian syndrome).
    - **Diagnosis:** karyotype.
  - **Normal** FSH and LH are → rule out common diseases and chronic diseases with:
    - TSH
    - FT4
    - Prolactin
    - ESR
    - LFTs
    - MRI
    - **Consider:** CAH - hypothyroid - bulimia - pituitary disorders
  - **Negative** workup is → constitutional → look at family history + reassure if the girl's parents had a late puberty.
- **Growth hormone is never the right answer!!**

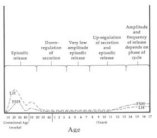
439 Summary

Puberty Disorders

Definition:

- The transitional period of development during which an individual mature from childhood to sexual and reproductive maturity
- Age of onset
  - Females: 8-13
  - Males: 9-14

Physiology of puberty:



- **In utero:** development of HPO axis: ovaries are responsive to gonadotropins (inc. during the 10th week and peak in 20th) → estrogen production→ **negative** feedback (and suppressed by maternal estrogen)
  - Fetoplacental unit is the primary source of estrogen in utero
- **Early infancy:** ↓ estrogen (lost maternal estrogen) → ↑FSH & LH → ↑estrogen
- **Childhood:** CNS inhibitory mechanism gradually develops with continued growth and maturation→ minimum FSH & LH secretion for 6-8 years
- **Normal puberty:** unknown initial trigger → pulsatile GnRH secretion→ ↑ FSH and ↑ LH secreted by the anterior pituitary gland → stimulation of the leydig cells and sertoli cells in the testicles, and the theca and granulosa cells in the ovary

Plasma LH concentration

Prepubertal	Early pubertal	Late pubertal
Low LH pulses; similar during sleep and awake	LH pulse increases during sleep	LH pulse increases in day and night

Sequence of somatic changes of puberty

9.6 years	10.6 years	11.2 years	12 years	12.7 years
Onset of growth spurt	Thelarche	Pubarche	Maximal growth velocity	Menarche

Phases of pubertal changes:

1. **Gonadarche:**
   a. Reactivation of HPO axis→ activation of reproductive glands by the pituitary hormones FSH and LH
2. **Adrenarche:** activation of adrenal androgen production (independent of reproductive organs). Adrenal androgens (DHEA, DHEAS) effect: pubic & axillary hair, acne, oily skin, and **increase bone age and linear growth.**
3. **Thelarche:** onset of breast development
   a. First visible change of puberty
   b. Induced by estrogen
4. **Pubarche:** onset of pubic hair growth (occurs after thelarche)
5. Growth(-arche): growth spurt
6. **Menarche:** onset of menstrual bleeding
   a. Anovulatory cycle: The menstrual cycle may be irregular in adolescents during the first few months/years after menarche.
      i. Immaturity of the hypothalamic-pituitary-gonadal axis → irregular secretion of gonadotropins → short luteal phase, and lack of progesterone → endometrium remains in the proliferative phase → irregular menses and heavy menstrual bleeding
      ii. Does not require treatment because menses become regular as hypothalamic-pituitary-gonadal axis matures

Tanner scale (IMP)

- Used to assess the development of secondary sexual characteristics (e.g., breast, genital, pubic hair development)

- Other morphological changes during puberty: (EXTRA)
  - Growth spurt: Linear growth during adolescence, Includes ↑ growth in trunk and limbs
    - Generally occurs between ages 13–15 years
  - Bone growth
  - Gradual increase in body fat (in girls)
  - Dermatological changes

Precocious puberty

Criteria for diagnosis

- Accelerate growth before the age of:
  - In girls: 8 years
  - In boys: 9 years
- Development of female secondary sexual characteristics

Classification of precocious puberty:

- Heterosexual precocious puberty: masculinization of girls or feminization of boys
  - **Leydig cell tumors:** secrete androgen
  - **Congenital adrenal hyperplasia:** secrete androgen
  - **McCune-Albright syndrome:** Continuous stimulation of endocrine functions
    - Clinical features: 3 P's of are Polyostotic fibrous dysplasia, Pigmentation (café-au-lait spots), and Precocious puberty
      - Polyostotic fibrous dysplasia: bone lesions usually occur on one side of the body
      - Pigmentation: Unilateral *café-au-lait* spots: hyperpigmented macules, occur on the same side as the bony lesions.

      - **Peripheral precocious puberty (most common)** and other endocrinopathies: cushing syndrome, acromegaly, hyperthyroidism
- Isosexual precocious puberty
  - **Complete** precocious puberty
    - Central (true) precocious puberty
    - Peripheral (pseudo) precocious puberty
  - **Incomplete** precocious puberty/ Benign pubertal variants
    - Premature thelarche
    - Premature adrenarche
    - Premature menarche

Isosexual: Complete precocious puberty

	Central (true) precocious puberty (CPP)	Peripheral (pseudo) precocious puberty (PPP)
Overview	• Precocious puberty with elevated GnRH levels **(GnRH dependant)** ○ Early activation of the HPO axis → ↑GnRH pulses → ↑gonadotropins & ovarian estrogen production & eventual ovulation→ abnormally **early** initiation of pubertal changes and development of secondary sexual characteristics • Follows the pattern of normal pubertal development but earlier in age • More common in girls than boys	• Precocious puberty without elevated GnRH level **(GnRH independent)** • Due to ↑ peripheral synthesis of or **exogenous exposure to sex hormones**

Etiology	**Idiopathic:**
	• **Most common cause (80-90%)**
	• Diagnosis is usually one of exclusion after CNS imaging
	CNS lesions:
	• **CNS Tumors:**
	  ○ **Hypothalamic hamartomas:**
	  ■ Most common type of CNS tumors that causes CPP
	  ■ Congenital malformation
	  ■ Rapidly progressing CPP in a child <2 yrs suggests this diagnosis
	  ○ Optic gliomas
	  ○ Craniopharyngioma
	• Trauma
	• Infections (e.g., encephalitis, meningitis)
	• Hydrocephalus
	• Obesity-related precocious sexual development
		• **Exogenous steroid use or gonadotropins**
		• ↑ Androgen production:
		  ○ Congenital adrenal hyperplasia
		  ■ Presentation: ambiguous genitalia on birth
		  ○ Granulosa cells & granulosa-theca cell ovarian tumors (70% present with PP)
		  ■ Presentation: vaginal bleeding & breast development
		  ○ Sertoli-leydig ovarian tumor
		  ○ Adrenocortical tumors
		• ↑ Estrogen production:
		  ○ McCune-Albright syndrome
		  ○ HCG-secreting germ cell tumors (e.g., dysgerminomas)
		• ↑ β-hCG production
		• Primary hypothyroidism:
		  ○ TSH acts on FSH receptors (TSH has a lot of similarity with FSH and can work on FSH receptors)→ **PP**
		• Obesity-related precocious sexual development

