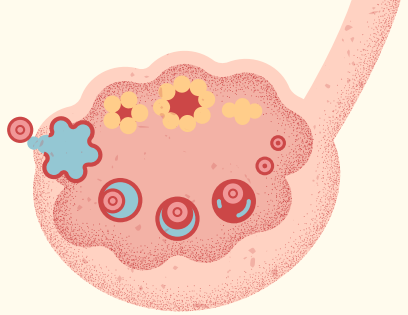

Puberty and it's complications

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1. Puberty: Definition and Normal Physiology

• Definition:

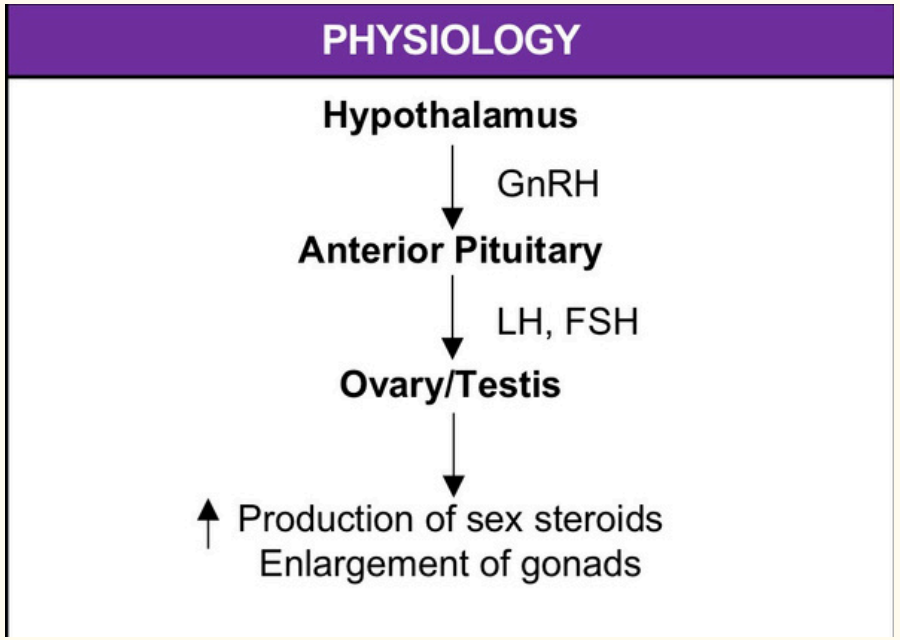
- A phase of development between childhood and complete, functional maturation of the reproductive glands and external genitalia (adulthood).
- **For females**, the normal age of onset : 8-13 years (average 11 years).
- **For males**, the normal age of onset : 9-14 years (average 13 years).
- This period is characterized by ;
- the maturation of the Hypothalamic-pituitary-gonadal axis as it is tightly regulated by a negative feedback mechanism
- Appearance of secondary sexual characteristic
- Acceleration of growth
- Capacity for fertilization
- Psychosocial changes

• Phases of puberty:

- The age of pubertal onset may vary,but the order of changes that occur in each person is consistent.
- **Adrenarche:** activation of adrenal androgen production (axillary andpubic hair, body odor,andacne).
- **Gonadarche:** activation of reproductive glands by the pituitary hormones FSH and LH.
- **Thelarche:** onset of breast development.
- **Pubarche:** onset of pubic hair growth.
- **Menarche:**onset of menstrual bleeding.

• Physiology:

- Unknown initial trigger →↑ activators and/or↓ inhibitors of GnRH secretion
- →**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**.



• Puberty in females:

- **Normal age of onset: 8–13 years (average 11 years)**
- Normal order of changes:

adrenarche(The initial endocrine change in puberty)→ **gonadarche**→ **thelarche** (age of onset 8–11 years a

the first physical sign of puberty)→ **growth spurt** (age of onset 11.5–16.5 years)→ **pubarche** (mean age of

onset 12 years)→ **menarche** (age of onset 10–16 years, mean age: 13 years).

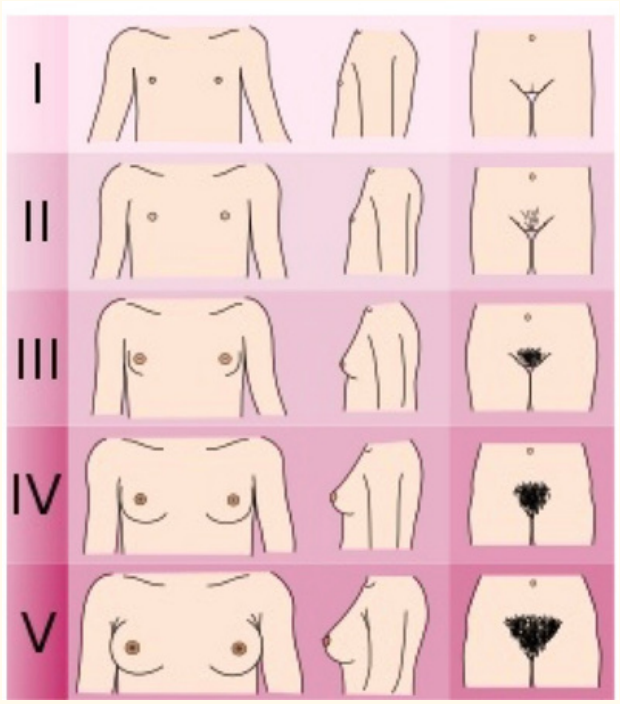
- **Influential factors of puberty :**
- General health (nutritional state, bodyweight).
- Genetics.
- Social environment(e.g., family stress).

