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 $\rightarrow$ G-protein coupled receptor.
• Ligand: kisspeptin $\rightarrow$ modulate the negative feedback on GnRH secretion exerted by sex steroids.
• Gain-of-function mutations $\rightarrow$ central precocious puberty.
• Loss-of-function mutations $\rightarrow$ autosomal recessive idiopathic hypogonadotrophic hypogonadism.
• Thelarche
• Pubarche
• Adrenarche
• 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Image</th>
<th>Age Range</th>
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<tbody>
<tr>
<td>Childhood</td>
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<tr>
<td>Early Puberty</td>
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<tr>
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<td>Adulthood</td>
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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
  - Astrocytomomas
  - 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 hepatotoxicity.
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