Clinical features	• Premature sexual development typically follows the normal pattern of puberty, except that it is early. • **Increased growth velocity:** Children tend to be taller than their peers during adolescence, but are of shorter stature by the time they reach adulthood **(due to early closure of the epiphyseal plate).**	• **May not follow the normal developmental pattern** (signs of estrogen or androgen excess) • May exhibit possible features of an underlying condition • Girls with prolonged PPP→ prolonged exposure of CNS to estrogen→ **CPP**

439 Summary

Isosexual: Complete precocious puberty

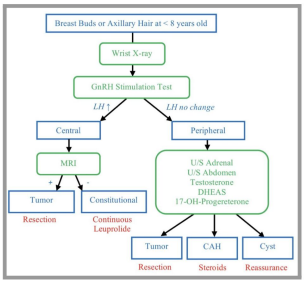
Diagnosis	**Wrists X-ray**	• Assess and confirm accelerated bone growth. • Puberty likely has not started: bone age is within 1 year of a child's age⟶ most likely normal early puberty • Positive: Bone age is > 2 years of the child's age	
	Serum LH & FSH	↑	↓
	LH:FSH ratio	**> 1** pubertal gonadotropin response	**< 1** pre-pubertal gonadotropin response
	Serum testosterone /estradiol	↑	↑
	GnRH stimulation test (gold standard): • Evaluates the reactivity of the hypothalamic-pituitary-axis to GnRH stimulation • Method: base LH and FSH values ⟶ administer GnRH ⟶ blood is drawn after a certain time for reevaluation of LH and FSH levels		
		↑↑LH & FSH	**No change in FSH & LH**
	Others	• HCG • MRI/CT of the brain with contrast: when ↑ LH is confirmed • TSH, T3 hormone: suspicion of hypothyroidism for PPP • In androgen secreting tumors: ○ ↑DHEAS is consistent with adrenal tumors ○ ↑Testosterone is consistent with ovarian tumors	
Management	• Goal is to **gain normal adult height** by prevention of growth plate fusion • Indication: **accelerated growth and advanced skeletal age** • **GnRH agonists (e.g., leuprolide,** buserelin, goserelin): ○ Treatment of choice ○ Prevents premature fusion of growth plates ○ Adult height of treated pt is higher than untreated (related to skeletal age age at the onset of treatment) • Medroxyprogesterone acetate: ○ Suppresses progression of puberty and menses ○ **Has no effect on skeletal maturation and adult height** • Manage underlying causes.	• Manage underlying cause ○ Tumors = surgical removal If cause couldn't be reversed: • Testolactone: ○ inhibits conversion of testosterone to estrogen • Ketoconazole: ○ inhibits steroid biosynthesis • Cyproterone acetate: ○ potent progestin and antiandrogen • Spironolactone: ○ inhibits androgen at receptor level • Medroxyprogesterone acetate: ○ Suppresses progression of puberty and menses	

Isosexual: Incomplete precocious puberty

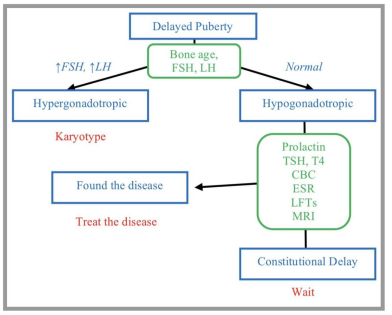
- Partial (often transient) pubertal development in the absence of the stigmata of puberty (premature but isolated secondary characteristics)
- Slow progression, no change or waning of the physical findings may occur

	Premature thelarche	**Premature adrenarche/puberace**	**Premature menarche**
Features	• **Isolated breast development** <8 years in girls (May be unilateral or bilateral, without areolar development) • **Absence of the signs of sexual maturation** • May be present in toddlers and neonates	• Onset of pubic and/or axillary hair growth <8 years in girls • HPO axis is NOT activated • Slightly accelerated growth velocity & advanced skeletal maturation • Associated with obesity, insulin resistance, and later development of PCOS	• Isolated uterine bleeding • Absence of secondary sexual characteristics
Diagnosis	• Clinical diagnosis By exclusion of CPP and PPP (follow up should distinguish slow progressing CPP) • Normal bone age	• ↑ Serum androgen concentrations (DHEA-S, testosterone) • Advanced bone age	• Neonatal period bleeding may occurs due to estrogen withdrawal • Other causes: hypothyroidism, mcCine albright syndrome • Trauma, infection, and sexual abuse need to be excluded • Normal bone age

Precocious puberty (Online MedEd)



Delayed puberty (Online MedEd)



Quiz

Question 1:

→ **Regarding puberty, all of the following are true EXCEPT:**

A. It is the transitional period of development during which an individual matures from childhood to sexual & reproductive maturity.
B. Breast budding is the 1ST visible sign of puberty.
C. The maximum growth velocity occurs at 12 years.
D. The age of menarche has decreased over the last 3-4 decades due to improved nutrition, general health & lifestyle changes.

