Approach to Precocious Puberty

Definition of PP:

- Secondary sexual development more than 2.5 standard deviations earlier than the median or mean age.

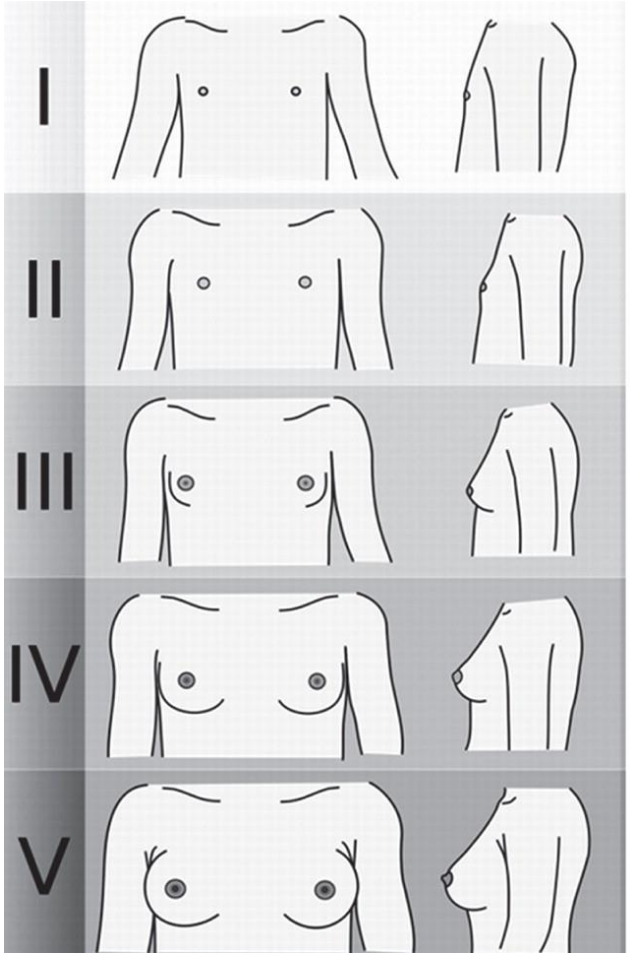
- The HPG axis is active during fetal life continues to function in infancy until it enters a relative dormant state.

- 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 exerted by sex steroids.
- Gain-of-function mutations → central precocious puberty .
- Loss-of-function mutations → autosomal recessive idiopathic hypogonadotropic hypogonadism .