• Physical changes during puberty:

- **Sexual maturity rating (Tanner staging):**

A scale used to assess the development and progression of secondary sexual characteristics

- Breast development (girls)
- Genital development (boys)
- Pubic hair (boys and girls)



Sexual maturity ratings in girls [13][3][1]		
Sexual maturity rating	**Breast development (B1–B5)**	**Pubic hair development (Ph1–Ph5)**
1	• Prepubertal appearance	• Prepubertal (usually no pubic hair)
2	• Enlarged mammary glands form a subareolar breast bud. • Slight increase in areolar diameter; nipple protrusion	• Sparse, lightly pigmented hair (straight or curled) on the labia
3	• Further enlargement of mammary glands • Breast bud extends beyond the areolar diameter	• Dark, coarse, curly hair spreading over the pubic symphysis
4	• Nipple and areola form a secondary mound, which projects above the breast tissue	• Adult pubic hair that does not extend to the inner thighs
5	• Adult breast • Areola with projection of nipple only	• Adult pubic hair extending to the inner thighs with horizontal upper border

• Physical changes during puberty:

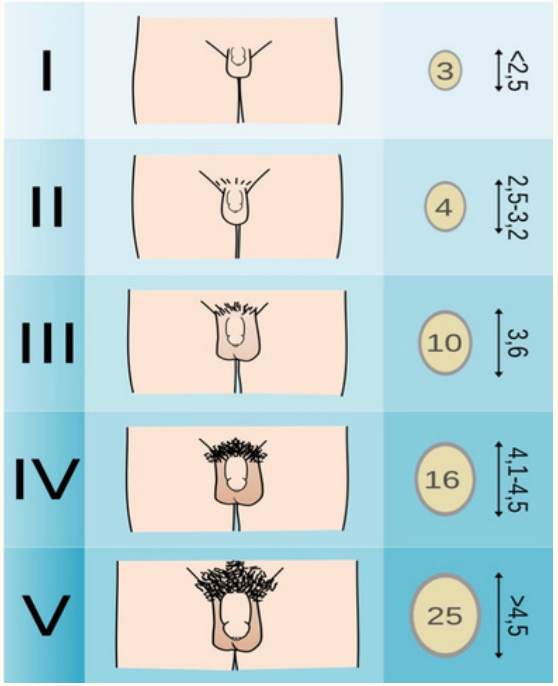
- **Sexual maturity rating (Tanner staging):**

A scale used to assess the development and progression of secondary sexual characteristics

- Breast development (girls)
- Genital development (boys)
- Pubic hair (boys and girls)

Sexual maturity ratings in boys [13][3][1]

Sexual maturity rating	Genital development (G1–G5)	Pubic hair development (Ph1–Ph6)
1	• Prepubertal appearance and size of the testes, scrotum, and penis	• Prepubertal (usually no pubic hair)
2	• Testicular volume 4–5 mL and length ≥ 2.5 cm • Increase in scrotal size • Penile growth has not begun • Scrotal skin reddens [8]	• Sparse, lightly pigmented hair (straight or curled) on the base of the penis
3	• Continued enlargement of the testes and scrotum • Penile growth begins	• Dark, coarse, curly hair spreading over the pubic symphysis
4	• Continued enlargement of the testes • Continued scrotal enlargement and darkening • Increase in penile growth and diameter • Development of glans penis	• Adult pubic hair that does not extend to the inner thighs
5	• Testes, scrotum, and penis attain adult appearance and proportions	• Adult pubic hair extending to the inner thighs
6 (pubic hair only)	• N/A	• Further growth of pubic hair along linea alba in the direction of the umbilicus [5]



• Physical changes during puberty:

