Precocious Puberty

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Objectives

1. Define precocious puberty in boys and girls

2. Distinguish between precocious puberty and normal variants of pubertal development

3. Initiate a work-up for precocious puberty

Case – 6 year old girl with early puberty

• 6 year and 2 month old girl with breast development

• Breast buds started about 3 months ago

• No other signs of puberty

• History of hydrocephalus with a VP shunt

• Maternal age at menarche 12 years
Case

Physical Exam:
- Tanner II breasts
- No pubic or axillary hair
- No acne
- Normal neurological exam

- Parents are worried. Will she have her period soon?

What is puberty?

Puberty is the gradual development of secondary sexual characteristics, reproductive capability, growth spurt, and final adult stature.
Physiology – hypothalamic pituitary gonadal axis (HPG)

Physiology – activation of HPG axis

Three periods of activation

1. Mid-gestational fetus then silenced toward the end of gestation

2. Reactivation at birth – mini-puberty of infancy followed by active inhibition of GnRH secretion

3. Puberty – sustained increase in pulsatile GnRH secretion
Progression of puberty

Girls:
- Breast development
- Growth spurt
- Pubic hair
- Menarche

Boys:
- Testicular enlargement
- Penile growth and pubic hair
- Growth spurt
- Spermacarche

Gonarche versus adrenarche

Gonadarche: activation of gonads to produce estrogen or testosterone
- Ovaries: Thelarche $\rightarrow$ Menarche
- Testes: Testicular growth, pubarche, spermacarche

Adrenarche: increase in androgen production from adrenal cortex (DHEAS, androstenedione)
- Pubarche (Development of pubic hair)
Hypothalamic pituitary adrenal axis

HYPOTHALAMUS
CRH

PITUITARY
ACTH

ADRENAL GLANDS
DHEAS
17OHP
Testosterone

Pubic hair
Axillary hair
Acne
Body odor

Tanner Staging -Breasts

- Stage 1: No palpable breast tissue.
- Stage 2: Breast bud, subareolar, with enlargement of the areolar diameter.
- Stage 3: Enlargement of the breast beyond the areola.
- Stage 4: Areola and papilla project above the breast, “secondary mound.”
- Stage 5: Recession of the areola to match the contour of the breast.
Tanner Staging – Pubic Hair

• Stage 1: No pubic hair.

• Stage 2: Sparse straight hair on labia majora.

• Stage 3: Darker, coarser, curlier, extends to mons pubis.

• Stage 4: Adult-like hair on labia and mons.

• Stage 5: Adult-like hair extending to thighs.

Testicular volume

• Stage 1: 1-3 mL

• Stage 2: 4-5 mL

• Stage 3: 6-8 mL

• Stage 4: 10-12 mL
  • Growth spurt

• Stage 5: 15-25 mL
Tanner staging – pubic hair

- Stage 1: No pubic hair.
- Stage 2: Sparse straight hair at base of penis.
- Stage 3: Darker, coarser, curlier, extends to mons pubis.
- Stage 4: Adult-like hair at base of penis and mons.
- Stage 5: Adult-like hair extending to thighs.

Growth velocity

Girls:
Peak height velocity at mean age of 11.5 years

Boys:
Peak height velocity at mean age of 13.5 years
Pubertal timing - female

Sexual Development: Girls

Pubertal timing - male

Sexual Development: Boys

Control of pubertal timing

- Genetics
  - Internal Signals
    - kisspeptin
    - GABA
    - leptin
    - glutamate
  - External Signals
    - metabolic
    - stressors
    - sleep
    - light
- Internal Signals
  - GnRH
  - Pituitary
  - Hypothalamus
  - LH
  - FSH
  - Testosterone
  - Estrogen
  - Progesterone
  - Testes
  - Ovary

Precocious Puberty

- Onset of puberty that is 2-2.5 standard deviations earlier than the population mean
- Breast development prior to 8 years (7 years for African-American girls)
- Testicular development prior to 9 years
- Rapid progression of pubertal milestones
What Causes Precocious Puberty?

Central

Precocious Puberty

Peripheral

Benign variants

Central precocious puberty (CPP)

HPG Axis

Central Precocious Puberty

Hypothalamus

GnRH

Pituitary

LH

FSH

Testis

Ovary

Testosterone

Estrogen

Progesterone
Central precocious puberty

Causes

- Idiopathic
  - Girls 80-90%
  - Boys 25-60%
- CNS Lesions/disorders
  - Hypothalamic hamartoma
  - Tumors
    - Optic glioma, astrocytoma, etc
  - Encephalitis
  - Static encephalopathy
  - Brain Abscess
  - Head trauma
  - Hydrocephalus
  - Arachnoid cyst
  - Myelomeningocele
  - Vascular lesion
  - Cranial irradiation
- Genetic variations

