

# Puberty and pubertal disorders

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# Definition

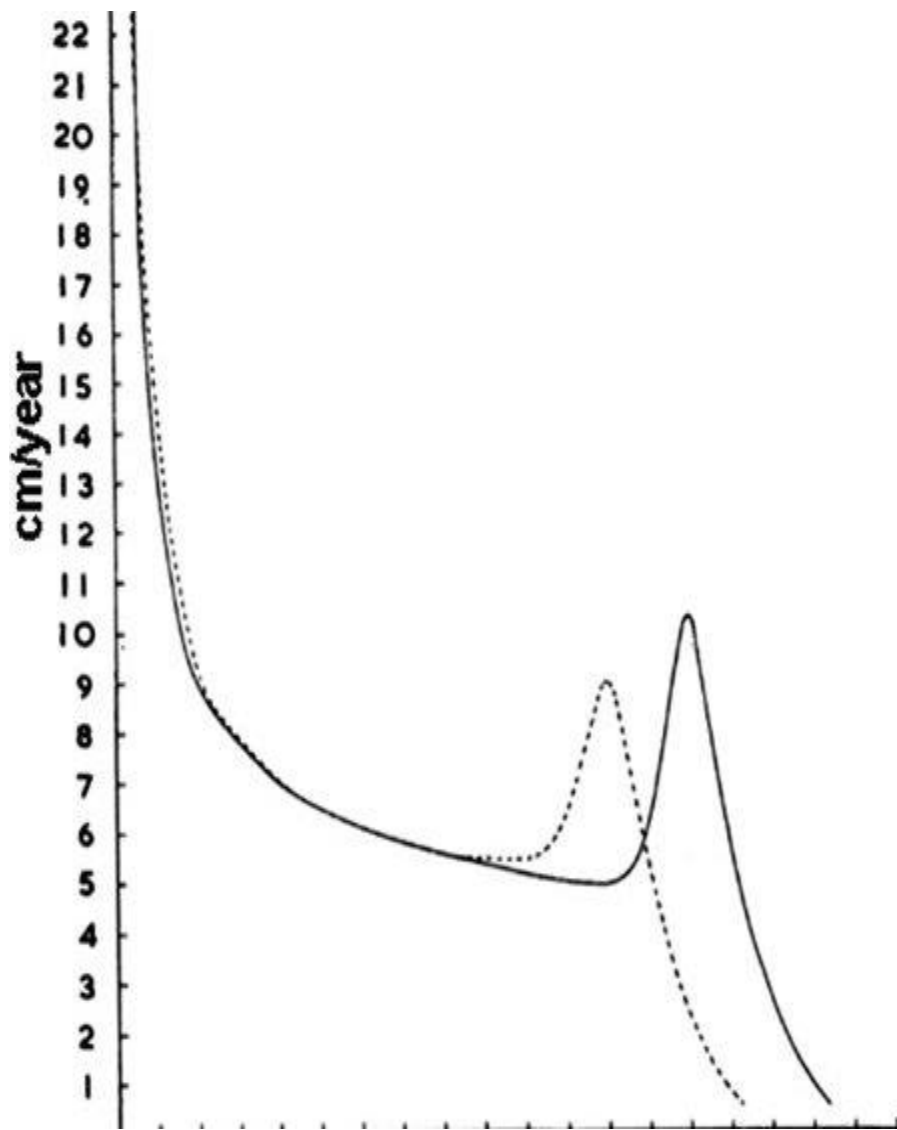
- Refers to the process of physical changes by which a child's body becomes an adult body capable of reproduction, it takes around 2 years to be completed .
- Transitional stage from sexual immaturity to maturity manifested by physiological **changes & development of SSC.**, statural growth , brain , and cardiovascular system development which would be variable in the start point and the end point .

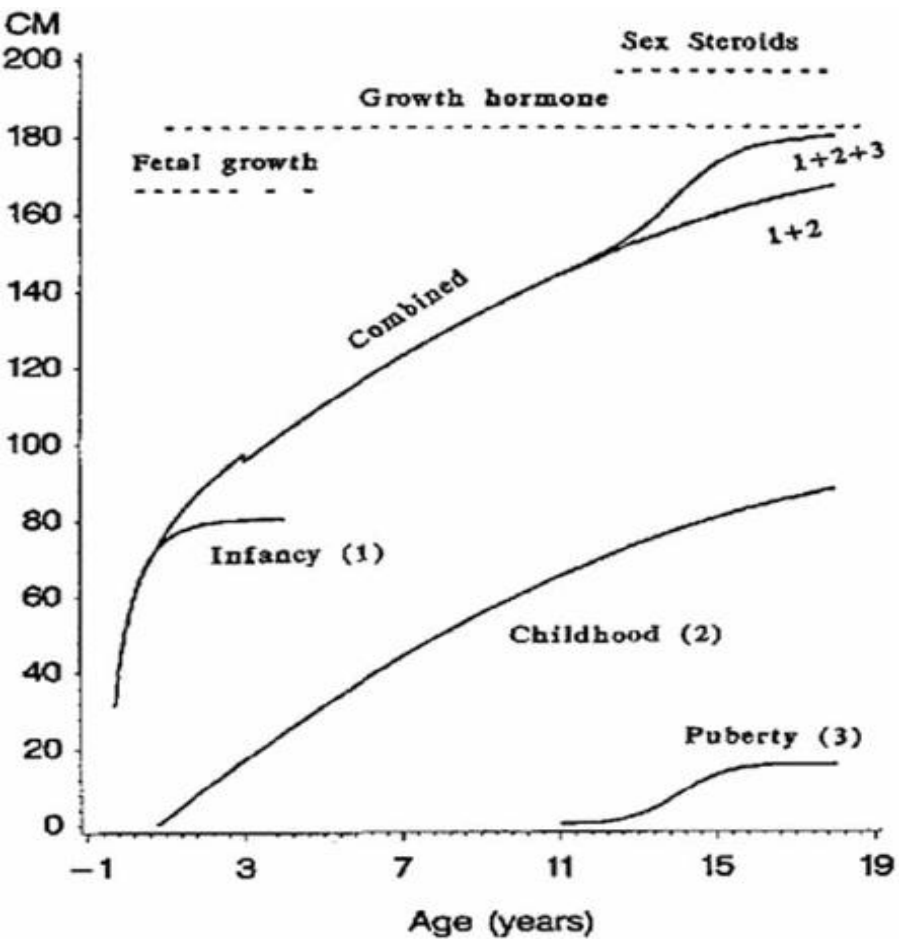
The normal age of puberty :

