Disclosures

• None
Objectives

- State normal timing of puberty
- Describe the work up for precious puberty
- Report the etiologies of delayed puberty
- Perform basic work up for pubertal pathologies
Pretest Question

What is the best indicator of precocious puberty in girls?

A. Body odor
B. Growth spurt
C. Pubic hair
D. Breast development
E. Advanced bone age
Peak Growth Velocity
- Tanner 2-3
- Precedes menarche
- Growth complete 2 yrs from menarche

Thelarche
- 10-11 yrs of age

Menarche
- 2-2.5 years after
- Tanner 4

Adrenarche
- 6-12 mo after

- Peak Growth Velocity
  - Tanner 2-3
  - Precedes menarche
  - Growth complete 2 yrs from menarche
• Testicular growth first with thinning of scrotal skin
  – Average age 11-12 yo
• Penile lengthening & Pubic hair follow
• Peak Growth Velocity at Tanner 4
Testicle volume measured in mL

Puberty
Benign Abnormalities of Puberty in Young Children
Mini-Puberty of Infancy

• Activation of HPG axis during neonatal period
• Occurs in 2 weeks of life up to 6 months

• Develops genital organs
  – Boys: penile and testicular growth
  – Girls: breast tissue development

• Creates basis for future fertility
  – Primes pituitary LH and FSH response to GnRH during reproduction.

• May impact growth and adipose tissue development in boys
Timing of Mini Puberty of Infancy

**FIGURE 1** | Patterns of fetal and postnatal luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone (T) secretion in males.

**FIGURE 2** | Patterns of fetal and postnatal luteinizing hormone (LH), follicle stimulating hormone (FSH) and oestradiol secretion in females.
Isolated scrotal hair of infancy

- Occurs between 8-15 months of age
- Diminished by 13-21 months of age
- No underlying pathological cause found
- No other signs of androgenisation found
Benign Premature Thelarche

- Nonprogressive, isolated breast development
  - Unilateral or bilateral
- Usually occurs before 3 yrs
  - may persist up to 8 yrs
- Prepubertal LH, FSH, and estradiol
  - FSH ~2x LH
- Menarche at normal age
- 10% may progress to CPP

Neonatal Galactorrhea (Witch’s Milk)

- Colostrum like milk production
- Occurs 3-4 days after birth
- Lasts no longer than 2 wks of life
- Occurs in 5% of newborns

What Starts Puberty?

- **Unknown exact trigger**
  - Genetic factors of KISS1 leading to Kisspeptin release

- **Sustained increase in pulsatile release of GnRH**
  - Genetic input association known by parents age at puberty
  - Metabolic signals

Abnormal Puberty

Precocious
- Girls:
  - Before 8 yrs
  - Thelarche
- Boys
  - Before 9 yrs
  - Testicular development

More common in girls

Delayed
- Girls:
  - No thelarche by 13 yrs
  - Menarche by 16 yrs
  - Over 4 yrs from thelarche to menarche
- Boys
  - No Testicular development by 14 yrs

More common in boys
Precocious Puberty

• Signs
  – Rapid advancement through Tanner Stages
  – Bone age advanced
  – Short predicted height

• Causes
  – Exogenous: soy, lavender, tea tree oil
  – Central Precocious Puberty
  – Gonadotropin Independent Precocious Puberty
Tanner staging of breast development in girls

Stage 1: Prepubertal.
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola.
Stage 3: Further enlargement of breast and areola; no separation of their contour.
Stage 4: Areola and papilla form a secondary mound above level of breast.
Stage 5: Mature stage with projection of papilla only, related to recession of areola.
Testicular/Penile Enlargement

Etiology and mechanisms of precocious puberty

Precocious development of secondary sexual characteristics

**Etiology**

**Central precocious puberty**
*eg, CNS tumors or malformations, idiopathic*

**Peripheral precocity**
*eg, adrenal, ovarian, testicular tumors, autonomous gonadal activation [such as McCune Albright syndrome, familial male-limited precocious puberty], congenital adrenal hyperplasia, exposure to exogenous sex steroids*

**Benign or nonprogressive pubertal variants**
*eg, nonprogressive or intermittently progressive precocious puberty, premature thelarche, premature adrenarche, isolated premature menarche*

**Mechanism**

**Central precocious puberty**
- Activation of hypothalamic-pituitary-gonadal axis with GnRH secretion leading to increased LH and FSH secretion

**Peripheral precocity**
- Excess sex steroid production (↑estradiol or testosterone) with suppression of hypothalamic-pituitary axis (↓LH and FSH)

**Benign or nonprogressive pubertal variants**
- Unknown but not associated with full activation of the hypothalamic-pituitary-gonadal axis

CNS: central nervous system; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone.