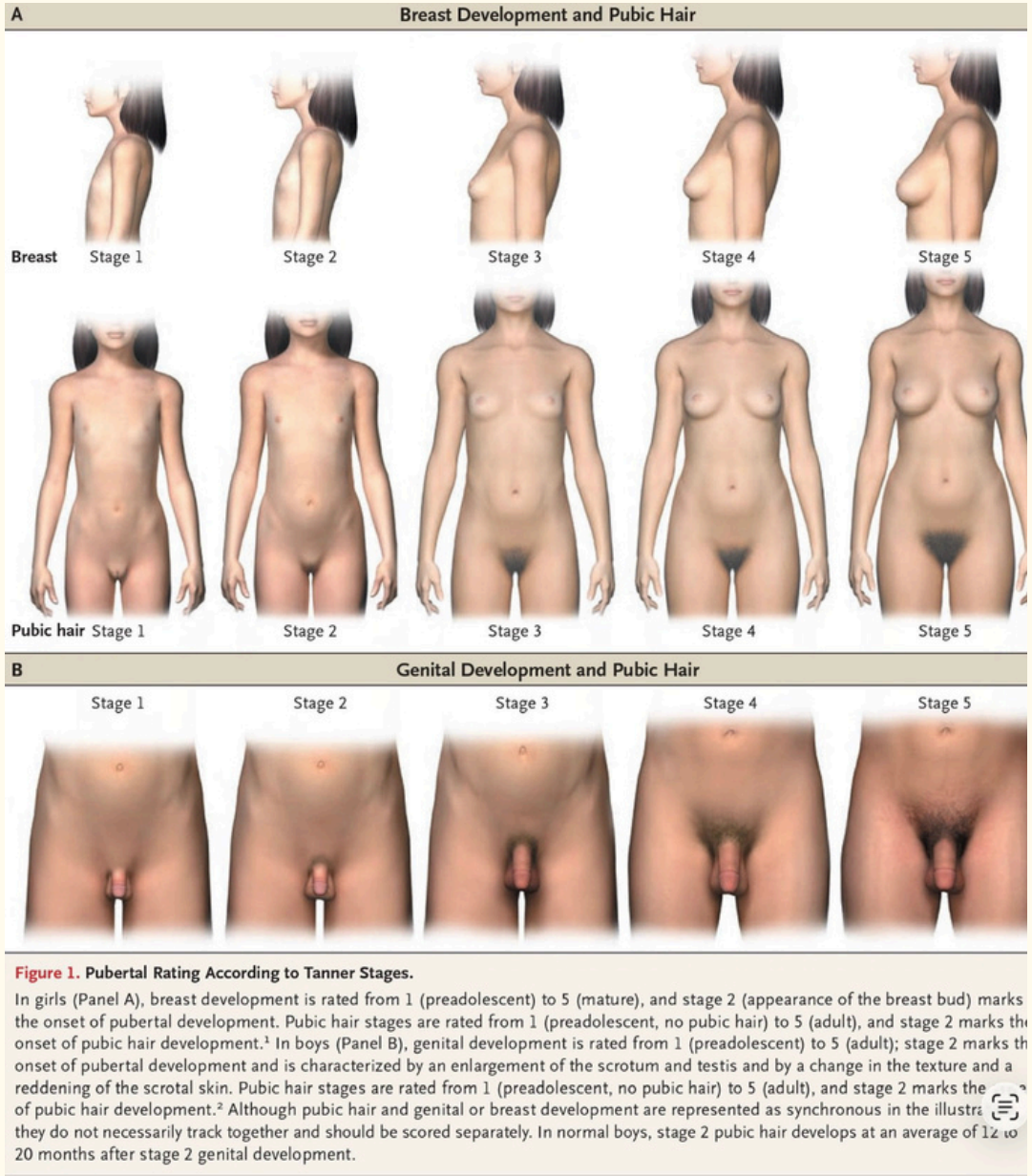
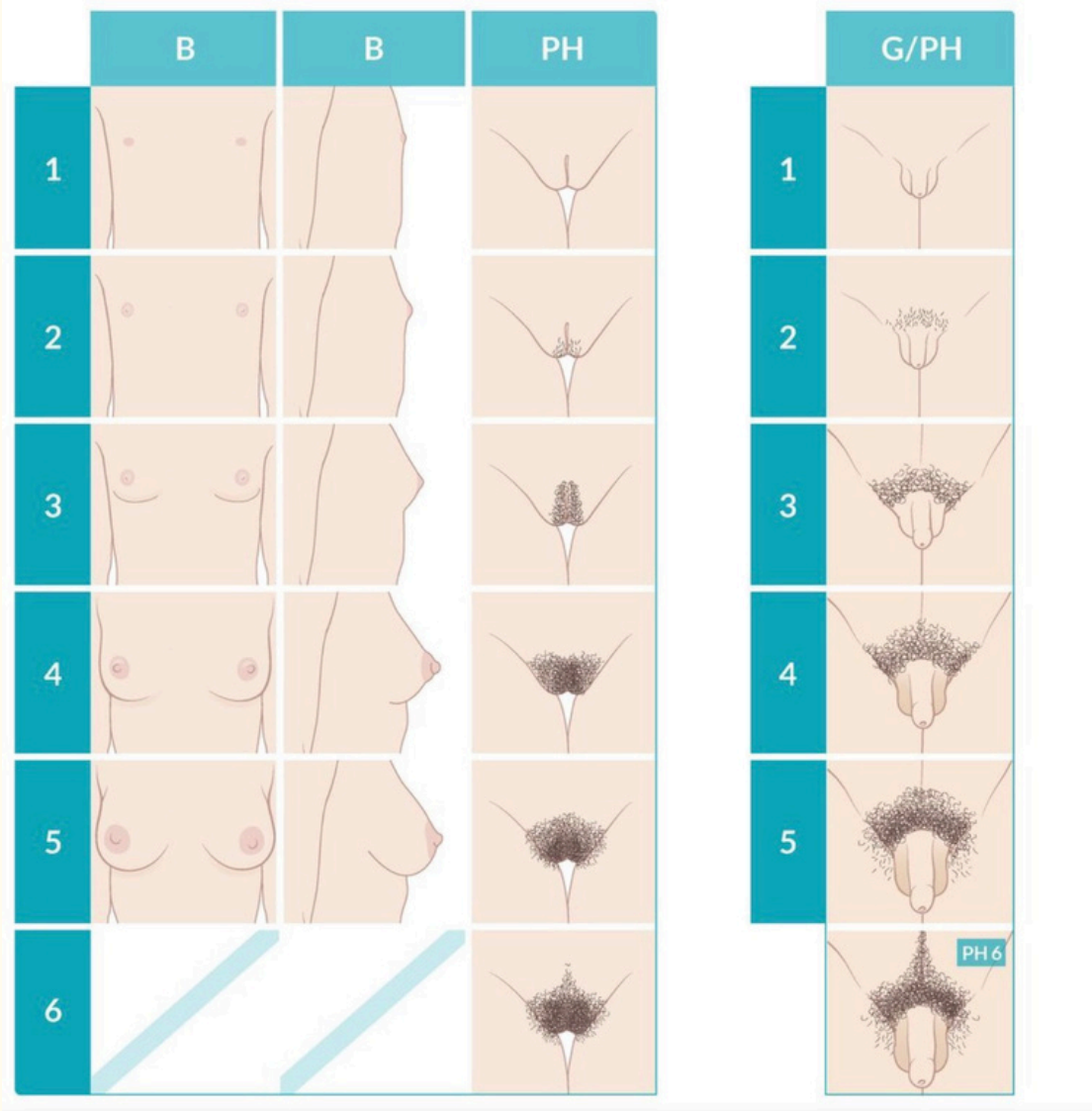


Figure 1. Pubertal Rating According to Tanner Stages.