1- in male : about 9-14 years, testicular enlargement

2- in female : about 8-13 years, variable range , breast bud

- **Menarche**  
the first menstrual period; the establishment of menstruation usually without ovulation.
- **thelarche:**  
the beginning of development of the breasts in the female due to the effect of estradiol.
- **Pubarche:**  
The onset of puberty, particularly as manifested by the appearance of pubic hair, controlled by the adrenal glands
- **Adrenarche** is the term for the maturational increase in adrenal androgen production → appearance of pubic hair, axillary hair, acne, adult type body odor or oily hair.





Its important to integrate the pubertal phase with any complaint of short stature or when the assessment of the height is necessary , because of the growth spurt that will happen during the pubertal phase

The pubertal phase is characterized by a growth spurt of 8 to 14 cm per year due to the synergistic effects of increasing gonadal steroids and growth hormone

growth

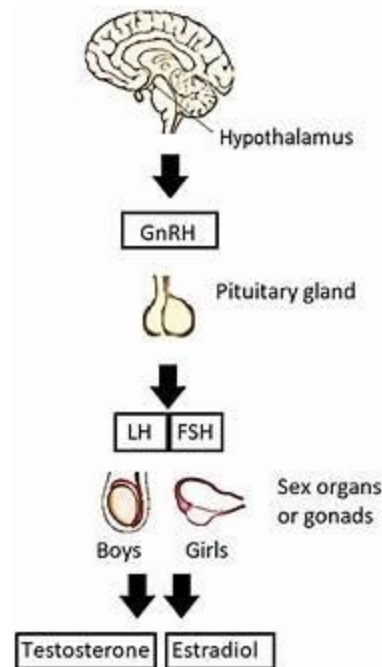
Average difference between male and female height about 12-14 cm

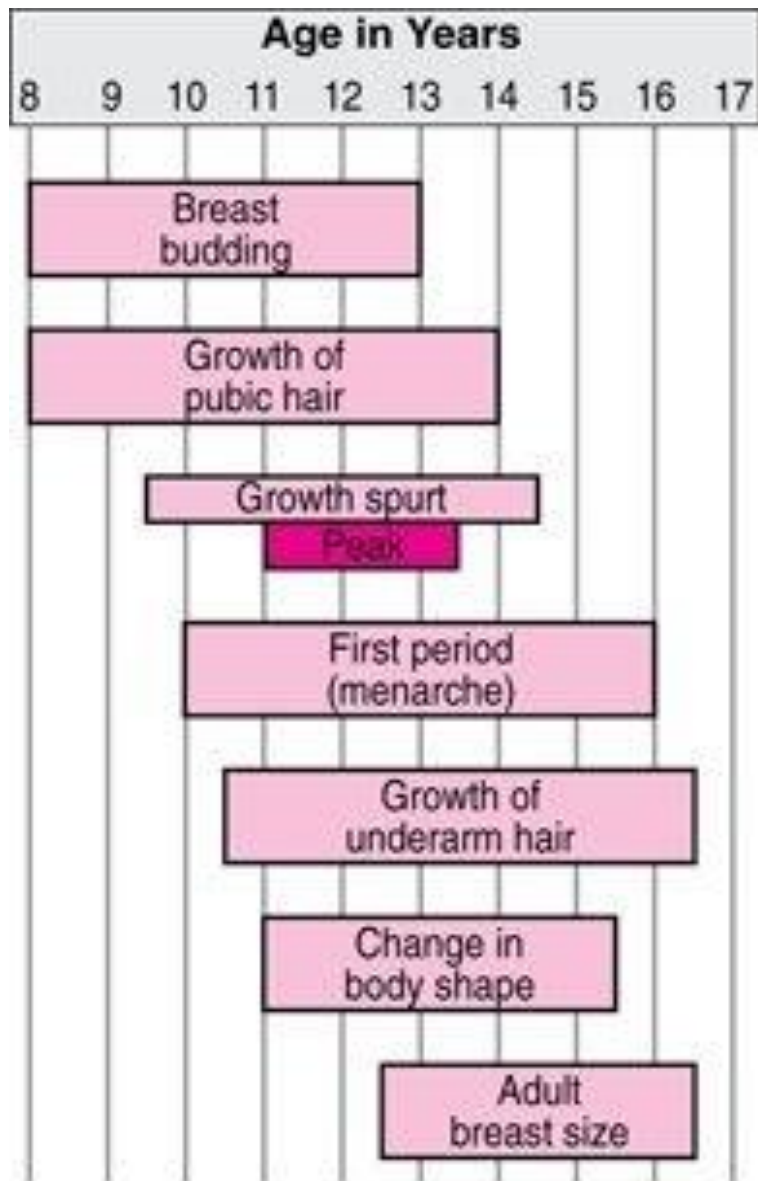
What happened in puberty, high level estrogen will cause the closure of epiphysis