Early Puberty Work Up

• Luteinizing Hormone
• Follicle Stimulating Hormone
• Estradiol
• Total Testosterone (male)
• TSH and FT4
• Bone Age
• If CPP is real – MRI of brain and pituitary
Central Precocious Puberty

• Idiopathic F > M
• Premature onset with normal progression
• It’s all about the LH
  – Levels surge during sleep – get labs in the morning!
  – Random LH detectable in 50-75% of girls with central precocity
    • LH >0.4 IU/L concerning
  – GnRH stimulation (Leuprolide Stimulation test)
    • LH can still remain low until mid-puberty in girls
    • Stimulated LH > 4 IU/L concerning
    • Increase in FSH >> LH suggests prepubertal status
    • LH:FSH ratio >0.66 suggestive of CPP
Treatment of CPP

• GnRH analog interrupts pulsatile endogenous GnRH
  – Histrelin acetate (Supprelin LA) Implant
  – Lueprolide acetate (Lupron Depot-Ped)
  – Triptorelin (Triptodur)
CNS Lesions Commonly Associated

- **Craniopharyngioma**
  - Benign tumor
  - Papilledema or optic atrophy
  - Visual problems

- **Hypothalamic Hamartoma**
  - Most commonly associated brain lesion
  - Ectopic neural tissue of GnRH secretory neurons
  - Associated with Gestault sz

[Image showing anatomical structures with labels such as Tumor, Optic, Pituitary stalk, Pituitary gland.]
Gonadotropin Independent Precocious Puberty

- **Gonadal Tumor**
  - Most common reproductive neoplasm in children
  - < 5% are malignant
  - Majority are germ cell tumors, epithelial cell tumors, and sex cord-stromal tumors
  - Tumor markers: α-fetoprotein, hCG, CEA
  - Secrete estrogen, androgens, or gonadotropin like hCG

- **Ovarian cysts**
  - can grow to 1-6cm
  - precocity regresses when cysts removed
Case

7 year 2 month old AA female c/o pubic hair. Present and progressive since 5 years of age. “Always seemed to need deodorant”
No breast development, vaginal bleeding or dc
No exposure to testosterone creams or gels

Fam Hx:
Mother 10 years of age at menarche and has PCOS
Father unknown age of pubertal development
Physical Exam:

- BP: 109/58, pulse 99, height: **131.5 cm**, weight: **36.3 kg**. >99 %ile (Z= 2.39) BMI: 20.99 kg/m² 98th %ile (Z= 2.00)
- GENERAL APPEARANCE: alert, no dysmorphic features
- SKIN/Eyes/ENT/Resp/CV/ABD/Musculoskeletal: unremarkable
- THYROID: not enlarged, no nodules palpated
- BREAST/CHEST: symmetric, Tanner stage 1 - glandular tissue not palpable. Lipomastia noted
- GU: pubic hair Tanner Stage 3 - very few hairs noted on labia majora, No clitoromegaly
- Axillary: 2-3 Fine hyperpigmented hairs noted
### Tanner Staging of Pubic Hair

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanner I</td>
<td>No pubic hair</td>
</tr>
<tr>
<td>Tanner II</td>
<td>Small amount of long, pigmented, downy hair, straight or slightly curled hair along the labia majora</td>
</tr>
<tr>
<td>Tanner III</td>
<td>Hair becomes darker, rough and curly. Some hair is also found over the junction of the pubis</td>
</tr>
<tr>
<td>Tanner IV</td>
<td>Adult like hair quality in a small and limited area. There is sparing hair in the medial thighs</td>
</tr>
<tr>
<td>Tanner V</td>
<td>Adult hair quality which extends to medial surface of the thighs in the shape of an inverse triangle</td>
</tr>
</tbody>
</table>
Differential Diagnosis

- Premature Pubarche/Adrenarche
- Exogenous testosterone
- Non-classic CAH
- Gonadal tumor secreting testosterone or bHCG
- Adrenocortical tumor
- Cushings

Work-up

Total testosterone, DHEAS, androstenedione, 17OHP progesterone, and Bone Age
Bone Age:
FINDINGS: Patient's chronological age is 7 years 2 months. According to the radiographic atlas of skeletal development of the hand and wrist by Greulich and Pyle method, patient's bone age is 8 years 10 months.

IMPRESSION: Advanced bone age.
Case Diagnosis

Benign Premature Adrenarche
Premature Adrenarche
Not “true” precocious puberty

• Secondary sexual hair, acne, body odor
  – No breast development; clitoromegaly
  – Prepubertal to 4 mL testicular size in boys

• Need to monitor for development of CPP
• DHEA-S may be elevated to appropriate Tanner stage
• Increased incidence of hyperandrogenism later
  – PCOS
Algorithm for Investigation of Children Presenting with Adrenarche

See soon (within 6 wks) in clinic
History and examination should focus on:
Features of androgen excess and puberty
Seek family history of PCOS/T2D/Adrenarche

ABNORMAL
History and examination consistent with early development of secondary sexual characteristics (<8yr girls and 9yr boys)

Clinical Picture of Androgen Excess
Pubic/axillary hair
Body odour or acne
Absence of breast development (♀)
Height acceleration
INVESTIGATIONS
Bone Age +/- adrenal USS
DHEAS / A4 / testo / 17OHP
Synathen test if clitoromegaly (♀)
or genital enlargement (♂),
If IUGR or acanthosis nigricans,
fasting insulin and glucose