Question 2:

→ **The normal sequence of pubertal changes in the female is ?**

A. Thelarche, adrenarche, growth, menarche.
B. Menarche, adrenarche, thelarche ,growth.
C. Growth. thelarche, adrenarche, menarche
D. Adrenarche,thelarche,growth,menarche

Question 3:

→ **A 6 years old girl presented to the clinic with signs and symptoms of precocious puberty. GnRH stimulation test was done, the result showed FSH levels were higher than LH levels. Which one of the following is the type of precocious puberty ?**

A. True) Central precocious puberty
B. (Pseudo) peripheral precocious puberty

Question 4:

→ **Which one of the following is the most common type of CNS tumor that cause CPP ?**

A. Hypothalamic hamartomas
B. Optic gliomas
C. Craniopharyngia
D. Ependymoma

1	2	3	4
D	A	B	A

Quiz

Question 1:

→ **Which one of the following is NOT under the effect of Dehydroepiandrosterone, Dehydroepiandrosterone Sulfate or Androstenedione?**

A. Development of pubic & axillary hair
B. Breast Development
C. Acne, oily skin & hair
D. Adult type body odor

Question 2:

→ **Which one of the following is the most common cause of central precocious puberty?**

A. Idiopathic
B. Hypothalamic hamartoma
C. Congenital Adrenal Hyperplasia
D. Ovarian Tumor

Question 3:

→ **A 7 year old girl presented to the clinic with sign and symptoms of precocious puberty, Café-au-lait spots, hyperthyroidism, history of easily fractured bones and signs of cushing disease. Which one of the following is the diagnosis?**

A. Peutz-Jeghers Syndrome
B. Kallmann Syndrome
C. Swyer Syndrome
D. McCune-Albright Syndrome

Question 4:

→ **A 7-year-old girl had her menarche 2 months after breast development. Which one of the following can be the cause of her condition?**

A. CNS tumor
B. Congenital adrenal hyperplasia
C. Mullerian agenesis
D. Turner syndrome

1	2	3	4
B	A	D	A

Reference

CHAPTER 32

Puberty and Disorders of Pubertal Development

SARA CHURCHILL • CAROLYN J. ALEXANDER

CLINICAL KEYS FOR THIS CHAPTER

- Both genetic and environmental factors determine the onset of pubertal change in young girls. Puberty may be delayed or may occur earlier, depending on nutrition-related factors and physical activity. Obesity causes earlier onset of puberty, and excessive exercise causes delay. Psychological disorders and chronic isolation may also affect the normal onset of puberty.
- The Frisch hypothesis states that an invariant mean weight (48 kg/106 lb) is essential for the initiation of the first menses (menarche). Leptin (a peptide hormone) secreted by adipose tissue may provide the "triggering link" for the initiation of menarche.
- The female fetus has the highest lifetime number of oocytes by mid-gestation. Brief follicular maturation and negative feedback on gonadotropin release due to follicular estradiol production also occurs in utero. Peak serum levels of gonadotropins are seen by 3 months after birth and then slowly decline, reaching their nadir at age 4 years. Between the ages of 4 and about 10 years, the "gonadostat" is said to regulate the hypothalamic–pituitary–ovarian axis. A combination of high sensitivity to low levels of estradiol resulting in negative feedback on gonadotropin release, and an intrinsic central nervous system inhibition of gonadotropin-releasing hormone secretion, keep gonadotropins at low levels. By age 11 years (the usual onset of pubertal development), there is a gradual loss of the negative feedback to low levels of sex steroids, and pubertal development begins.
- The usual sequence of physical signs of puberty in girls is (1) thelarche (breast budding), (2) adrenarche and/or pubarche (axillary and pubic hair growth), (3) peak height velocity, (4) menarche (first menses), and (5) mature sexual hair and breast growth.
- Disorders of puberty include precocious development and delayed puberty. *Precocious puberty* refers to the development of any sign of secondary sexual maturation at an age earlier than 8 years in girls. Failure to undergo thelarche by the age of 14 years constitutes significant delay of pubertal development and requires evaluation.

Puberty encompasses the development of secondary sexual characteristics and the acquisition of reproductive capability. During this transition, usually between 10 and 16 years of age, a variety of physical, endocrinologic, and psychological changes accompany the increasing levels of circulating sex steroids.

The onset of pubertal changes is determined primarily by genetic factors, including race, **and is also influenced by geographic location** (girls in metropolitan areas, at altitudes near sea level, or at latitudes close to the equator tend to begin puberty at an earlier age) and **nutritional status** (obese children have an earlier onset of puberty, and those who are malnourished or have chronic illnesses associated with weight loss have a later onset of menses). **Excessive exercise** relative to the caloric intake can also delay the onset of puberty. **It has been proposed that an invariant mean weight of 48 kg (106 lb) is essential for the initiation of menarche** in healthy girls. Leptin, a peptide secreted by adipose tissue, may be the link between weight and the initiation of menarche. **Psychological factors,** severe neurotic or psychotic disorders, and chronic isolation may interfere with the normal onset of puberty through a mechanism similar to adult hypothalamic amenorrhea.

In the United States and Western Europe, a decrease in the age of menarche (i.e., age at first menses) was noted between 1840 and 1970, from an estimated mean age of 17 years in 1840 down to a reported mean age of 13 years in 1970. This trend has plateaued since then, and currently **the mean age of menarche is approximately 12.4 years in the United States.**

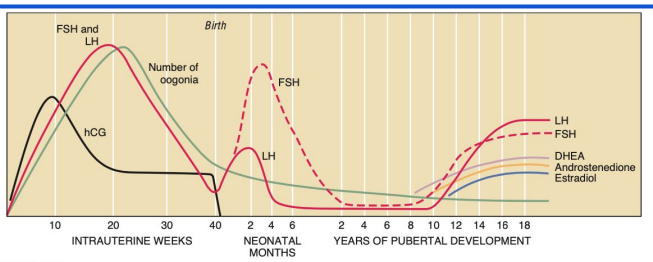


FIGURE 32-1 Changes in the concentration of gonadotropins (LH and FSH), sex steroids (DHEA, androstenedione, and estradiol), and the number of oogonia throughout fetal life and pubertal development. *DHEA,* Dehydroepiandrosterone; *FSH,* follicle-stimulating hormone; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone. Adapted from Speroff L, Fritz MA: Neuroendocrinology. In Speroff L, Fritz MA, editors: *Clinical gynecologic endocrinology and infertility,* ed 7, Baltimore, MD, 2005, Lippincott Williams & Wilkins.

Endocrinologic Changes of Puberty

FETAL AND NEWBORN PERIOD

The fetal hypothalamic–pituitary–gonadal axis is capable of producing adult levels of gonadotropins and sex steroids. **By 20 weeks' gestation, levels of gonadotropins**—follicle-stimulating hormone (FSH) and luteinizing hormone (LH)—**rise dramatically in both male and female fetuses** (Figure 32-1). Late in gestation, a surge in levels of glucocorticoids in the fetal circulation occurs. This is essential for normal maturation of fetal lungs and critical for the development of the fetal thyroid, kidney, brain, and pituitary. Recently, it has been suggested that excessive exposure of the developing fetus to glucocorticoids or exposure at the wrong time may lead to lifelong alterations in the function of the hypothalamic–pituitary–adrenal axis.