- A simple description of hormonal puberty is :

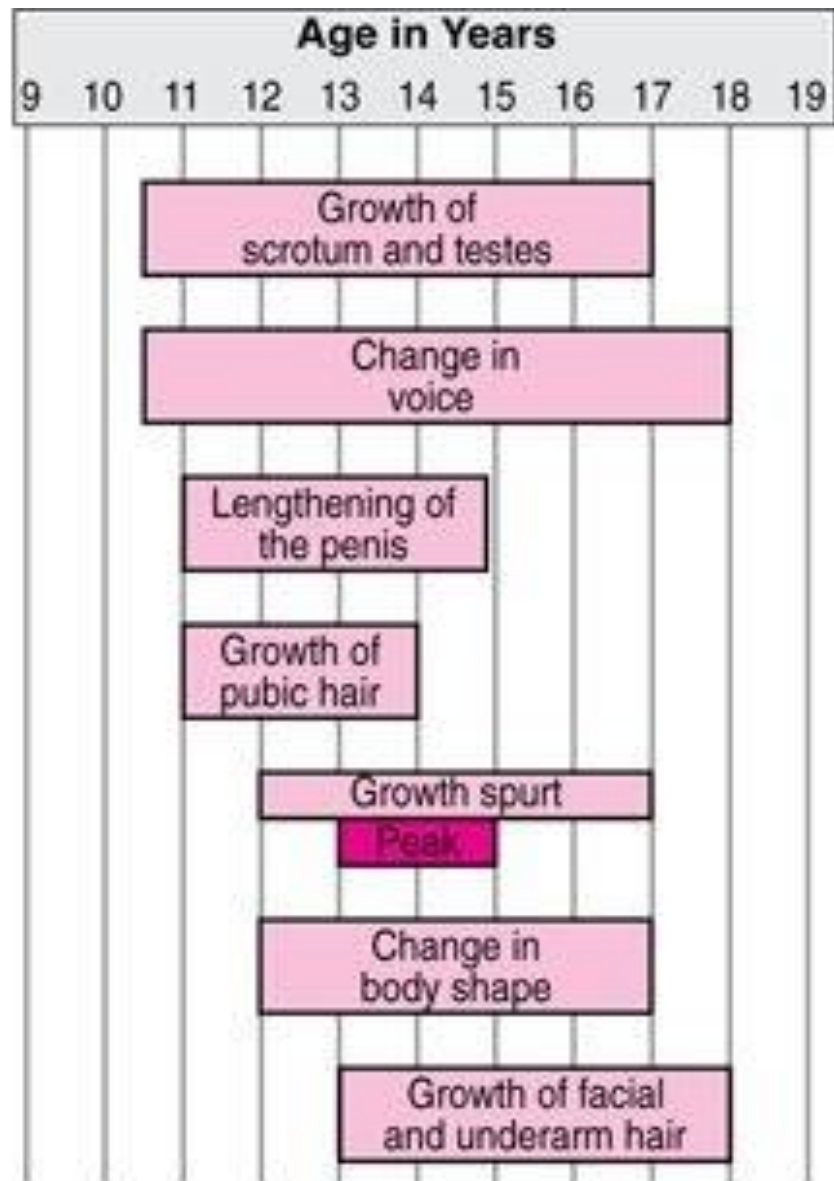
The hypothalamic-pituitary-gonadal axis is biologically active in utero and briefly during the first week of life. It then becomes more active again during infancy, with peak activity between one and three months of age ..mini –puberty

- Between early childhood and approximately 8-9 yr of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant\*active suppression\*, as reflected by undetectable serum (LH) and sex hormones (estradiol in girls, testosterone in boys. >> serum level of LH increases during sleep >>episodic discharge of GnRH(disinhibition of the axis )
- The [ovaries](#) or [testes](#) respond to the rising amounts of LH and FSH by growing and beginning to produce [estradiol](#) and [testosterone](#)
- Estrogen cause epiphyseal closure and can mediate the increased production of growth hormone, which along with a direct effect of sex steroids on bone growth, is responsible for the pubertal growth spurt