Investigations Normal
Bone age < 1-2yr advanced
Androgens not elevated

PREMATURE ADRENARCHE
Follow up with clinical examination
May then discharge to primary care if acceptable

Clinical Picture of Central Puberty
♀ Breast development and height
♂ Acceleration +/- pubic or axillary hair
♀ Increased testicular volume
INVESTIGATIONS
Bone Age
Estradiol (♀), testosterone (♂),
Gonadotrophins (LH and FSH)

Investigations Abnormal
Bone age > 2yr advanced
Androgens elevated

Investigate further as indicated
17OHP elevated, short synathen/rein/ genetics [CAH]
Other androgens elevated; look for adrenal tumour [CT]
Urinary steroid profile

Investigations Normal
Bone age <1-2yr advanced
Normal investigations

Observe Only
Normal history and examination at first appointment
Premature thelarche
Normal investigations

Investigations Abnormal
Bone age >2yr advanced
Increased baseline LH/FSH and estradiol / testosterone
OR clinically in central Puberty

Prepubertal response or Predominant FSH response
(Suggests thelarche)

GnRH Stimulation Test

Central Precocious Puberty
Request MRI brain
Start GnRH analogue or
Monitor pubertal tempo closely (clinical exam and bone age)

Rachel M Williams et al. Arch Dis Child 2012;97:250-254
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Delayed Puberty – What Could IT Be?

• Primary Hypogonadism
  – Turner Syndrome
  – Klinefelter Syndrome
  – Gonadal injury (chemo, autoimmune, infection, cryptorchidism)
  – DSD (testosterone biosynthesis disorders, CAIS, receptor defects)

• Secondary Hypogonadism
  – Constitutional Delay of growth and puberty
  – GnRH deficiency
    • Kallman Syndrome
    • Hypopituitarism
      – Tumors
      – SOD
  – Functional HH
    • Anorexia, Poorly controlled chronic disease
Delayed Puberty

• **Work Up**
  - LH
  - FSH
  - Estradiol/Testosterone
  - TSH and Free T4
  - Bone Age
  - Screen for chronic Medical Disease
    - Celiac screen, CBC, ESR, CMP, ?Prolactin
  - Consider karyotype

• **Treatment**
  - Time in CDGP
  - Testosterone
    - 3-6 months low dose
  - Estrogen

* Patient and Family history is most helpful
You are seeing a 16-year-old girl for the first time who complains of amenorrhea. The mother’s menarche was at age 12 years. The girl developed pubic hair at age 11 years and breast buds at age 12 years. She has no other symptoms. The mother reports that the girl eats well and has been active all her life. Physical examination reveals a height of 57 in, weight of 89 lb, BMI of 19.3, breast tissue at SMN rating 2, and pubic hair at SMR 4. A urine pregnancy test shows negative results. Laboratory results include: LH of 10mIU/mL (normal adult female, 2-95mIU/mL), FSH of 42mIU/mL (normal adult female, 1-30mIU/mL), and prolactin of 27ng/mL (normal, 5-23ng/mL).

Of the following, the MOST likely cause of this girl’s primary amenorrhea is

A. congenital adrenal hyperplasia
B. excessive exercise
C. imperforate hymen
D. prolactinoma
E. Turner syndrome

Question
A 7 yr old girl presents to you for concern for precocious puberty with progressive breast development. She is overweight but otherwise healthy. Her mother had menarche at 15 years and is concerned if her daughter is starting puberty now. On PE you were able to palpate a small amount of breast tissue, but an appreciable amount of adipose tissue around her breast area. She has no pubic hair. You are concerned about precocious puberty but also consider that she may simply be overweight and not have true breast tissue. You need to determine if further workup is necessary. Of the following the BEST test to help you make this decision is

A. Bone age  
B. MRI brain  
C. estradiol level  
D. 17 OHP  
E. LH level
An 8-year-old boy presents for a routine physical. On exam, he has Tanner 2 pubic hair and 5 cc bilaterally descended testes.

Which of the following is the next best diagnostic test?

A. testicular ultrasound
B. testosterone level
C. adrenal CT
D. bone age
E. brain and sella MRI
14yo male presents to you clinic with a “swollen left nipple” for 2 weeks. Occasionally it is tender. No discharge. No redness or fever. He has had no chronic illnesses.

On physical examination, he appears healthy. He has a 2cm, firm, freely moveable, subareolar mass on the left breast that is mildly tender. No redness or discharge. No mass is palpated in the right breast.

Which of the following is the most likely diagnosis?

A. Rhabdomyosarcoma
B. Liposarcoma
C. Physiologic pubertal gynecomastia
D. Subareolar abscess
E. Breast cancer
Pattern of gonadotropin secretion throughout life

Gestation  Infancy  Childhood  Puberty  Adult-reproductive period  Senescence

FSH>LH  GnRH  LH>FSH

www.memorangapp.com/flashcards/105707/Physiology+L45+Development+and+Puberty/