In girls (Panel A), breast development is rated from 1 (preadolescent) to 5 (mature), and stage 2 (appearance of the breast bud) marks the onset of pubertal development. Pubic hair stages are rated from 1 (preadolescent, no pubic hair) to 5 (adult), and stage 2 marks th onset of pubic hair development.[1] In boys (Panel B), genital development is rated from 1 (preadolescent) to 5 (adult); stage 2 marks th onset of pubertal development and is characterized by an enlargement of the scrotum and testis and by a change in the texture and a reddening of the scrotal skin. Pubic hair stages are rated from 1 (preadolescent, no pubic hair) to 5 (adult), and stage 2 marks the of pubic hair development.[2] Although pubic hair and genital or breast development are represented as synchronous in the illustra they do not necessarily track together and should be scored separately. In normal boys, stage 2 pubic hair develops at an average of 12 to 20 months after stage 2 genital development.



• other morphological changes during Puberty:

- **Growth Spurt :**

• Linear growth during adolescence ≈ 5 cm/year from age 4 until puberty.

• Varies between sexes:

• Generally occurs between 13–15 years

• **In girls:** may begin 2 years earlier

- Characteristics Includes:
  - ↑ growth in trunk and limbs
- Assessed using:
  - Growth velocity chart
- **Duration**
- Lasts about 2 years
- Completion:
- Girls: ~15 years
- Boys: ~17 years

- **Bone Growth:**
- **Features** : Accelerated during puberty
- **Hormonal Control Determined by:**

• Testosterone

• Estrogen

• IGF-1

• Calcitriol

• Growth hormone (GH)

- **Order of Growth**

1. ↑ Length
2. ↑ Width
3. ↑ Mineral content
4. ↑ Density

• other morphological changes during Puberty:

- **Body weight and composition during adolescence:**
- **Boys:** initial↓ body fat (early puberty) →↑ lean body mass (late puberty)
- **Girls:** gradual increase in body fat
- Affected by nutritional status
- **Dermatological changes:**
- Acne vulgaris,hyperhidrosis, and hair problems (e.g.,seborrheic dermatitis).
- Activation of the adrenal cortex→pubertal hormonal fluctuation →↑sebum secretion and excessive sweating →skin and hair changes.

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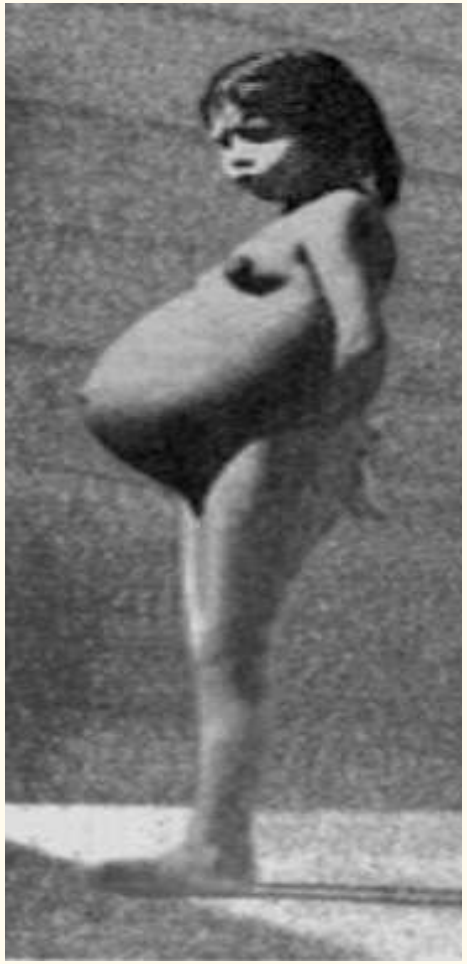


2. Precocious Puberty

What is 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.

• Classification:

- **Central (True) precocious puberty** (gonadotropin-dependent).
- **Peripheral (Pseudo) precocious puberty** (gonadotropin-independent).
- **Benign / non-progressive pubertal variants.**

- GABA and Neuropeptide Y (NPY): are inhibitory signals in the brain.
- Glutamate and kisspeptin: are excitatory signals in the brain.

    - Before normal puberty:
    - GABA + NPY = HIGH

    → They inhibit the hypothalamus

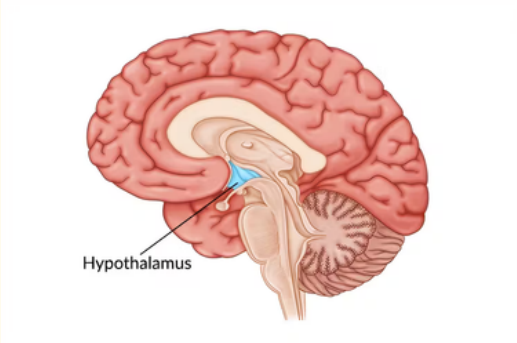
    → No GnRH release

    → No activation of puberty

- **In Central Precocious Puberty (CPP):**

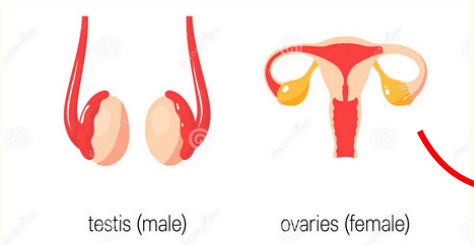
- GABA + NPY = LOW / inactive

- Hypothalamus becomes active early.