**Girls**



**Boys**

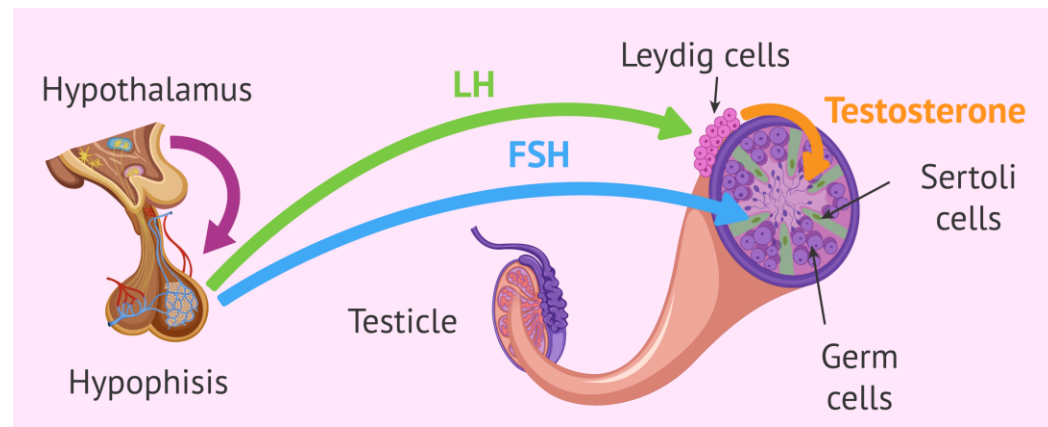
***Physical changes in males  
(secondary sexual characteristics)***



# 1-Testicular size, function, and fertility

- In boys, testicular enlargement is the first physical sign of puberty (more than 4 ml in size and 2.5 cm in length )
- Testes in prepubertal boys change little in size from about 1 year of age to the onset of puberty, averaging about 2–3 cc in volume and about 1.5-2 cm in length.
- Testicular size continue to increase throughout puberty, reaching maximal adult size about 6 years later.
- While 18-20 cc is an average adult size, there is wide variation in the normal population

- The testes have two primary functions:
  - 1- to produce hormones, by Leydig cells
  - 2- to produce sperms, by Sertoli cells.
- The Leydig cells produce testosterone , which in turn produces most of the changes of male sexual maturation and maintains libido , Testosterone modulates LH secretion
- However, most of the increasing bulk of testicular tissue is spermatogenic tissue..
- Inhibin B produced by the Sertoli cells exerts a negative feedback effect on FSH secretion.
- Sperm can be detected in the morning urine of most boys after the first year of pubertal changes
- Potential fertility is reached at about 13 years old in boys, but full fertility will not be gained until 14-16 years of age.



# Orchidometer

Testicular size beads



## 2-Pubic hair

Pubic hair often appears shortly after the genitalia begin to grow..

the hair growing continue till it spread the thighs and upward towards the umbilicus as part of the developing abdominal hair.

## 3-Body and facial hair

Other areas of skin which respond to androgens develop heavier hair ([androgenic hair](#)) in roughly the following sequence: axillary hair, perianal hair, upper lip hair, preauricular hair, and the rest of the body area.

There is a large range in amount of body hair among adult men, and significant differences in timing and quantity of hair growth among different ethnic groups

## 4-Voice changes

## 5-muscle development and body shape

- By the end of puberty, adult men have heavier bones and nearly twice as much as skeletal muscle.
- Arms, legs, hands, and feet may grow faster than rest of body.
- Grow taller and shoulders grow broader.
- Muscles get bigger.
- Gain more weight

## 6-Body odor, skin changes, acne

Rising levels of androgens can change the fatty acid composition of perspiration, resulting in a more "adult" body odor.



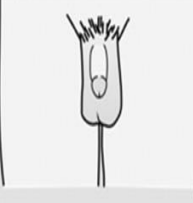


## Tanner staging for males

### Pubic Hair Scale (both males and females)

- Stage 1: No hair
- Stage 2: scant hair
- Stage 3: terminal hair
- Stage 4: Terminal hair that fills the entire triangle overlying the pubic region
- Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh

### Male External Genitalia Scale

- Stage 1: Testicular volume < 4 ml
- Stage 2: 4 ml-8 ml , 1st pubertal sign in males
- Stage 3: 9 ml-12 ml
- Stage 4: 15-20 ml
- Stage 5: > 20 ml

I		3 ↕ <2,5
II		4 ↕ 2,5-3,2
III		10 ↕ 3,6
IV		16 ↕ 4,1-4,5
V		25 ↕ >4,5

**Stage I:** prepubertal; testicular size less than 4 cc in volume and 2.5 cm in longest dimension

**Stage II:** enlargement of scrotum and testes; scrotal skin reddens and changes in texture; growth of testes to 4 cc or greater in volume

**Stage III:** enlargement of penis (length at first); further growth of testes

**Stage IV:** increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker

**Stage V:** adult genitalia

***Physical changes in  
females***

- LH stimulates proliferation of follicular and theca cells, and during the follicular phase of the menstrual cycle induces androgen secretion by theca cells.
- FSH induces proliferation of granulosa cells; enhances aromatase activity so that androstenedione is converted to oestradiol (E2); and increases progesterone (P) production.
- E2 induces secondary sexual development.



# 1-Breast development

- The first physical sign of puberty in females is usually a firm, tender lump under the center of the areola of one or both breasts, occurring on average at about 10 years of age. ( breast budding)
- Within six to 12 months, the swelling has clearly begun in both sides, softened, and can be felt and seen extending under the edges of the areola .
- By another 12 months , the breasts are becomes mature size and shape .there is so much variation in sizes and shapes of adult breasts
- Peak height velocity occurs early (at breast stage II–III, typically between 11 and 12 yr of age) in girls and always precedes menarche.