Causes of precocious puberty

- Precocious Puberty
  - Central
  - Peripheral
  - Benign variants
Peripheral precocious puberty

Causes:
- Girls
  - Ovarian cysts
  - Ovarian tumors
- Boys
  - Leydig cell tumor
  - HCG secreting germ cell tumor
  - Familial male limited precocious puberty
- Both
  - Congenital adrenal hyperplasia
  - Hypothyroidism
  - Exogenous exposure to sex steroids
  - McCune-Albright syndrome

• Gonadotropin independent
• Pubertal hormones increase without activation of HPG axis
• Pubertal milestones may occur in an unusual order

Peripheral Precocious Puberty

Hypothalamus

GnRH

Pituitary

LH

FSH

Testis

Ovary

Testosterone

Estrogen

Progesterone
Causes of precocious puberty

- Precocious Puberty
  - Central
  - Peripheral

Benign variants of normal puberty

- Appearance of pubertal milestones at an unexpected age
- Non-progressive
- Require monitoring but not treatment
Premature thelarche

- Separate from neonatal breast hypertrophy
- Idiopathic
- Isolated breast development
- < 2 years old or 6-8 years old
- Normal height velocity
- Non-progressive (10-20% may progress to central puberty)

Premature adrenarche

- Appearance of pubic hair, axillary hair, or body odor in girls before 8 and boys before 9 years

Causes:
- Benign premature adrenarche
- Congenital adrenal hyperplasia
- Adrenal tumors

Diagram:
- Hypothalamus
  - CRH
  - PITUITARY
    - ACTH
  - Adrenal glands
    - Cortisol
    - DHEAS
    - 17OHP
    - Testosterone
Pubic hair of infancy

- Isolated pubic hair
- No other signs of sexual development
- Develops by 12 months of age, usually by 6 months
- Hair can be in atypical location (scrotum or mons)
- Always consider pathologic causes of hyperandrogenism

Evaluation of precocious puberty: History and physical

Medical History:
- Timing- When first noticed, rate of change
- Linear growth
- Headaches, seizures, vision changes
- Exposures
- Past history of CNS disease
- Family history of pubertal timing or endocrine disorders

Physical Exam:
- Height, weight, growth velocity
- Pubertal staging
- Neurological exam
- Visual field testing
- Café-au-lait spots
Evaluation of precocious puberty: Bone age and initial labs

- Bone age – precocious puberty versus benign variant

- Initial lab work-up – Morning sample
  - Signs of gonadal activation (breast/testicular enlargement)
    - LH
    - FSH
    - Estradiol
    - Testosterone

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<tr>
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<th>Central Precocious puberty</th>
<th>Peripheral precocious puberty</th>
<th>Benign variant</th>
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<tbody>
<tr>
<td>LH</td>
<td>↑</td>
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<tr>
<td>FSH</td>
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<tr>
<td>Estradiol</td>
<td>↑</td>
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Evaluation of precocious puberty: GnRH simulation test

If initial evaluation is consistent with precocious puberty but the LH, FSH and estradiol are pre-pubertal – consider a GnRH stimulation test to distinguish between central precocious puberty and a benign variant

GnRH stimulation test:
- LH, FSH and estradiol/testosterone are measured at baseline
- Single dose of GnRH agonist is administered
- LH measured every 30-60 minutes for 2 hours and estradiol/testosterone measured 24 hours later
Evaluation of precocious puberty: Adrenal evaluation and other labs

- If there are signs of early androgen exposure (pubic or axillary hair, body odor) check androgen levels:
  - Testosterone
  - 17 hydroxyprogesterone
  - DHEAS

Mildly elevated DHEAS is consistent with benign premature adrenarche.

17OHP levels > 82 ng/dl need further evaluation of congenital adrenal hyperplasia. > 200 ng/dl highly sensitive and specific for CAH.

DHEAS > 135 mcg/dl or testosterone > 35 ng/dl needs for further evaluation for CAH or adrenal tumor

**Adrenal labs should be drawn in the morning**

Other labs: TSH, free T4, HCG, karyotype

Evaluation of precocious puberty: Imaging

- Brain MRI
  - All boys with central precocious puberty
  - Girls with central precocious puberty starting before age 6 years, consider between 6-8 years based on clinical factors

- Pelvic ultrasound
  - Helps to differentiate between central precocious puberty and benign variant
  - Evaluate for ovarian cyst or tumor

- Adrenal ultrasound:
  - Premature adrenarche with very elevated androgens

- Testicular ultrasound:
  - Evaluate for leydig-cell tumor
Treatment of CPP

- Treatment of underlying cause if indicated
- GnRH agonist

GnRH agonist inhibits pulsatile LH & FSH secretion

Does not treat adrenarche: pubic hair will progress

Hypothalamus → GnRH → Pituitary (LH, FSH) → Testosterone, Estrogen, Progesterone

Treatment of CPP

- GnRH agonists:
  - Leuprolide monthly injection
  - Leuprolide every 3 month injection
  - Triptorelin every 6 month injection
  - Histrelin implanted subcutaneously by minor surgical procedure lasts at least one year
Treatment of CPP – who needs treatment?