- ↑ **GnRH secretion.**

- ↑ **LH & FSH.**



- **Puberty starts early.**
- **Sex hormones.**

- Early activation of GnRH neurons
- → Premature activation of the HPG axis
- causes:
- Idiopathic CNS lesion.
- Genetics(MRF3,KISS 1)
- Others

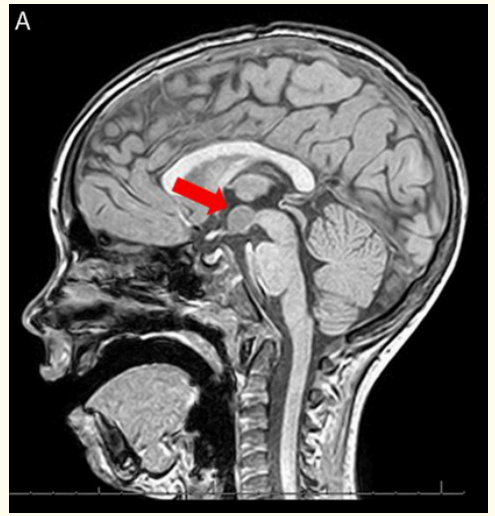
• Central Precocious Puberty (CPP):

Etiology:

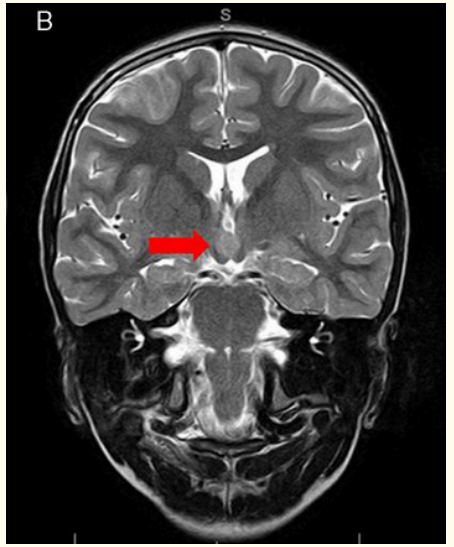
- Idiopathic (most common).
- CNS lesions : Intracranial tumors (e.g., hypothalamic hamartoma, glioma, craniopharyngioma,Hydrocephalus).
- Trauma.
- Infections (e.g., encephalitis, meningitis).
- Radiation.
- Genetics (MRF3 , KISS1).
- internationally adopted children.
- Familial precocious puberty.
- Syndromes (Neurofibromatosis type 1, Sturge Weber syndrome).

• Central Precocious Puberty (CPP):

• Hypothalamic Hamartoma (HH):



- **Definition:** is a benign (noncancerous) tumor-like growth in hypothalamus.
- The ectopic neural cells in the lesion serve as an accessory GnRH pulse generator.
- It presents with precocious puberty in infancy as early as 12 months of age.
- The most common brain lesion causing CPP is hypothalamic hamartoma.
- **clinical features:**
- The most characteristic association is gelastic seizures(focal or partial seizures with bouts of uncontrolled laughing or giggling) which are usually refractory to medications.
- The other associated features include cognitive, behavioral, and psychiatric symptoms.

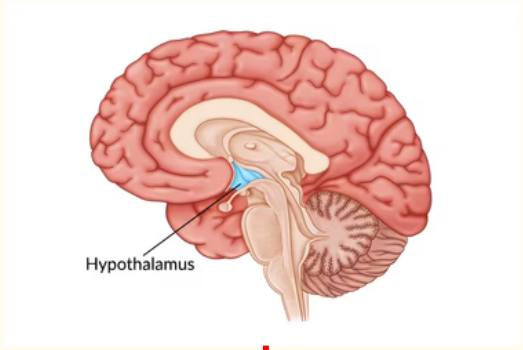


• Management:

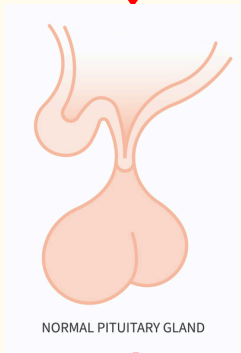
Central Precocious Puberty (CPP, GnRH-dependent)

- Treatment: Continuous GnRH agonists
- Examples: leuprolide, buserelin, goserelin
- Follow-up: Every 4–6 months to assess progression
- Manage underlying cause.

- **In Peripheral Precocious Puberty (CPP):**



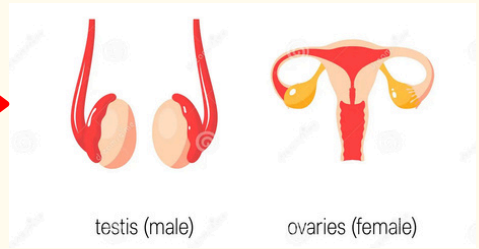
- **GnRH secretion.**



- **LH & FSH.**

- **Normal or low**

- Sex steroid increased
- Exogenous steroids
- McCune-Albright syndrome
- Congenital adrenal hyperplasia
- Others



- **Sex hormones.**
- **↑estrogen and ↑testosterone.**

• Peripheral Precocious Puberty (PPP):

Etiology:

- ↑ **Androgen:** Congenital adrenal hyperplasia ,Virilizing ovarian and adrenal tumors.
- ↑ **estrogen production**: McCune-Albright syndrome, HCG- secreting germ cell tumors (e.g., dysgerminomas) , Ovarian tumor (e.g. granulosa cell tumor).
- **Exogenous steroids**
- **Primary hypothyroidism.**

• Pubertal Variants (Non-Progressive / Benign):

- **Premature Thelarche:** premature unilateral or bilateral development of the breast tissue in girls between the age of 12 to 24 months.
- **Premature Adrenarche :**It presents with pubic or axillary hair, body odor, or acne before the age of 8 years.
- **Premature menarche:**Isolated premature menarche is the onset of vaginal bleeding in girls less than 7 years of age., Sexual abuse, vaginal foreign body, and infections of the vulva and vagina need to be ruled out.