## 2-Hair:

- increased activity of the suprarenal cortex at puberty with increased production of adrenal androgens which lead to appearance of pubic and axillary hair
- Hair growth begins shortly after breast development .

## 3- Vagina, uterus, ovaries

- The mucosal surface of the vagina also changes in response to increasing levels of estrogen, becoming thicker and a more pink in color
- Whitish secretions are a normal effect of estrogen as well.
- The uterus and ovaries increase in size, and follicles in the ovaries reach larger sizes.

## 4- Menstruation and fertility

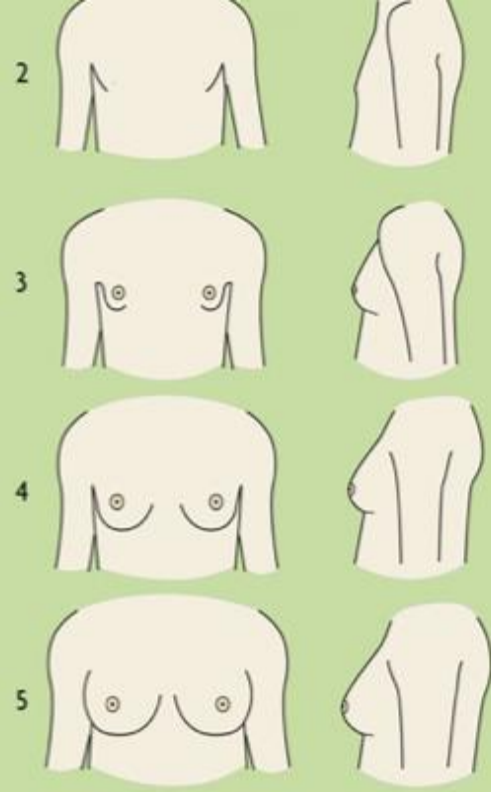
- The first Menses is referred to as menarche which is usually not regular and occurs monthly and last from 3 to 7 days .
- Ovulation is necessary for fertility, but may or may not present in The first Menses.
- The mean age of menarche is about  $12\frac{3}{4}$  yr.
- Positive correlation with adiposity

## 4- Body shape, fat distribution, and body composition

- During this period, also in response to rising levels of estrogen, the lower part of the pelvis and hips widen.
- Fat tissue increases to a greater percentage of the body composition than in males, especially in the typical female distribution of breasts, hips, buttocks, thighs, upper arms, and pubis.

# Female Breast Development Scale

- Stage 1: No glandular breast tissue palpable
- Stage 2: Breast bud palpable under the areola (1st pubertal sign in females)
- Stage 3: Breast tissue palpable outside areola; no areolar development
- Stage 4: Areola elevated above the contour of the breast, forming a “double scoop” appearance
- Stage 5: Areolar mound recedes into single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion



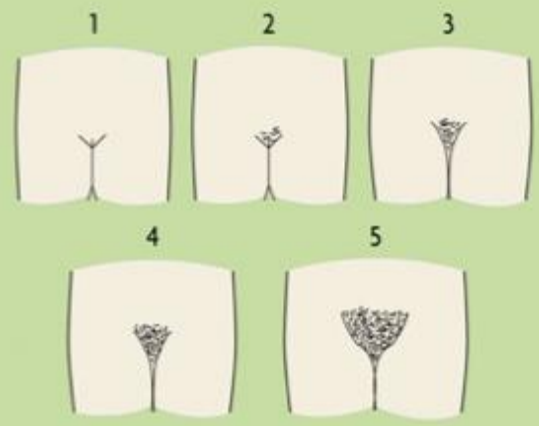
**Stage 2:** The first sign of breast development has appeared. This stage is sometimes referred to as the breast budding stage. Some palpable breast tissue under the nipple, the flat area of the nipple (areola) may be somewhat enlarged.

**Stage 3:** The breast is more distinct although there is no separation between the contours of the two breasts.

**Stage 4:** The breast is further enlarged and there is greater contour distinctness. The nipple including the areola forms a secondary mound on the breast.

**Stage 5:** Size may vary in the mature stage. The breast is fully developed. The contours are distinct and the areola has receded into the general contour of the breast.

## Pubic Hair



**Stage 1:** No pubic hair.

**Stage 2:** There is a small amount of long hair chiefly along the vaginal lips.

**Stage 3:** The hair is darker, coarser, and curly and spreads sparsely over the skin around the vaginal lips.

**Stage 4:** The hair is now adult in type, but the area covered is smaller than in most adults. There is no pubic hair on the inside of the thighs.

**Stage 5:** The hair is adult in type, distributed in an inverse triangle. There may be hair on the inside of the thighs.

# Precocious puberty

- appearance of any of the secondary sexual characters before the age of:

**8 years in females**

**9 years in males**

**It could be central or peripheral**

**OR**

**Pseudo precocious puberty or true**

# In females

- Is usually idiopathic or familial and follows the normal sequence of puberty.
- the organic causes are rare and are associated with :
  - Dissociative when the sequence of pubertal changes is abnormal , eg: isolated pubic hair with virillisation of the genitalia , suggesting excess androgen
  - rapid onset
  - neurological symptoms and signs , eg : neurofibromatosis

# In males

- this is uncommon and usually has an organic cause.
- examination of the testes may be helpful :
  - bilateral enlargement suggest gonadotrophin release
  - small testes suggest an adrenal cause
  - a unilateral enlarge testis suggest a gonadal tumor

# Causes of precocious puberty:

## 1) Gonadotrophin dependent = (central , true ) (increased LH, FSH ), more in females .

- familial /idiopathic
- CNS abnormalities
- congenital anomalies , eg: hydrocephalus
- acquired , eg: post irradiation , infections
- Hypothyroidism , FSH like action by TSH (dec growth velocity, delayed bone age )

## 2) Gonadotropin independent = (peripheral , false ) (decreased LH, FSH)

- adrenal disorders - tumors, congenital adrenal hyperplasia
- ovarian tumors
- testicular tumors
- Inadvertent exposure to estrogen and testosterone , tea tree oil , lavender oil .