The female fetus acquires the lifetime peak number of oocytes (in utero) by mid-gestation and also has a brief period of follicular maturation and sex steroid production in response to elevated gonadotropin levels in utero. This transient increase in serum estradiol (a sex steroid) acts on the fetal hypothalamic-pituitary unit, resulting in a reduction of gonadotropin secretion (a negative feedback effect), which in turn reduces estradiol production. This indicates that the inhibitory effect of sex steroids on gonadotropin release is operative before birth.

In both male and female fetuses, serum estradiol is primarily of maternal and placental origin. With birth and the acute loss of maternal and placental sex steroids, the negative feedback action on the hypothalamic-pituitary axis is lost, and gonadotropins are once again released from the pituitary gland, reaching adult or near-adult concentrations in the early neonatal period. **In the female infant, peak serum levels of gonadotropins are generally seen by 3 months of age, then they slowly decline until a nadir is reached by the age of 4 years.** In contrast to gonadotropin levels, sex steroid concentrations decrease rapidly to prepubertal values within 1 week of birth and remain low until the onset of puberty.

During fetal development, the adrenal glands are large in proportion to their size in adult life (similar to the fetal kidneys). Early in gestation, the fetal adrenal gland produces abundant dehydroepiandrosterone sulfate (DHEA-S), which serves as a precursor for estrogen production by the placenta and is also able to convert placental progesterone into cortisol. It is not until about 23 weeks' gestation that the fetal adrenal cortex expresses the enzyme to directly synthesize cortisol from cholesterol or pregnenolone. In the first few months of postnatal life, the innermost part of the adrenal cortex (the fetal zone) largely regresses, and there is a rapid decrease in the production of DHEA-S.

CHILDHOOD

The hypothalamic–pituitary–gonadal axis in the young child is suppressed between the ages of 4 and 10 years. The hypothalamic–pituitary system regulating gonadotropin release has been termed the ***gonadostat.*** **Low levels of gonadotropins and sex steroids during this prepubertal period are a function of two mechanisms: (1) maximal sensitivity of the gonadostat to the negative feedback effect of the low circulating levels of estradiol** present in prepubertal children, **and (2) intrinsic central nervous system inhibition of hypothalamic gonadotropin-releasing hormone (GnRH) secretion.** These mechanisms occur independently of the presence of functional gonadal tissue. This is clearly demonstrated in children with gonadal dysgenesis. Agonadal children display elevated gonadotropin concentrations during the first 2 to 4 years of life, followed by a decline in circulating FSH and LH levels by 6 to 8 years of age. By 10 to 12 years of age, gonadotropin concentrations spontaneously rise once again, eventually achieving castration levels. This pattern of gonadotropin secretion in early childhood is similar to that of children with normal gonadal function. **These data suggest that an intrinsic central nervous system regulator of GnRH release is the principal inhibitor of gonadotropin secretion from 4 years of age until the peripubertal period.** Furthermore, after regression of the fetal zone of the adrenal gland (a few months after birth), very low concentrations of adrenal androgen precursors are available, resulting in decreased adrenal androgen production in early childhood.

LATE PREPUBERTAL PERIOD

In general, androgen production and differentiation by the zona reticularis of the adrenal cortex are the initial endocrine changes associated with puberty. Serum concentrations of DHEA, DHEA-S, and androstenedione rise between the ages of 8 and 11 years. **This rise in adrenal androgens induces the growth of both axillary and pubic hair and is known as *adrenarche* or *pubarche.*** This increase in adrenal androgen production occurs independently of gonadotropin secretion or gonadal steroid levels, and the mechanism of its initiation is not understood at this time. Some studies have suggested that the morphologic and functional changes in the zona reticularis are induced by increasing cortisol levels. In cellular studies, human fetal adrenal cells exposed to cortisol in high concentrations produce DHEA, whereas in human studies, infants treated with high-dose adrenocorticotropic hormone for infantile spasms have been noted to have adrenal androgen production.

Recent studies indicate that **girls who undergo premature pubarche are more likely than other girls to develop polycystic ovarian syndrome (PCOS) as adults** (see Chapter 33).

PUBERTAL ONSET

By approximately the 11th year of life, there is a gradual loss of sensitivity by the gonadostat to the negative feedback of sex steroids (Figure 32-2). As a consequence, GnRH pulses (with their mirroring pulses of FSH and LH) increase in amplitude and frequency. The factors that reduce the sensitivity of the gonadostat are incompletely understood. **Some studies indicate that a rise in the concentration of leptin, a hormone produced by adipocytes (fat cells) that mediates appetite satiety, precedes and is necessary for this change.** This, in turn, supports the association between minimum weight or total body fat and the onset of puberty. The Frisch hypothesis suggests that a critical body weight is necessary for pubertal onset. Further investigations support the concept that fat stores might influence pubertal onset through several mechanisms. First, adipocytes secrete adipokines such as leptin. Leptin appears to serve as a signal to the hypothalamic GnRH pulse generator that there are sufficient energy stores for fertility to commence. Studies have shown that every 1-kg gain in body weight lowers the onset of menarche by 13 days and that every increase of 1 ng/ml in serum leptin lowers the age of menarche by 1 month. Second, aromatase activity in adipocytes is dependent on fat mass, and obesity results in greater peripheral conversion of androstenedione to estrone and of testosterone to estradiol. Last, increasing adipose tissue is related to increasing insulin resistance, which decreases serum levels of sex hormone binding globulin. This leads to an increased level of bioavailable sex hormones.

A further decrease in sensitivity of the gonadostat combined with the loss of intrinsic central nervous system inhibition of hypothalamic GnRH release is heralded by sleep-associated increases in GnRH secretion. This nocturnal dominant pattern gradually shifts into an adult-type secretory pattern, with GnRH pulses occurring every 90 to 120 minutes throughout the 24-hour day.