• EVALUATION:

1. history:

- Age of onset of pubertal signs.
- Rate of progression (rapid = more concerning).
- Family history of early puberty.
- Growth history – Any growth spurts?
- Any relevant history of head trauma, brain infections
- Neurological symptoms – Headaches, visual disturbances → Possible CNS involvement.
- Medication history – Use of exogenous hormones, steroids, or endocrine disruptor

2. PHYSICAL EXAMINATION:

- Café-au-lait spots → Suggests McCune-Albright Syndrome, Neurofibromatosis type 1
- Acne and oily skin → Suggests androgen excess from adrenal or gonadal sources.
- Hyperpigmentation → May indicate adrenal disorders (e.g., congenital adrenal hyperplasia).
- Hirsutism (excess facial/body hair in girls) → Suggests androgen excess (ovarian/adrenal tumor or CAH).

• EVALUATION:

3. imaging:

- wrist x ray bone age it is an initial screening test. If the bone age is advanced (greater than two standard deviations) than the chronologic age, further testing should follow.
- MRI is to be performed in all cases of CPP.
- Pelvic ultrasonography , in cases of PPP, detects ovarian tumors or cysts in females.

4. Labs:

Test	CPP (Central	PPP (Peripheral)
LH and FSH	high	low or normal
estrogen	high	high
GnRH stimulation test TSH	high LH	Low LH
T4	normal	high TSH, low T4 in primary hypothyroidism
DHEA-S	normal	High in CAH

• Management:

Peripheral Precocious Puberty (GnRH-independent)

Goal: Eliminate the source of sex steroids

Treatment based on cause:

- Gonadal or adrenal tumors → Surgery
- Classic Congenital Adrenal Hyperplasia (CAH) → Glucocorticoids
- McCune-Albright Syndrome (MAS) →

Aromatase inhibitors to block estrogen synthesis (e.g., anastrozole, letrozole)

Selective estrogen receptor modulators (e.g., tamoxifen)

- Familial male-limited precocious puberty →Androgen antagonist (spironolactone) + aromatase inhibitor (anastrozole, testolactone)
- Optimal treatment not fully established.

• Central vs Peripheral Precocious Puberty:

Aspect	Central Precocious Puberty (CPP)	Peripheral Precocious Puberty (PPP)
Definition	Increase GnRH (early activation of HPG axis)	increase Sex steroids from gonads/adrenal/exogenous
LH / FSH	Increased	Decreased
Estrogen / Androgen	Increased	Increased
Sexual Development	Present	Present
Reproductive Development	present	absent

3. Delayed Puberty

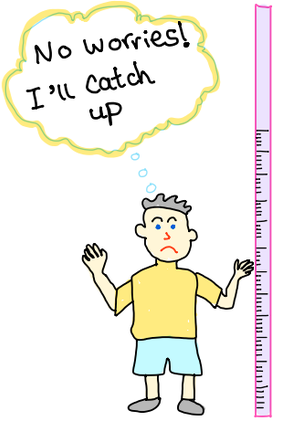
• **Delayed Puberty :-** The absence or incomplete development of secondary sexual characteristics beyond the expected age range (12 in girls , 15 in boys).

* Causes :-

Most common.

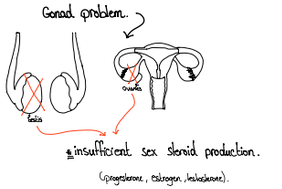
① physiological delay (Constitutional delay).

- Likely genetic cause ⇝ A family history of similar pubertal delays.
- Delayed puberty occurs due to delay in pulsatile hypothalamic GnRH release.
- Don't cause infertility.
- Don't require treatment.



pathological delay.

- Primary Hypogonadism (Hypergonadotropic Hypogonadism)



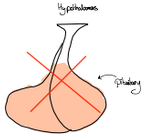
* A Condition in which the gonads (ovaries / testes) fail to function properly, resulting in :-
① ↓ sex steroid production (estrogen & progesterone, testosterone).
② ↑ FSH & LH due to lack of negative feedback.

* Causes :-

Congenital
- Turner syndrome.
- Klinefelter syndrome.

Aquired
- Following Chemotherapy or radiotherapy for childhood Cancer.
- trauma to the gonads.

- Secondary Hypogonadism (Hypogonadotropic Hypogonadism)



* A Condition of decreased gonadal function due to a disease that primarily affects the pituitary gland & or Hypothalamus.
• Characterized by :-
① ↓ Concentrations of pituitary gonadotropins (FSH & LH).
② ↓ Concentrations of sex hormones (estrogen , progesterone, testosterone).

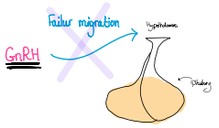
* Causes :-

Congenital
- Panhypopituitarism.
- Kallmann syndrome.