## 3). **Mixed** : happened in McCune –Albright syndrome





## 41) McCune-Albright syndrome (MAS)

### ❖ Clinical features

#### Classic triad

- ✓ Precocious puberty
- ✓ Café-au-lait macules
- ✓ Polyostotic fibrous dysplasia

### ❖ What is the most characteristic laboratory finding?

- ✓ High growth hormone
- ✓ High prolactin
- ✓ High luteinizing hormone (LH)
- ✓ High follicle-stimulating hormone (FSH)
- ✓ Hypophosphatemia & hyperphosphaturia

### ❖ What is the classic presenting sign of Precocious puberty in MAS?

- ✓ Vaginal bleeding

### ❖ How to differentiate café-au-lait macules from those of neurofibromatosis (NF)

#### In MAS

- ✓ Coast of Maine borders
- ✓ Irregular borders
- ✓ Never cross midline

#### In NF

- ✓ Coast of California
- ✓ Smooth borders
- ✓ Cross midline



### ❖ What is the other common endocrine association in MAS?

- ✓ Hyperthyroidism

### ❖ Mode of inheritance?

- ✓ Sporadic
- ✓ Mutation in the GNAS1 gene
- ✓ More common in girls

### ❖ Treatment

- ✓ GnRH agonist
- ✓ Oral phosphate and calcitriol



# NORMAL VARIANTS

- Premature Thelarche:

isolated breast development before 8 years ,with 2 peaks at years and 6 years

- Key features of premature telarche are:(early activation of the axis )
- Isolated breast development, either unilateral or bilateral – Typically not developing beyond Tanner stage 3
- Absence of other secondary sexual characteristics
- Normal height velocity for age (not accelerated)
- Normal or near-normal bone age

- Exaggerated Thelarche

increased growth rate and bone age, intermediate between PP an PT

FSH, LH, E2 usually low

Pelvic Us

Bone Age

Height, looking for growth spurt

It may regress with time ...it should be followed up regularly

- Premature Adrenarche

- Adrenarche is the onset of the adrenal androgen production
- Premature adrenarche occurs before 8 years of age.
- is more common in girls than boys.
- Usually overweight and taller.
- Dx requires exclusion of other causes of androgen excess.
- Usually no need for treatment.

- DHEAS (high), bone age, height (accelerated growth), puberty.  
Link to polycystic ovarian syndrome or insulin resistance

# Investigations

- Basal LH with sensitive assays ( $>0.3 - 0.6$  u/l in Central PP)
- FSH
- Estradiol  $> 10$  pg/mL
- GnRh stimulation test : LH(  $> 5$  units/L in central pp) , FSH and on second day E2 ( $>50$  pg/mL).
- Pelvic US in girls: enlargement of the ovaries and the uterus (uterine length  $> 3.8$  cm. ,uterine volume more than 2.5 ml , ovary  $>1.6 - 3$  ml) .
- Pituitary MRI ?
- Adrenal CT / MRI?
- Pelvic US

# Rx

## **In Central PP**

The object of treatment is:

- to prevent early epiphyseal closure to maintain the height
- To decrease psychological distress to the girl and her family.

Treatment with GnRH agonist

# Rx

## In peripheral PP

- Androgen receptor blockers—cyproterone acetate, flutamide and spironolactone
- 5 alpha-reductase inhibitors
- Testosterone biosynthesis inhibitors—ketoconazole
- Aromatase inhibitors—testolactone, anastrozole, letrozole
- Estrogen receptor blocker-----Tamoxifen

# Delayed puberty

- The absence of pubertal development by 14 years of age in males,,,
- and by 13 years in females if no SSC appeared or, by 15 if SSC appeared but menses is still absent.
  
- In contrast to precocious puberty , the problem is common in males , in whom it is mostly due to constitutional delay.

Causes of delayed puberty :

1) **constitutional delay** of growth and puberty

2) **High gonadotrophin secretion**  
(hypergonadotropic hypogonadism)

- chromosomal abnormalities ( klinefelters syndrome,turner syndrome)—primary gonadal failure.
- steroid hormone enzyme deficiencies.
- acquired gonadal damage –secondary gonadal failure



### 3) **Low gonadotrophin secretion** (hypogonadotropic hypogonadism)

- Systemic disease (functional): cystic fibrosis , severe asthma , crohns disease , anorexia nervosa
- Hypothalamic-pituitary disorders (organic): panhypopituitarism , intracranial tumors,
- kallmanns syndrome (LHRH deficiency and anosmia )
  
- The patient need to be evaluated ,if there's hx of medical disease , family hx of the same complaint, recent intervention ,anosmia
- PE: growth parameters,dysmorphic features, pubertal assesment
- Then general tests like CBC,CRP,celiac screen
- LH , FSH , Sex hormones,T4,TSH,IGF-1
- Treatment : estrogen and testosterone to induce puberty
- Hormone replacement in hypo hypo

# Ambiguous genitalia , DSD

- Infants born with genitals that do not appear typically male or female, or that have an appearance discordant with the chromosomal sex

# TYPICAL SEX DEVELOPMENT

- **Gonadal differentiation** : absence or presence of SRY genes

Individuals with DSDs may have complete absence of gonadal development , incomplete gonadal development , a gonad atypical for chromosomal sex (eg, XX testicular DSD).

