

Approach to Precocious Puberty

Definition of Precocious Puberty :

- Appearance of secondary sexual development more than 2.5 standard deviations earlier than the mean age.

- The HPG axis is active during fetal life continues to function in infancy until it enters a relative dormant state.
- Increased GnRH secretion at the onset of puberty.

- GPR54 gene - chromosome 19p13.3 → G-protein coupled receptor.
- Ligand : kisspeptin → modulate the negative feedback on GnRH secretion.
- Gain-of-function mutations → central precocious puberty .
- Loss-of-function mutations → autosomal recessive idiopathic hypogonadotropic hypogonadism .

- Thelarche
- Pubarche
- Adrenache
- Menarche

Tanner Staging- females

I		Stage I: prepubertal
II		Stage II: breast bud with elevation of breast and papilla; enlargement of areola
III		Stage III: further enlargement of breast and areola; no separation of contour
IV		Stage IV: areola and papilla form secondary mound above level of breast
V		Stage V: mature stage; projection of papilla only, related to recession of areola

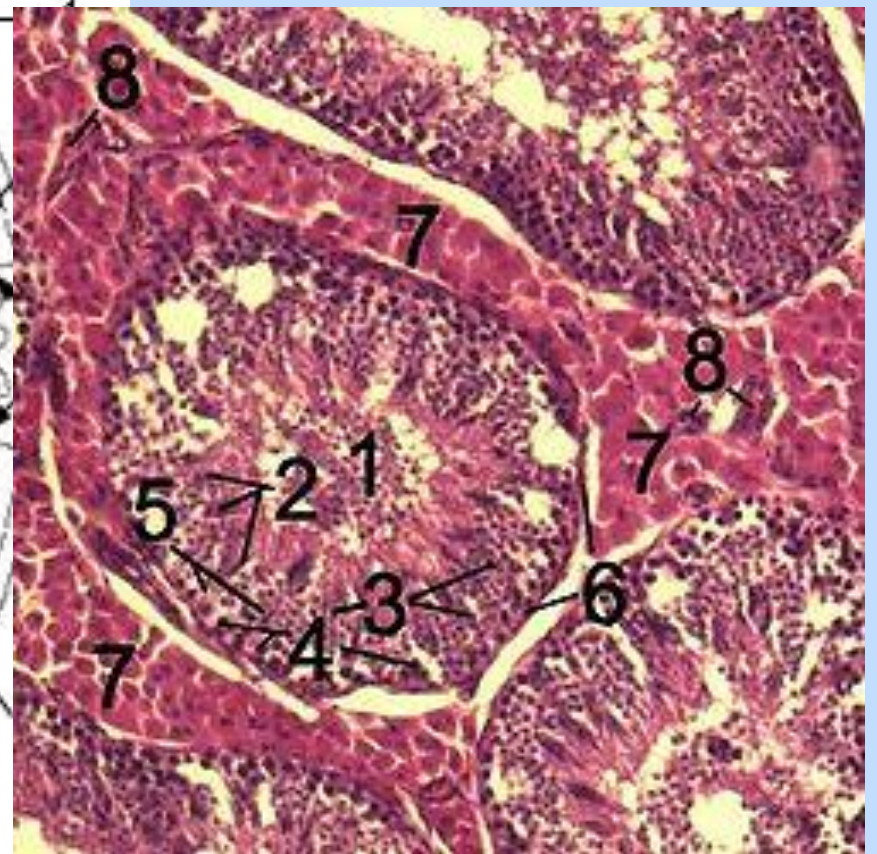
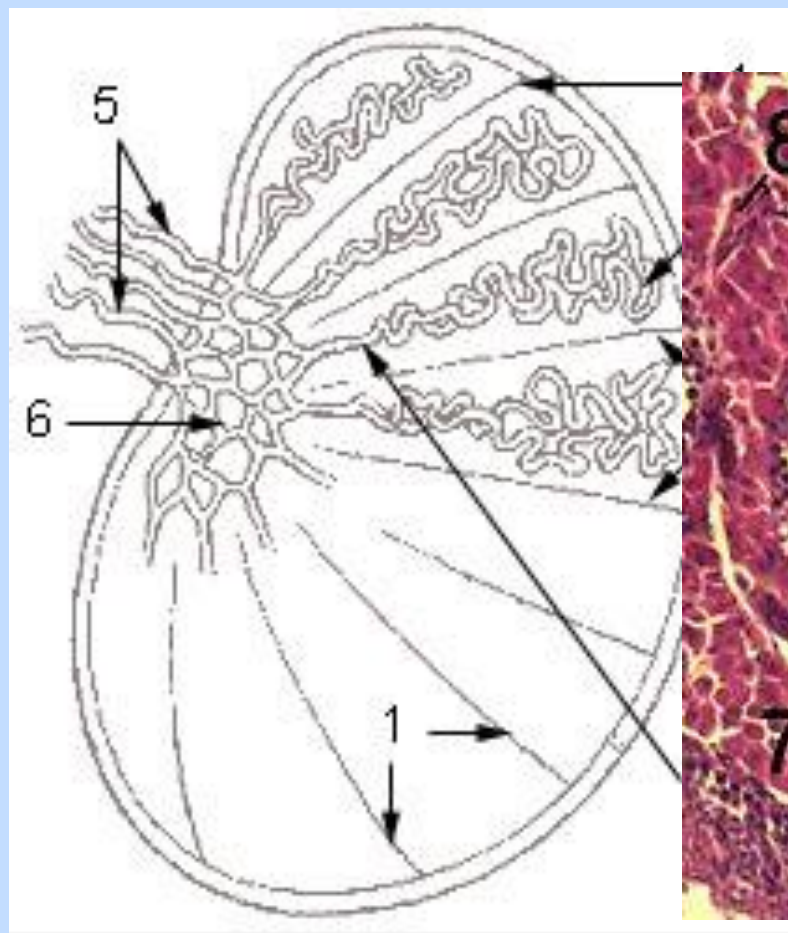
Tanner Staging- males