Aquired
- Chemotherapy or radiotherapy
- General ⇝ Any stress ↑ Cortisol production which ↓ sensitivity pituitary to the GnRH
- Tumors ⇝ prolactinoma , Craniopharyngioma.

• KALLMANN syndrome :-

defective migration of GnRH cells.



↓↓ GnRH in the hypothalamus

↓↓ GnRH

↓↓ FSH / LH

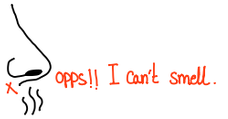
↓↓ Sex hormones.

♂ → ↓ Testosterone → ↓ Sperm count

♀ → ↓ estrogen & ↓ progesteron → Amenorrhea

defective formation of olfactory bulb.

Anosmia



± KALLMANN syndrome :- ⇝ Hypogonadotropic hypogonadism associated with anosmia.

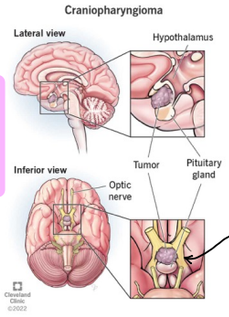
- Normal height.
- Infantile ⇝ The external & internal genital organs are structurally normal but they have not matured to the pubertal stage.
- Normal pituitary & hypothalamus in MRI.
- Genetics
  - X-linked (KAL gene)
  - Autosomal mutations
- Treatment ⇝ Hormone replacement therapy (HRT).

• Craniopharyngioma :-

Benign tumor arising from remnants of (Rathke's pouch)

The embryological precursor of the anterior pituitary gland.

- Most common supratentorial tumor in children.



Typically in the suprasellar region may extend into the intrasellar region.

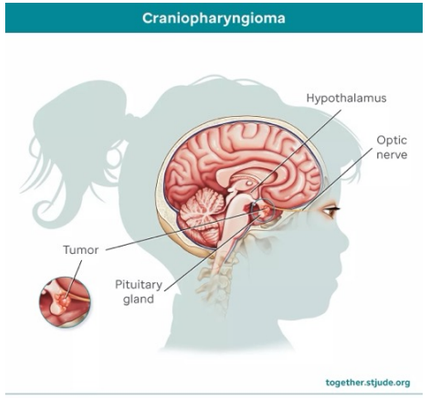
• Clinical features :-

pituitary symptoms (Hypopituitarism).

- Hypogonadotropic hypogonadism ⇝ delayed puberty
- Growth failure / Failure to thrive ⇝ low GH
- Central diabetes insipidus ⇝ Polyuria, polydipsia

Compression symptoms.

- visual filed defect
- Headache
- Hydrocephalus



• Prolactinoma :-

Tumor

Benign tumor (adenoma) on the pituitary gland that secrets excess prolactin

- Clinical features :-

♀ (Women) :-	♂ (Men) :-
• Amenorrhea (absent periods).	• Gynecomastia (breast enlargment)
• Galactorrhea (milk secretion unrelated to pregnancy).	• ↓ libido
• Infertility	• Infertility.

- Complications :-

① Mass effect (if tumor enlarges) ⇝ Headache, visual loss.

② Hypogonadism ⇝ ↓ estrogen / testosterone ⇝ osteoporosis & fracture.

- Diagnosis :-

① Imaging → MRI or CT ⇝ visualize pituitary adenoma

② Laboratory ⇝ Serum prolatin > 100 ng/ml

- Treatment :-

① Medical (1st line) :-

↳ dopamine agonist (Cabergoline).

② Surgery.

③ Radiation therapy.

• Diagnosis of delayed puberty ♂

1. Clinical assessment ♂

- Compare Sexual development with Tanner scale (stages of puberty).
- Take detailed medical history
  - Chronic illnesses
  - Family history of delayed puberty or genetic disorders.

2. Radiological imaging

- Bone x-ray (hand / wrist).
  - assess skeletal maturation
- pituitary or hypothalamic imaging
  - if central cause suspected.

3. Hormonal evaluation

identify type of Hypogonadism

- Hypogonadotropic (central).
  - ↓ FSH / LH.
- Hypergonadotropic (primary gonadal failure).
  - ↑ FSH / LH.

4. Genetic testing

karyotype analysis (detect Chromosomal genetic abnormalities)

WHAT IS DELAYED PUBERTY?

- Puberty that happens late is called delayed puberty.
- means a child's physical signs of sexual maturity don't appear by age 12 in girls or age14 in boys.
- This includes breast or testicle growth, pubic hair, and voice changes.

CAUSES OF PUBERTY DELAY:

- The causes of delayed onset of puberty can be divided into:
- Pathological delay(Primary & Secondary Hypogonadism)
- Physiological delay (Constitutional delay)

Primary Hypogonadism (Hypergonadotropic Hypogonadism)

- Decrease or absence of sex hormones due to dysfunction in the gonads, despite high gonadotrophins.
- Cells cannot respond to FSH and LH or cells cannot produce hormones.
- The result is a decrease or absence of estrogen and progesterone in females and testosterone in males so NO negative feedback on the hypothalamus, leads to overproduction of LH and FSH.

Causes of Primary Hypogonadism:

- **Congenital:** Turner syndrome, and Klinefelter syndrome.
- **Acquired:** following chemo-or radiotherapy for childhood cancer, or trauma to the gonads.