The increase in gonadotropin release promotes ovarian follicular maturation and sex steroid production, which induces the development of secondary sexual characteristics. By middle to late puberty, maturation of the positive feedback mechanism of estradiol on LH release from the anterior pituitary gland is complete, and ovulatory cycles are established.

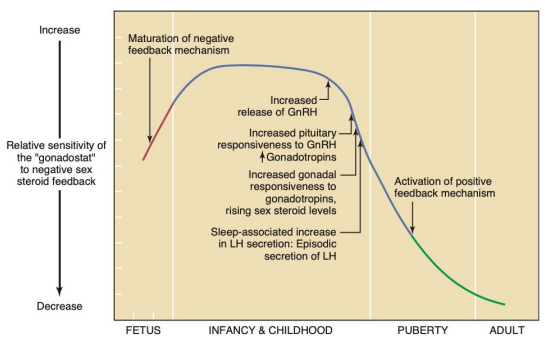


FIGURE 32-2 Changes in set point of the hypothalamic-pituitary unit (gonadostat) *(solid lines)* and the maturation of the negative and positive feedback mechanisms from fetal life to adulthood in relation to the normal changes of puberty. This figure does not illustrate the change in the sex steroid–independent intrinsic central nervous system inhibitory mechanism that is observed from late infancy to puberty. *GnRH,* Gonadotropin-releasing hormone; *LH,* luteinizing hormone. Adapted from Styne DM, Grumbach MM: Disorders of puberty in the male and female. In Yen SSC, Jaffe RB, editors: *Reproductive endocrinology: physiology, pathophysiology and clinical management,* ed 2, Philadelphia, Saunders, 1991.

Somatic Changes of Puberty

Physical changes of puberty involve the development of secondary sexual characteristics and the acceleration of linear growth (gain in height). The Marshall and Tanner classification of breast and pubic hair development is employed for descriptive and diagnostic purposes (Figures 32-3 and 32-4). A useful acronym for remembering the usual chronologic order of the stages of female pubertal development is TAPuP ME (standing for thelarche, adrenarche, pubarche, peak growth velocity, and menarche).

STAGES OF PUBERTAL DEVELOPMENT

The first physical sign of puberty is usually breast budding (thelarche), followed by the appearance of axillary or pubic hair (adrenarche/pubarche). Unilateral breast development is not uncommon in early puberty and may last up to 6 months before the development of the contralateral breast. **Maximal growth or peak height velocity is usually the next stage, followed by menarche (the onset of menstrual periods).** The final somatic changes are the appearance of adult pubic hair distribution and adult-type breasts. In approximately 15% of normally developing girls, the development of pubic hair occurs before breast development. The sequence of pubertal changes generally occurs over a period of 4.5 years, with a normal range of 1.5 to 6 years (Figure 32-5).

Race plays a role in determining the age of the onset of puberty. African American girls begin puberty earlier than girls in other racial groups (on average between the ages of 8 and 9 years), followed by Mexican Americans and whites (Table 32-1). In African American girls, thelarche and adrenarche can occur as early as 6 years

TABLE 32-1

AGE AT ONSET OF PUBIC HAIR DEVELOPMENT, BREAST DEVELOPMENT, AND MENARCHE FOR THREE RACIAL/ETHNIC GROUPS OF U.S. GIRLS: NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY III, 1988-1994

Puberty Milestone	Non-Hispanic White (mean age*)	Black (mean age*)	Mexican American (mean age*)
Pubic hair†	10.5	9.5	10.3
Breast development†	10.3	9.5	9.8
Menarche‡	12.7	12.1	12.2
Menarche‡	12.7	12.3	12.5

Modified with permission from Wu T, Mendola P, Buck GM: Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988-1994. *Pediatrics* 110:752–757, 2002.
*Estimated with application of weights for the examination sample of the National Health and Nutrition Examination Survey III (NHANES III).
†Estimated using probit model for the status quo data of the puberty measurements.
‡Estimated using failure time model for the recalled age at menarche.

Reference

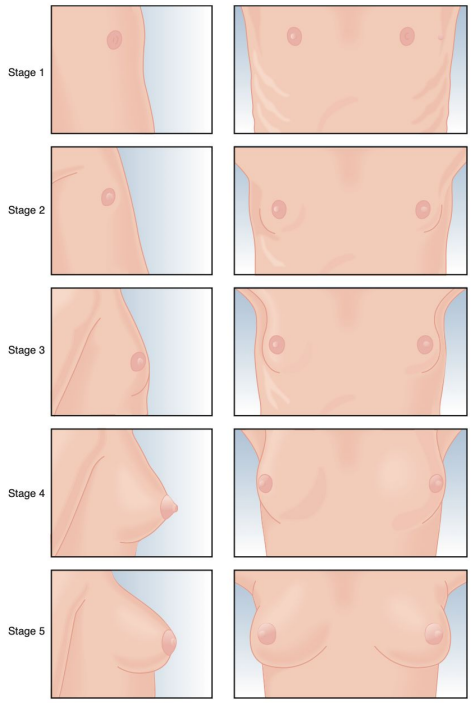


FIGURE 32-3 Stages of breast development as defined by Marshall and Tanner. *Stage 1*, Preadolescent; elevation of papilla only. *Stage 2*, Breast bud stage; elevation of breast and papilla as a small mound with enlargement of the areolar region. *Stage 3*, Further enlargement of breast and areola without separation of their contours. *Stage 4*, Projection of areola and papilla to form a secondary mound above the level of the breast. *Stage 5*, Mature stage; projection of papilla only, resulting from recession of the areola to the general contour of the breast. Adapted from Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. *Arch Dis Child* 44:291, 1969.

