Puberty and Pubertal Disorders

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Objectives

• Review normal pubertal development

• Recognize common pubertal disorders

• Identify recent trends in pubertal development
What is the normal timing of puberty?

• Females*
  ▫ Thelarche typically 8-12(13) years, avg 10.5 years
  ▫ Menarche occurs 2-2.5 years after thelarche, avg 12.5 years

• Males
  ▫ Testicular enlargement starts 9-14 years, avg 11.5 years

• Tempo

• Secular trends
The Reproductive Axis

**Internal Signals**
- kisspeptin
- GABA
- leptin
- glutamate

**External Signals**
- metabolic
- sleep
- stressors
- light

**Genetics**

**Others**

Figure modified from Sisk and Foster '04
Hypothalamic-pituitary-gonadal axis activation: 3 time periods

1. HPG axis is active in the mid-gestational fetus, and silenced towards the end of gestation

2. Reactivation of the axis at birth
   ▫ “Minipuberty of infancy”
   ▫ Followed by active inhibition of GnRH secretion

3. Puberty
   ▫ Sustained increase in pulsatile GnRH
   ▫ Trigger(s) remain unknown
Pubertal timing

I bring you social anxiety! and hair!

Nobody likes The Puberty Fairy.
Pubertal timing

• Genes involved in GnRH regulation
• Data suggest that around 50–80% of the variation in pubertal onset might be genetically determined

• Identifying GnRH neural inputs: genetic studies in patients with pubertal disorders
Kisspeptin system
Gonadarche vs Adrenarche

- **Gonadarche**: activation of gonads to produce estrogen or testosterone
  - Ovaries: Thelarche → Menarche
  - Testes: Pubarche, Spermarche

- **Adrenarche**: increase in androgen production from adrenal cortex (DHEA, androstenedione)
  - Pubarche
Adrenal androgen production

Diagram showing the process of Adrenal androgen production involving the CNS, Hypothalamus, Pituitary, Adrenal cortex, Androstenedione, DHEA, and their development of symptoms such as pubic hair, armpit hair, and acne.
Adrenal androgen production
Tanner Staging - Girls

- **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.
• 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.
Tanner Staging - Girls

- Breasts – lipomastia vs true breast tissue
  - Breast bud forms as a subareolar disk
  - **Clinical tip – doughnut sign**

- Pubic Hair – vellous hair vs terminal hairs
  - **Clinical tip – describe what you see if exam is not a “classic” Tanner stage**
Tanner Staging - Boys

- **Stage 1**: 1-3 cc
- **Stage 2**: 4-5 cc
- **Stage 3**: 6-8 cc
- **Stage 4**: 10-12 cc
  - Growth spurt
- **Stage 5**: 15-25 cc
Tanner Staging - Boys

- 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.
Tanner Staging - Boys

- Pubarche versus puberty
  - Testicular volume

- Pubic Hair – vellous hair vs terminal hairs
Progression of Puberty

- **Girls**
  - Breast development (Pubic hair)
  - Growth spurt (Tanner 3-4)
  - Menarche (Tanner 4-5)

- **Boys**
  - Testicular enlargement
  - Pubic hair
  - Penile enlargement
  - Growth spurt (Tanner 4-5)
Growth Velocity
Puberty is starting earlier

- 1997: Pediatric Research in Office Settings (PROS)
  - Compared to norms from 1960s, girls in the US were starting puberty 6 months to 1.5 years earlier

- Why? What changed?
  - Influences of prematurity, endocrine disruptors, stress, family structure, epigenetics, and other factors can impact pubertal onset puberty

Associations Between Maternal Obesity and Pregnancy Hyperglycemia and Timing of Puberty Onset in Adolescent Girls: A Population-Based Study

Ai Kubo, Julianna Deardorff, Cecile A Laurent, Assamira Ferrara, Louise C Sreenan, Charles P Quezenberry, Lawrence H Kushi

American Journal of Epidemiology, https://doi.org/10.1093/aje/kevy040

Published: 15 March 2018  Article history ▼
Contemporary studies of the onset of puberty (breast development) in girls.

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>Estimated years of birth</th>
<th>Mean age breast stage 2</th>
<th>Mean age of menarche</th>
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<tbody>
<tr>
<td>Reynolds &amp; Wines</td>
<td>1930–35</td>
<td>10.8</td>
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<td>Marshall &amp; Tanner</td>
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<td>Harlan; MacMahon (NHES)</td>
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<td>Herman-Giddens (PROS)</td>
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<td>8.9 / 10.0</td>
<td>12.2 / 12.9</td>
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<td>Sun (NHANES III)</td>
<td>1978–85</td>
<td>9.5 / 10.4</td>
<td>12.1 / 12.6</td>
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<td>(Sun et al 2002)</td>
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<td>Biro (NGHS)</td>
<td>1978–79</td>
<td>9.8 / 10.4</td>
<td>12.0 / 12.6</td>
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<td>Aksglaede (Copenhagen)</td>
<td>1991</td>
<td>10.9</td>
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Studies by Herman-Giddens, Sun, and Biro reflect ages of African-American girls, followed by Caucasian girls. Study by Aksglaede reflects two cohorts of girls from the Copenhagen Puberty Study, born 15–16 years apart.
EDs → Environment → Prenatal growth → Energy balance → Obesity Visceral fat