Secondary Hypogonadism (Hypogonadotropic Hypogonadism)

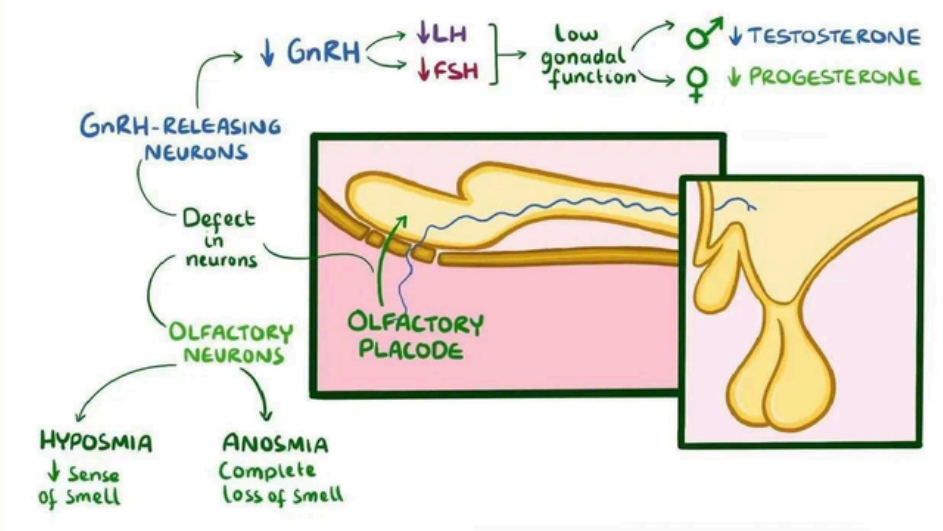
- Defined as Hypothalamus & pituitary dysfunction. So Inability to produce GnRH, LH & FSH,or suppression from other hormones like prolactin &and thyroid hormones.

Causes of secondary Hypogonadism:

- **Congenital:** Kallmann syndrome and Panhypopituitarism.
- **Acquired:** radiotherapy, chemotherapy, trauma
- **General:**anorexia nervosa,excessive exercise,stress(all this increases cortisol production which decreases sensitivity pituitary to the GnRH), Malnutrition, Obesity.
- **Tumors**: prolactinoma, craniopharyngiom

• KALLMANN SYNDROME:

- (Hypogonadotropic hypogonadism + anosmia).



Key Features:

- Normal height.
- Normal internal and external genitalia but remain infantile.
- Loss of sense of smell (anosmia).

Cause:

- Mutation in the KAL gene on the X chromosome or autosomal mutations
- Prevents migration of GnRH neurons to the hypothalamus during embryonic development
- Result: ↓GnRH → ↓LH & ↓FSH → ↓Estrogen/Progesterone (in females) or ↓Testosterone (in males)

KALLMANN SYNDROME:

- (Hypogonadotropic hypogonadism + anosmia).

Diagnosis:

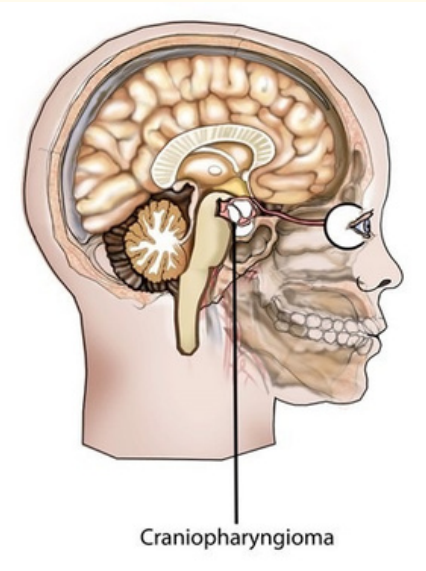
- Hormone levels:
- ↓GnRH,↓LH, ↓FSH,↓Estrogen / ↓Progesterone
- Genetic testing
- Smell test
- MRI: Normal hypothalamus and pituitary

Treatment

- Hormone replacement therapy (HRT).

• CRANIOPHARYNGIOMA:

- A benign tumor arising from a remnant Rathke pouch (embryological origin for anterior pituitary gland)
- Most common childhood supratentorial tumor
- The tumor arises in the suprasellar region and can extend into the intrasellar region.
- (Compression symptoms):
- Compression of the pituitary gland due to intrasellar extension→hypopituitarism (Hypogonadotropic hypogonadism, Failure to thrive, central diabetes insipidus).



• PROLACTINOMA:

- BenignTumor(Adenoma)of the pituitary gland that secretes excess prolactin hormone .
- **Signs & Symptoms:**
- Amenorrhea,Galactorrhea ,Gynecomastia, decrease Libido, infertility.
- **Complications:**

1.Loss of vision &headache (if left untreated aprolactinoma may grow large enough to compress your optic nerve).

2.Osteoporosis & fractures (low level of estrogen Will decrease bone density

- **Diagnosis:**
- CT & MRI
- prolactin serum level >100 ng/mL

- **Treatment:**
- •Pharmacotherapy: dopamine agonists (cabergoline)
- •Surgery
- •Radiation

• CONSTITUTIONAL DELAY:

- Temporary delay puberty (puberty onset and progression can be normal, itonly happens later in age).
- Caused by immature pulsatile release of gonadotrophin-releasing hormone.
- Slow rate of maturation, not pathological.
- Do not cause infertility.
- Typically, genetic components (run in the family).
- Do not require treatment.

• DIAGNOSIS OF DELAYED PUBERTY:

- Comparing the individualized sexual development with Tanner scale.
- Detailed medical history(underlyingmedical illness andfamily history).
- Radiological image .
- Hormone test(Typeof Hypogonadism).
- Karyotype(to examine chromosomes,identify genetic problems).

Thanks