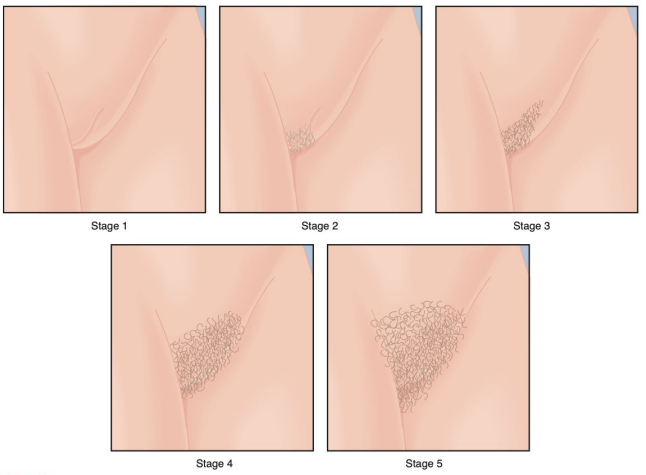


FIGURE 32-4 Stages of female pubic hair development according to Marshall and Tanner. *Stage 1*, Preadolescent; absence of pubic hair. *Stage 2*, Sparse hair along the labia; hair downy with slight pigmentation. *Stage 3*, Hair spreads sparsely over the junction of the pubes; hair is darker and coarser. *Stage 4*, Adult-type hair; no spread to the medial surface of the thighs. *Stage 5*, Adult-type hair with spread to the medial thighs assuming an inverted triangle pattern. Adapted from Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. *Arch Dis Child* 44:291, 1969.

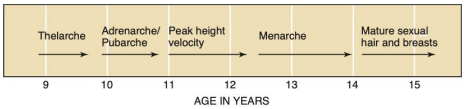


FIGURE 32-5 Sequence of physical changes during pubertal development. The acronym *TAPuP ME* has been used as a mnemonic device for **T**helarche, **A**drenarche/**Pu**barche, **P**eak height velocity, and **ME**narche, which precede mature sexual hair and breast development.

BODY COMPOSITION AND BONE AGE

There are no significant differences in skeletal mass, lean body mass, or percentage of body fat between prepubertal boys and prepubertal girls. After attaining sexual maturity, girls generally have less skeletal and lean body mass and a greater percentage of body fat than boys do.

Bone age correlates well with the onset of secondary sexual characteristics and menarche. Bone age is determined by obtaining radiographs of the left (or nondominant) hand and wrist, elbow, or knee and comparing them with an index population. Osseous maturation is particularly useful in the evaluation of adolescents with delayed onset of puberty. Bone maturation, chronologic age, and height can also be used to predict the final adult stature based on standardized nomograms.

Precocious Puberty

Precocious puberty **refers to the development of any sign of secondary sexual maturation at an age 2.5 standard deviations earlier than the expected age of pubertal onset.** In North America, these ages are 8 years for girls and 9 years for boys. The incidence of precocious puberty is 1 in 10,000 children in North America, and it is approximately five times more common in girls. **In 75% of cases of precocious puberty in girls, the cause is idiopathic.** A thorough evaluation to eliminate a serious disease process, and to arrest potential premature osseous maturation that may affect the normal growth pattern, is mandatory.

The early development of secondary sexual characteristics may promote psychosocial problems for the child and should be addressed carefully. **Typically, these girls are taller than their peers as children but ultimately are shorter as adults, due to the premature fusion of the long bone epiphyses.** A classification system for female precocious puberty is shown in Box 32-1.

Precocious puberty may be divided into two major subgroups: **heterosexual precocious puberty (development of secondary sexual characteristics opposite those of the anticipated phenotypic sex) and isosexual precocious puberty (premature sexual maturation that is appropriate for the phenotype of the affected individual).**

Investigations for females with precocious puberty are shown in Box 32-2.

HETEROSEXUAL PRECOCITY

In females, heterosexual precocity results from virilizing neoplasms, congenital adrenal hyperplasia, or exposure to exogenous androgens.

Androgen-secreting neoplasms in females are either ovarian (most commonly an arrhenoblastoma) or adrenal in origin and are exceedingly rare in childhood. They are diagnosed on the basis of physical and radiologic examinations of the abdomen and are treated by surgical removal.

Congenital adrenal hyperplasia most commonly results from a defect of the adrenal enzyme 21-hydroxylase that leads to excessive androgen production. More severe forms of this defect cause the birth of a female with ambiguous genitalia. If untreated, progressive virilization during childhood and short adult stature will result. The treatment of this disorder includes replacement of cortisol with a related glucocorticoid and surgical correction of any anatomic abnormalities in the first few years of life. A less severe form of this defect, referred to as *nonclassic (late onset) adrenal hyperplasia* can cause premature pubarche and an adult disorder resembling PCOS.

BOX 32-1

CLASSIFICATION OF FEMALE PRECOCIOUS PUBERTY

Heterosexual Precocious Puberty

Virilizing neoplasm
- Ovarian
- Adrenal

Congenital adrenal hyperplasia (adrenogenital syndrome)

Exogenous androgen exposure

Isosexual Precocious Puberty

Incomplete Isosexual Precocious Puberty

Premature thelarche
Premature adrenarche
Premature pubarche

Complete Isosexual Precocious Puberty

True isosexual precocious puberty
- Constitutional (idiopathic)
- Organic brain disease
  - Central nervous system tumors
  - Head trauma
  - Hydrocephalus
  - Central nervous system infection (abscess, encephalitis, meningitis)

Pseudoisosexual Precocious Puberty

Ovarian neoplasm
Adrenal neoplasm
Exogenous estrogen exposure
Advanced hypothyroidism
McCune-Albright syndrome
Peutz-Jeghers syndrome

Adapted from Brenner PF: Precocious puberty in the female. In Mishell DR Jr, Davajan V, Lobo RA, editors: *Infertility, contraception and reproductive endocrinology,* ed 3, Cambridge, MA, 1991, Blackwell Scientific, p 349.

ISOSEXUAL PRECOCIOUS PUBERTY

Complete isosexual precocious puberty results in the development of the full complement of secondary sexual characteristics and increased levels of sex steroids. It may arise from premature activation of the normal process of pubertal development involving the hypothalamic–pituitary–gonadal axis, which is called **true isosexual precocity.** Exposure to estrogen, independent of the hypothalamic–pituitary axis (such as from an estrogen-producing tumor), is called ***pseudoisosexual precocity.***

BOX 32-2

LABORATORY TESTS USED SELECTIVELY TO EVALUATE FEMALE PRECOCIOUS PUBERTY

Radiologic

Serial bone age (isosexual precocity)
Magnetic resonance imaging (MRI) or computed tomography (CT) of the brain with optimal visualization of hypothalamic region and sella turcica (true isosexual precocity)
MRI, CT, or ultrasonography of abdomen, pelvis, or adrenal gland (heterosexual precocity, pseudoisosexual precocity)