Childhood	I		3 <2.5
Early Puberty	II		4 2.5-3.2
Mid Puberty	III		10 3.3
Late Puberty	IV		16 4.1-4.5
Adulthood	V		25 >4.5

- Gonadotropins are at:
 - High levels in the middle of the fetal life.
 - Low in cord blood with high estrogen.
- Gonadotropin inhibition discontinues with placental separation.
- The hypothalamo-pituitary-gonadal axis is activated → mini puberty.

In boys:

- the level of LH increases approximately 10-fold in the minutes following delivery and the level of testosterone increases.
 - This state lasts approximately for 12 hours.



In Girls:

- The level of FSH is higher in girls. The hormones excluding FSH decrease from the 6th month after delivery.
- Increased FSH in girls continues until the age of 2-4 years.

- The dimensions of the ovary in female newborns are larger compared to the childhood.
- The size of the ovary is measured to be 1 mL until the age of one year.

- After the active mini-puberty of infancy, the HPG axis becomes dormant mainly due to central inhibition by gamma-aminobutyric acid.
- Precise reason for the release from inhibition and the predominance of stimulatory effects on the HPG axis at the time of pubertal onset is unknown.

Classification

- - Central (Gonadotropin-dependent precocious puberty).
 - Peripheral (Gonadotropin-independent precocious puberty).
- Isosexual Vs Contraseexual.

Gonadotropin-dependent precocious puberty (GDPP) - Causes

- Idiopathic
- Central nervous system (CNS) tumors
 - Hamartomas
 - Astrocytomas
 - Adenomas
 - Gliomas
 - Germinomas
- CNS infection
- Head trauma

- Iatrogenic
 - Radiation
 - Chemotherapy
 - Surgical
- Malformations of CNS
 - Arachnoid or suprasellar cysts
 - Septo-optic dysplasia
 - Hydrocephalus
- Genetic

Gonadotropin-independent precocious puberty (GIPP)

- CAH
- Testosterone/estrogen-producing tumors
 - Adrenal carcinoma or adenoma
 - Granulosa cell tumor -Theca cell tumor - Leydig cell tumor
- Ovarian cysts
- McCune-Albright syndrome
- Familial male–limited precocious puberty

- hCG-producing tumors
 - Choriocarcinoma
 - Dysgerminoma
 - Hepatoblastoma
 - Chorioepithelioma
 - Teratoma
 - Gonadoblastoma
- Exogenous exposure to androgen/estrogen
- Hypothyroidism

History

- Onset
- Progression
- Other associated pubertal changes
- Neurological symptoms
- History of previous CNS insult
- Abdominal pain
- Symptoms of hypothyroidism
- Growth velocity
- Family History
- Drug History

Physical examination

- Growth Parameters
- Tanner Staging
- Dermatological exam
- Neurological exam
- Thyroid exam

Investigations:

- Bone Age
- TFT
- LH,FSH
- Estradiol/Testosterone
- GnRH stimulation test
- Pelvic ultrasound
- Brain MRI
- Others: IGF-1, cortisol, DHEAS, 17-OH progesterone

Treatment- GDPP

- Depends on :
 - etiology
 - Pace of sexual maturation
 - Predicted adult height
 - Psychosocial ?

GnRH agonist

- slows accelerated puberty and improves final height
- - Leuprolide acetate
 - Triptorelin
 - Histrelin
- Treatment should be given until it appears that it is safe appropriate for puberty to proceed.

GIPP - treatment

- Tumors of the testis, adrenal gland, and ovary are treated by surgery.
- hCG-secreting tumors may require combination of surgery, radiation, and chemotherapy depending upon the site and histologic type
- Children with obvious defects in adrenal steroidogenesis should be treated with glucocorticoid therapy

McCune-Albright syndrome

- Rare disorder
- Somatic mutation of the alpha subunit of the G3 protein that activates adenylate cyclase.
- Triad: - peripheral precocious puberty
 - café-au-lait skin pigmentation
 - fibrous dysplasia of bone .
- Recurrent formation of follicular cysts and cyclic menses .
- Skin manifestations and the bone lesions may increase over time.
- May present with vaginal bleeding.

- Continued stimulation of endocrine function (eg, precocious puberty, gigantism, Cushing syndrome, adrenal hyperplasia, and thyrotoxicosis).
- Mutations in other organs → hepatitis, intestinal polyps, and cardiac arrhythmias.

Familial male-limited precocious puberty (testotoxicosis)

- Rare disorder
- Autosomal Dominant
- Age of presentation at age 1-4 year
- Activating mutation in the LH receptor gene → premature Leydig cell maturation → testosterone secretion.

THANK YOU