- Thelarche
- Pubarche
- Adrenache
- Menarche

Tanner Staging- females



Stage I: prepubertal

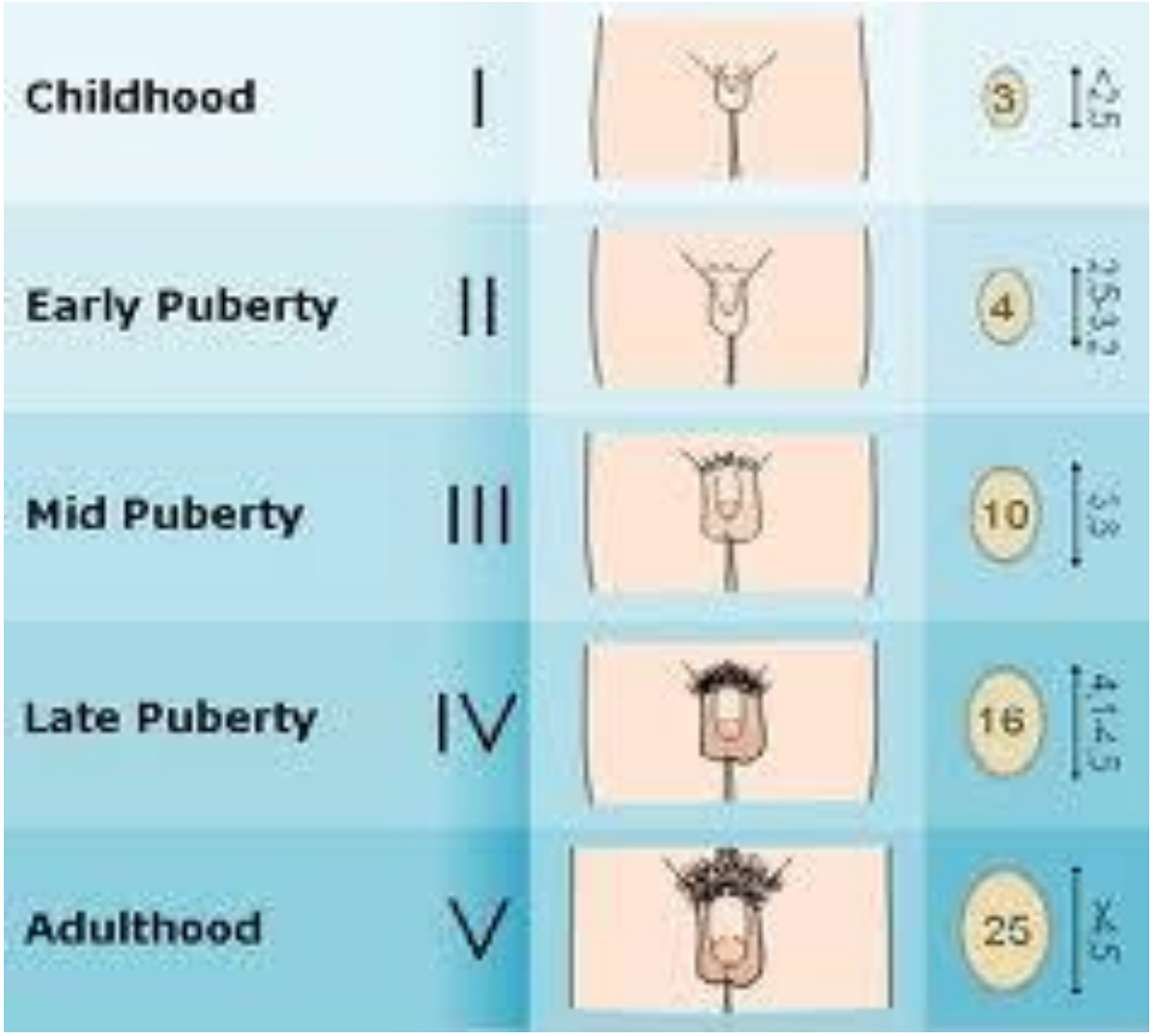
Stage II: breast bud with elevation of breast and papilla; enlargement of areola

Stage III: further enlargement of breast and areola; no separation of contour

Stage IV: areola and papilla form secondary mound above level of breast

Stage V: mature stage; projection of papilla only, related to recession of areola

Tanner Staging- males



Classification

- - Central (Gonadotropin-dependent precocious puberty).

  - Peripheral (Gonadotropin-independent precocious puberty).

- Isosexual Vs Contrasexual.

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

Incomplete precocious puberty

- Early development of secondary sexual characteristics and usually is a variant of normal puberty.

- Bone Age.
- Close Monitoring

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 or familial male-limited precocious puberty should be treated with drugs that inhibit gonadal steroidogenesis or gonadal steroid action rather than surgery to preserve fertility.

McCune-Albright syndrome

- Rare disorder
- Somatic mutation of the alpha subunit of the G3 protein that activities 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.

McCune-Albright syndrome - treatment:

- Testolactone- aromatase inhibitor- → decreases the recurrence of ovarian cysts → slowing pubertal progression.

- Newer-generation aromatase inhibitors fadrozole, anastrozole, letrozole

- Antiestrogen –tamoxifen-has been effective in reducing vaginal bleeding.

  - Long-term studies of outcomes such as skeletal growth ?

- Fibrous dysplasia of bone → bone pain and increased fractures → bisphosphonate pamidronate

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.

Familial male-limited precocious puberty - Treatment

- Combination of spironolactone (inhibits androgen action) and testolactone (which blocks the conversion of androgen to estrogen)

- Ketoconazole, an inhibitor of androgen synthesis. It may lower cortisol levels and is associated with heptotoxicity.

- In few cases a regimen of bicalutamide (highly selective nonsteroidal antiandrogen) and anastrozole (a third-generation aromatase inhibitor) appeared to be effective in reducing growth velocity and decreasing secondary sexual characteristics without serious adverse effects .

THANK YOU