Indications for treatment:

Height outcome
- For girls with CPP onset before 6 years of age – treatment with GnRH agonist results in adult height gain of 9-10 cm.
- Girls 6-8 years gain of 4-7 years.
- For boys – less data maybe prior to 7.6 years – 6.2 - 8.7 cm gain.
- More advanced bone age (girls or boys) means less height benefit from treatment

Psychosocial concerns
- Take into account maturity of patient and family attitude

Treatment of peripheral precocious puberty

- Does not respond to GnRH agonist therapy
- Treatment directed at removing or blocking the production of or response to sex steroids depending on the cause:
  - Tumors – surgical
  - Ovarian cysts – regress spontaneously – monitor
  - Exogenous sex steroid exposure - identify and remove exposure
  - Congenital adrenal hyperplasia – glucocorticoid
  - McCune Albright – aromatase inhibitors, selective estrogen receptor modulators
  - Familial male limited precocious puberty – antiandrogen combined with aromatase inhibitor
### Who should evaluate and treat?

| Primary care physician/NP/PA (Pediatrician, family medicine) | • Family and personal history  
• Chart growth velocity/history  
• Assess physical signs of puberty  
• Assess for underlying pathology |
|---------------------------------------------------------------|
| Primary care or Endocrinologist | • Bone Age  
• Determine predicted adult height  
• Sex Hormone evaluation  
• Pelvic ultrasound  
• Order MRI if indicated |
| Endocrinologist | • GnRHa stimulation test  
• Candidacy for GnRHa therapy  
• Initiate GnRHa therapy  
• Monitor response to therapy |

### Back to case

- 6 year and 2 month old girl with Tanner II breast development, increased linear growth velocity, history of hydrocephalus.

- Bone age: Eight years and 10 months (advanced)

- AM labs:
  - LH <0.1 IU/L
  - FSH 2.1 IU/L
  - Estradiol 7.7 pg/ml

- **GnRH stimulation test**

- **Brain MRI** – no change

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<thead>
<tr>
<th>LH (IU/L)</th>
<th>FSH (IU/L)</th>
<th>Estradiol pg/ml</th>
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<tr>
<td>Baseline</td>
<td>0.6</td>
<td>3.7</td>
</tr>
<tr>
<td>1 hour</td>
<td>14.6</td>
<td>9.1</td>
</tr>
<tr>
<td>2 hour</td>
<td>16.6</td>
<td>11.8</td>
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<td>24 hour</td>
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DIAGNOSIS: Central precocious puberty

TREATMENT: Leuprolide injections every 3 months
Is puberty starting earlier?

**Pediatric Research in Office Settings (PROS)**

- 1997 multicenter, cross-sectional study
- Evaluated age at onset of pubertal characteristics in girls
- Compared to norms from the 1960s, girls in the US starting puberty 6 months to 1.5 years earlier
- In Caucasian girls, Tanner II started 1 year earlier and in African-American girls, Tanner 2 started 2 years earlier.

Herman-Giddens et al, *Pediatrics* 1997
Is puberty starting earlier?
Breast cancer and the environment research study program (BECRP)

- Puberty arm investigating environmental exposures and timing of puberty
- Longitudinal study between 2004-2008, enrolling girls 6 - 8 years old and documenting age at Tanner II.
- Median age at Tanner II was 9.7 years for Caucasian girls, 9.3 years for Hispanic girls, and 8.8 years for African
- At 8 years of age: 18% of Caucasian girls, 31% of Hispanic girls and 43% of African-American girls had Tanner II breasts or more.
- BMI > 85th percentile was greatest predictor of earlier age at Tanner II breasts.


Is puberty starting earlier?
Comparison of PROS and BECRP data

Biro et al. Pediatrics 2013
What about age at menarche?

What about early puberty in boys?

- Less data available with mixed results

- Earlier studies suggested no change or minimal change in pubertal timing in boys in recent decades.

- 2012 study from PROS practices

- Tanner II development 1 year earlier
What is causing earlier puberty?

- Obesity
- Prematurity
- Stress
- Epigenetics
- Endocrine disruptors
  - Diethylstilbestrol (DES)
  - Bisphenol A (BPA)
  - Polybrominated biphenyls (PBB)
  - Polychlorinated biphenyl (PCB)
  - Pthalates
  - Perfluorooctanoic acid (PFOA)

Why is puberty starting earlier?

Adopted from Ahmed, Ong, Dunger 2009
Thank you!

Questions?