Laboratory

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
Dehydroepiandrosterone sulfate, testosterone (heterosexual precocity)
17-hydroxyprogesterone, 11-deoxycortisol (suspected congenital adrenal hyperplasia causing heterosexual precocity)
Thyroid function tests (thyroid-stimulating hormone, free thyroxine) (isosexual precocious puberty)
Gonadotropin-releasing hormone (GnRH) stimulation test: LH measurement after 100 µg of GnRH is given intravenously (to differentiate gonadotropin-dependent from gonadotropin-independent isosexual precocity)

True Isosexual Precocity

In females, 75% of cases are constitutional. True isosexual precocity may be diagnosed by the administration of exogenous GnRH (a GnRH stimulation test) with a resultant rise in LH levels equivalent to those seen in older girls who are undergoing normal puberty. **In approximately 10% of girls with the true form of precocious puberty, a central nervous system disorder is the underlying cause.** This includes tumors, obstructive lesions (hydrocephalus), granulomatous diseases (sarcoidosis, tuberculosis), infective processes (meningitis, encephalitis, or brain abscess), neurofibromatosis, and head trauma. It is postulated that these conditions interfere with the normal inhibition of hypothalamic GnRH release. **Children with precocious puberty secondary to organic brain disease often exhibit neurologic symptoms before the appearance of premature sexual maturation.** Evaluation of true isosexual precocity should include MRI of the head for lesions.

Pseudoisosexual Precocity

Pseudoisosexual precocity occurs when estrogen levels are elevated and cause characteristic sexual maturation without activation of the hypothalamic–pituitary axis. In these girls, a GnRH stimulation test does not induce pubertal levels of gonadotropins. Causes include ovarian tumors and cysts, exogenous estrogenic compound use, McCune-Albright syndrome, severe prolonged hypothyroidism, and Peutz-Jeghers syndrome. Curiously, when the initial cause of pseudoisosexual precocity is eliminated, some girls go on to develop true isosexual precocity.

Some ovarian tumors can be felt on abdominal examination and are usually unilateral. Other lesions may require radiologic or ultrasonic imaging for diagnosis. Treatment of these lesions is surgical.

The McCune-Albright syndrome (polyostotic fibrous dysplasia) **represents 5% of cases of female precocious puberty.** This syndrome consists of sexual precocity, multiple cystic bone defects that fracture easily, café au lait spots with irregular borders (most frequently on the face, neck, shoulders, and back), and adrenal hypercortisolism. Hyperthyroidism and acromegaly may also occur in this syndrome. The pathophysiology involves a somatic mutation in affected postzygotic tissues that causes them to function independently of their normal stimulating hormones.

Prolonged, severe hypothyroidism has been hypothesized to cause pituitary gonadotropin release in response to the persistently elevated secretion of thyroid-releasing hormone. Concomitant elevation of prolactin may also occur with the development of galactorrhea. Ovarian cysts may occasionally develop, and bone age may be retarded. This is the only form of precocious puberty associated with delayed bone age. Treatment is with thyroid replacement therapy.

The Peutz-Jeghers syndrome has been associated with a rare sex cord tumor with annular tubules, which may secrete estrogen. Because this syndrome of gastrointestinal tract polyposis and mucocutaneous pigmentation has also been reported in association with granulosa-theca cell tumors, children with this disorder should be screened for the development of gonadal neoplasms.

Incomplete isosexual precocity is the early appearance of a single secondary sexual characteristic. These conditions include **premature thelarche,** the isolated appearance of breast development before the age of 4 years (unilateral or bilateral) that resolves spontaneously within months and that is probably secondary to transient estradiol secretion; **premature adrenarche,** the isolated appearance of axillary hair before the age of 7 years that is the result of premature androgen secretion by the adrenal gland; and **premature pubarche,** the isolated appearance of pubic hair in girls before the age of 8 years.

of age, whereas in whites, they can occur as early 7 years of age.

ADOLESCENT GROWTH SPURT

In general, the growth spurt is seen 2 years earlier in pubertal girls than in boys. Growth hormone, estradiol, and insulin-like growth factor 1 (formerly somatomedin C) are involved in the adolescent growth spurt. Peak height velocity occurs approximately 1 year before the onset of menarche. There is limited linear growth after menarche, as gonadal steroid production accelerates fusion of the long bone epiphyses.

Reference

In general, premature thelarche and premature adrenarche are associated with appropriate sexual maturation, though they may be associated with the development of nonclassic adrenal hyperplasia and perhaps PCOS. Therapy for these conditions is not required. Both conditions are more common in girls than in boys. It is not possible to diagnose an incomplete form of sexual precocity on the basis of a single evaluation, and interval examinations of bone age are necessary to rule out true precocious puberty.

TREATMENT OF TRUE ISOSEXUAL PRECOCIOUS PUBERTY

Approximately 75% of cases of precocious puberty in girls prove to have a constitutional or idiopathic cause, and these patients are candidates for GnRH agonist therapy (e.g., leuprolide acetate). These girls require treatment to prevent further sex steroid release and accelerated epiphyseal fusion. **Less than 50% of girls with idiopathic precocity will attain an adult height of 5 feet if the condition is left untreated.**

GnRH agonists are the most effective therapy for idiopathic precocity. Long-term GnRH agonist treatment suppresses pituitary release of LH and FSH, resulting in decline of gonadotropin levels to prepubertal concentrations and arrest of gonadal sex steroid secretion. Clinically, normal gonadotropin release, sex steroid production, and pubertal maturation will resume 3 to 12 months after discontinuation of GnRH agonist therapy.

The final adult stature of girls with GnRH-dependent causes of precocious puberty is strongly influenced by their chronologic age at diagnosis and initiation of treatment. When GnRH agonist treatment is initiated before the chronologic age of 6 years, the final adult height is increased by 2-4%. In contrast, the final adult height is usually not affected when the chronologic age at diagnosis and treatment is greater than 6 years. Many studies have reported good long-term reproductive outcomes in GnRH-dependent precocious puberty after treatment with GnRH agonists and have shown no differences between regularity of menstrual cycles, pregnancy rates, and live births compared to a normal population. However, a few studies have suggested a higher prevalence (32% vs. 10%) of PCOS.

