Approach to Precocious Puberty

Definition of PP:

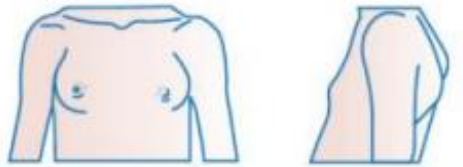
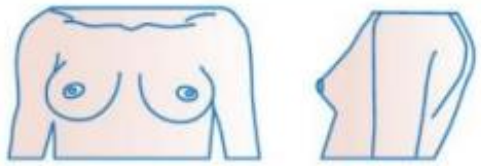
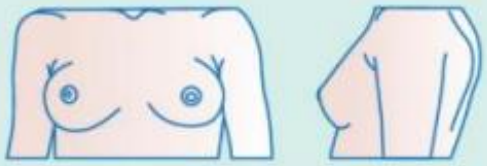
- Secondary sexual development more than 2.5standard deviations earlier than the median or mean age.

- 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.

- GPR54gene-chromosome19p13.3→ 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:

Tanner stage	Male genital appearance	Male genital description	Female pubic hair appearance	Pubic hair description	Breast appearance	Breast description
1		Testicular volume <3ml		No pubic hair		Elevation of papilla only
2		Testicular volume <3ml, change in texture to scrotal skin		Sparse growth chiefly along the labia/base of penis		Breast bud stage
3		Increase in size of penis with further testicular enlargement		Darker, coarser, more curled hair		Enlargement of breast and areola
4		Further enlargment of penis and testicles with development of glans penis		Adult type hair over a smaller area		Projection of the areola and papilla
5		Adult size and shape		Spread to the medial surface of the thighs		Recession of the areola to the contour of the breast, projection of papilla only

Classification

- Central (Gonadotropin-dependent precocious puberty).
- Peripheral (Gonadotropin-independent precocious puberty)

Gonadotropin-dependent precocious puberty (GDPP)-Causes

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

- 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 steroid oogenesis should be treated with glucocorticoid therapy

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

McCune-Albright syndrome

- Rare disorder
- Somatic mutation of the alpha subunit of the G3protein that activities adenylate cyclase.
- Triad: - peripheral precocious puberty
  - café-au-laitskin 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 age1-4year
- 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