**Gonadal function:** The Leydig cells of the testis produce testosterone, which is converted to dihydrotestosterone by the enzyme 5-alpha-reductase type 2, which is expressed outside of the testis

**Gonadal position:** testosterone cause the gonads to descend into the scrotum.

**Development of the labioscrotal folds:** The embryonic genital swellings give rise to the labioscrotal folds. In typical XY individuals, the action of testosterone and dihydrotestosterone cause the labioscrotal folds to fuse to form the scrotum and become rugated (wrinkled) and pigmented

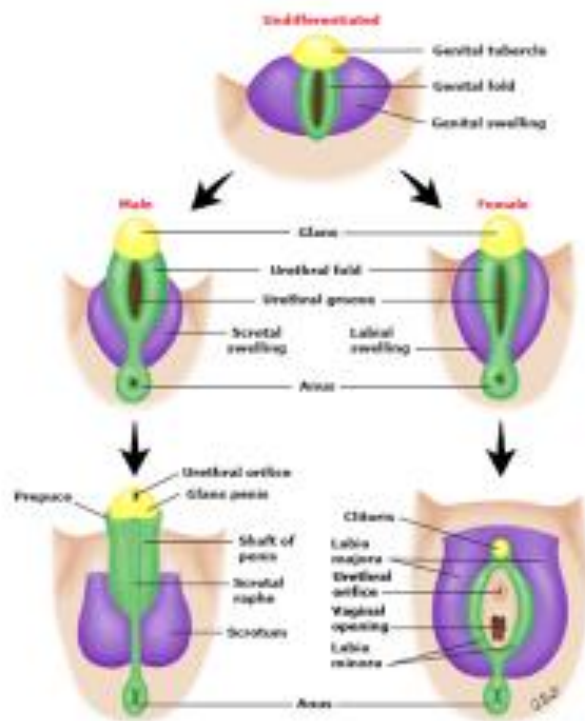
**Size and shape of the clitorophallus :**

In typical XY individuals, the action of testosterone and dihydrotestosterone cause the genital tubercle to increase in size and straighten to form the penis.