The majority of children with sexual precocity have few significant behavioral problems, but emotional support is important for these children. **Behavioral expectations by family members and teachers should be based on the child's chronologic age, which determines psychosocial development, and not on the presence of secondary sexual characteristics.**

Delayed Puberty

Although there is wide variation in normal pubertal development, the vast majority of girls in the United States begin pubertal maturation by the age of 13 years. **If thelarche does not occur by age 14 years, an evaluation is required.** A physiologic delay in the onset of puberty occurs in only 10% of girls with delayed puberty, and exclusion of other diagnoses is necessary. **Physiologic delay in puberty tends to be familial.** A careful history must be taken, with special attention to the patient's past general health, height, dietary habits, and exercise patterns. Details about the pubertal development of the patient's siblings and parents should be obtained. Box 32-3 lists tests that should be performed to evaluate girls with delayed puberty.

BOX 32-3

RADIOLOGIC AND LABORATORY TESTS USED TO EVALUATE FEMALE DELAYED PUBERTY

Radiologic

Magnetic resonance imaging or computed tomography of the brain with optimal visualization of hypothalamic region and sella turcica (hypogonadotropic hypogonadism)

Laboratory

Follicle-stimulating hormone
Karyotype (delayed puberty, ambiguous genitalia)
Progesterone (delayed puberty secondary to 17-hydroxylase [P450c17] deficiency)
Prolactin (hypogonadotropic hypogonadism)

In general, the causes of delayed onset of puberty can be subdivided into two categories: hypogonadotropic hypogonadism and hypergonadotropic hypogonadism. Disorders resulting in hypogonadotropic hypogonadism that may cause primary or secondary amenorrhea are discussed in Chapter 33. Of note, **anorexia nervosa,** which **can result in hypogonadotropic hypogonadism** and delayed puberty, can affect 0.5-1.0% of young women. It is important to recognize this disorder in the evaluation of these patients. **Chromosomal abnormalities or injury to the ovaries by surgery, chemotherapy, or radiation may cause hypergonadotropic hypogonadism.** When the patient's abnormal karyotype includes the presence of a Y chromosome or the *SRY* gene in the sex-determining region, gonadectomy is recommended to prevent potential malignant neoplastic transformation.

A growing list of single-gene disorders resulting in delayed or absent female puberty is being documented in the literature.

Turner syndrome affects approximately 1 in 2500 live-born females and is characterized by loss or structural anomalies of an X chromosome. Its clinical features vary, and multiple organ systems may be affected. Often these patients present with hypergonadotropic hypogonadism and clinical features such as short stature and infertility.

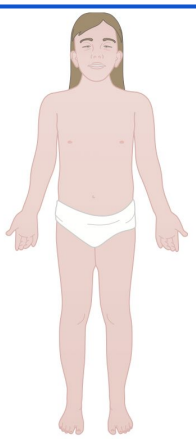


FIGURE 32-6 Kallmann syndrome is a genetic condition that results in hypogonadotropic hypogonadism caused by a defect in gonadotropin-releasing hormone (GnRH) production and release from the hypothalamus. Because the area in the hypothalamus where GnRH is produced is near the olfactory center, the sense of smell is usually affected, resulting in anosmia.

Kallmann syndrome (Figure 32-6) presents with hypogonadotropic hypogonadism and anosmia/hyposmia. It may result from a mutation of the *KAL* gene on the X chromosome or from autosomal mutations that prevent the embryologic migration of GnRH neurons into the hypothalamus. Individuals with this syndrome may have other anomalies of midline structures of the head. One in 50,000 females is affected.

Mutations of the GnRH receptor gene in females have resulted in low gonadotropin levels with primary amenorrhea or delayed puberty.

Mutations of the FSH β-subunit gene and the **FSH receptor gene** have been associated with primary amenorrhea and varying degrees of incomplete development of secondary sexual characteristics.

Females with **aromatase deficiency** present at puberty with progressive virilization, absence of thelarche, and primary amenorrhea.

17-Hydroxylase (P450c17) deficiency interferes with production of the androgenic and estrogenic steroids, resulting in deficient or absent pubertal development. The accumulation of progesterone before the block leads to excessive synthesis of the mineralocorticoid 11-deoxycorticosterone, which generally causes hypertension and hypokalemia.

Mutations of leptin and leptin receptor gene are associated with retarded pubertal development and childhood morbid obesity.

Mutations in the steroidogenic acute regulatory *(StAR)* gene result in complete loss of adrenal steroidogenesis and delayed puberty, which is called ***congenital lipoid adrenal hyperplasia.*** The StAR protein is necessary for the transportation of cholesterol from the outer mitochondrial membrane to the inner mitochondrial membrane, which is the rate-limiting step in steroidogenesis.

Adolescents who present with permanent hypoestrogenism require estrogen therapy to complete the development of secondary sexual characteristics. Hormone therapy with estrogen plus a progestin or with a low-dose oral contraceptive after establishment of secondary sexual characteristics is required to avoid menopausal symptoms and to prevent osteoporosis. To further optimize gradual bone mineral deposition, 1500 mg of elemental calcium and 400 mg of vitamin D daily are recommended. This should be combined with regular weight-bearing exercises.

Polycystic Ovarian Syndrome and Puberty

PCOS is the leading cause of female anovulatory infertility and is characterized by ovulatory dysfunction and hyperandrogenism. It is associated with obesity, insulin resistance, and metabolic dysfunction (see Chapter 33). During the transition from adrenarche/pubarche (adrenal androgen production dominance) to menarche, a relatively similar imbalance of hormones leads to irregular menses, polycystic ovaries, and a relative androgen excess. Because of these similar clinical findings, the diagnosis of PCOS in the adolescent population remains controversial.

Recently, it has been suggested that adolescents with congenital virilization, premature pubarche, or central precocious puberty are at higher risk of developing PCOS. **There is growing support for using a modified Rotterdam system to make a diagnosis of PCOS in adolescents.** This requires the presence of all three of the following criteria (rather than the standard two of three criteria): **oligo-ovulation or anovulation, hyperandrogenism, and polycystic ovaries visualized by pelvic ultrasonography.** Adolescent PCOS is associated with metabolic syndrome and sleep disorders, and treatment should include lifestyle modification. Other treatments commonly used to treat PCOS in an older population have not been studied thoroughly in adolescents.

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