**Location of the urethra**

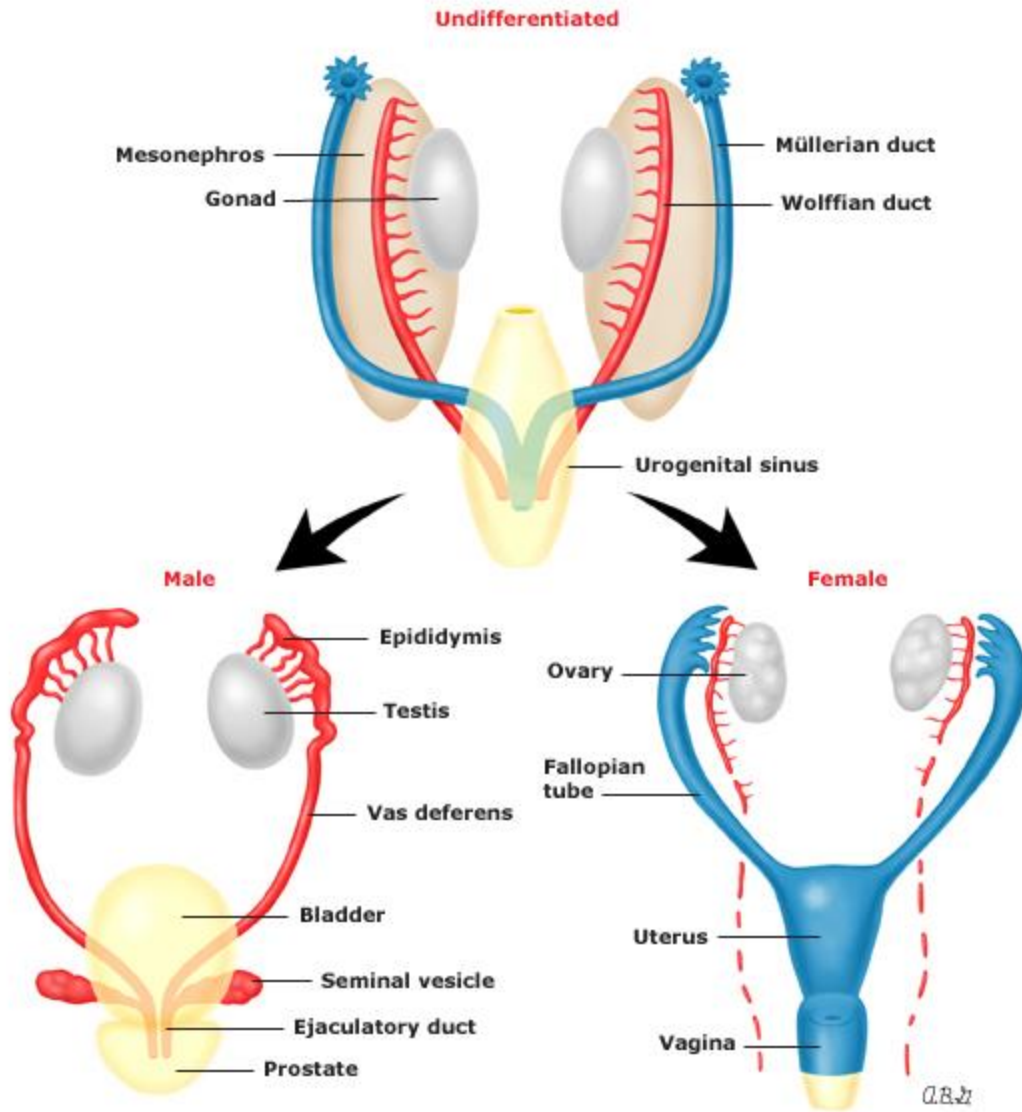
**Internal reproductive structures –**

## Phenotypic differentiation of the external genitalia in male and female embryos



In typical XX individuals, the genital tubercle becomes the clitoris, the genital swellings become the labia majora, and the genital folds become the labia minora. In typical XY individuals, the genital tubercle becomes the glans penis, the genital swellings fuse to become the scrotum, and the genital folds elongate and fuse to form the shaft of the penis and the penile urethra.

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**Atypical genital appearance**



Clitoromegaly in a 46,XX infant with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

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*Courtesy of Christopher P Houk, MD, and Lynne L Levitsky, MD.*

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## Bilateral undescended gonads



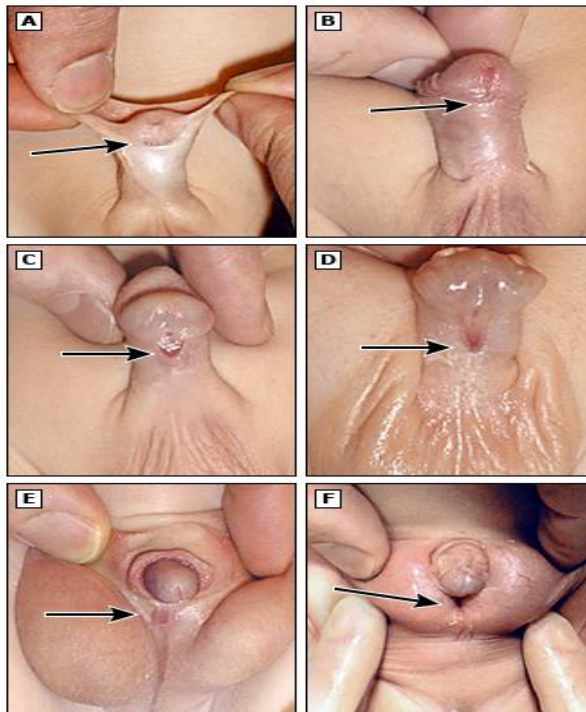
This patient with bilateral undescended gonads had a 46,XX karyotype and ovotesticular difference of sex development.

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*Courtesy of Christopher P Houk, MD and Lynne L Levitsky, MD.*

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## Degrees of hypospadias



Composite of cases demonstrating increasing severity of hypospadias. A through D show standard hypospadias, and E through F show severe hypospadias. The risk of differences of sex development is increased for cases of severe hypospadias and isolated standard hypospadias accompanied by micropenis and/or cryptorchidism (unilateral or bilateral). Refer to UpToDate content on evaluation and management of hypospadias.

Note the progressive severity of the location of the ectopic urethral meatus from coronal margin.

(A, B, C) Distal penile shaft.

(D) Mid-penile shaft.

(E) Scrotum.

(F) Perineum.

*Courtesy of Laurence S Baskin, MD, FAAP.*

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# History and physical

1. Prenatal exposure to androgens
2. History of consanguinity or genetically homogeneous population

Measurement of the clitorophallic structure: In a typical XY term infant, penile length is  $\geq 2.5$  cm and penile diameter measured at the middle of the shaft is  $\geq 0.9$  cm

Micropenis (microphallus) in XY  $\gg$  deficiencies of growth hormone and/or gonadotropins during the second and third trimesters, idiopathic hypogonadotropic hypogonadism/Kallmann syndrome, isolated growth hormone deficiency, and panhypopituitarism

Clitoral width in a typical XX neonate ranges from 2 to 6 mm. Clitoral length in the newborn infant may vary in different population groups, but lengths of more than 9 mm are unusual

Urethral opening

Associated features: high blood pressure

Associated GI anomalies

Assessment of the gonads

# Investigation

- Karyotyping with SRY gene sequencing
- FSH ,LH ,Testosterone\*after one week and before 6 months\* , AMH ,DHEA
- 17OHP
- Electrolyte
- pelvic US

# Management:

- **Factors to consider** – Guidance given to families about sex of rearing should be based on:
  - The most probable adult gender identity, based on the clinical outcomes for the specific DSD type (when available)
  - Potential for adult psychosocial and psychosexual function, including fertility potential
  - Degree of virilization as a marker of prenatal androgen exposure
  - The family's preferences and expectations, which may be influenced by their sociocultural background

*Thank you*