- Ovaries: ↑ Androgens
- Adrenals: ↑ Androgens
- Liver: ↓ SHBG
- Fat cells: ↑ Aromatase, ↑ Leptin, ↑ Adipokines

↑ Insulin resistance → Bioavailability of sex steroids → Promotion of earlier adrenarche, pubarche, thelarche, and central precocious puberty

Adopted from Ahmed, Ong, Dunger 2009
When Things Go Wrong

• Precocious puberty
  ▫ Breast development before age 8 years*
  ▫ Testicular enlargement before age 9 years

• Delayed puberty
  ▫ Breast development after age 12 years
  ▫ Testicular enlargement after age 14 years
Precocious Puberty

Central

Peripheral

Benign variants
Central Precocious Puberty

HPG Axis

Hypothalamus → GnRH → Pituitary → LH, FSH → Testis, Ovary → Estrogen, Testosterone → Development of: Pens, Pubic hair, Testes → 

Development of: Breasts, Ovaries, Uterus

LH, FSH
Central Precocious Puberty

• Idiopathic
  ▫ Girls: 80-90%
  ▫ Boys: 25-60%
• CNS lesions
• Genetic mutations
Peripheral Precocious Puberty

HPG Axis

Development of:
- Penis
- Pubic hair
- Testes

Testosterone

Development of:
- Breasts
- Ovaries
- Uterus

LH

FSH

GnRH

Hypothalamus

Pituitary

Testis

Ovary

Estrogen

Progesterone
Peripheral Precocious Puberty

- **Girls**
  - Ovarian cyst
  - Ovarian tumor

- **Boys**
  - Leydig cell tumor
  - hCG secreting germ-cell tumor
  - Familial male-limited precocious puberty
Other Causes

• Exogenous sex steroids
• Severe hypothyroidism

• McCune-Albright syndrome
  ▫ Peripheral precocious puberty
  ▫ Café au lait macules
    • Irregular, coast of Maine
  ▫ Fibrous dysplasia of bone
Evaluation

- History- timing of progression, family history
- Physical exam
- Laboratory evaluation – LH, FSH, estradiol/testosterone
  - Clinical tip: morning labs
- Bone age X-ray

Based upon results
- Leuprolide stimulation test
- Imaging – brain MRI, pelvic US
Treatment

• Central: GnRH agonist
  ▫ Leuprolide injection – monthly or every 3 months
  ▫ Histrelin implant

• Peripheral: Treat underlying cause
GnRH agonist stops pulsatile GnRH secretion
Premature Adrenarche

- Development of pubic hair, axillary hair, and/or body odor before age 8 years in girls or 9 years in boys
- Causes:
  - Benign
  - Non-classical congenital adrenal hyperplasia
  - Adrenal tumor
Evaluation

- History - timing of progression, family history
- Physical exam
  - Pubarche alone or with thelarche
  - Clitoral enlargement
- Laboratory evaluation – 17-OHP, DHEAS, Testosterone
  - First morning labs
  - +/- ACTH stim test
- Bone age x-ray
Treatment

- Idiopathic premature adrenarche ("benign")
  - Monitor growth
  - Increased risk of PCOS, metabolic syndrome
- Non-classical CAH: hydrocortisone
- Adrenal tumor: surgery
Pubic hair of infancy

- Isolated pubic hair
- No other signs of secondary sexual development
  - No penile or clitoral enlargement
  - No growth acceleration
  - No breast development
Pubic hair of infancy

• Develops within first year of life, often by 6 months
• Hair can be in atypical locations
  ▫ Scrotal
  ▫ Mons

• Differential diagnosis: premature adrenarche and pathologic hyperandrogenism
  ▫ Labs
  ▫ Monitoring
Breast buds in a toddler

• 20 month old girl referred to endocrine due to the presence of breast buds
• Present for “a long time” on right side, no breast tissue on the left
• No significant growth since mom first noticed it
• No vaginal bleeding, body odor, or pubic hair

Prepubertal Gynecomastia Linked to Lavender and Tea Tree Oils

Derek V. Henley, Ph.D., Natasha Lipson, M.D., Kenneth S. Korach, Ph.D., and Clifford A. Bloch, M.D.
Breast buds in a toddler

- **Chest**: Tanner 3 breast on right extending just beyond the nipple, no breast bud on left
- **GU**: dark pink vaginal mucosa, no pubic hair (fine vellous hairs only)
  - Clinical tip: vaginal mucosa as estrogen bioassay

- **Labs** (obtained prior to consultation):
  - Estradiol 4.4 pg/ml (pre-pubertal < 15)
  - LH 0.029 mIU/ml (pre-pubertal <0.3)
  - FSH 3 mIU/ml
Breast development in a toddler

- 4 month follow up:

- Chest: Tanner 2 breast on right with small amount of soft breast tissue just below the nipple, no breast tissue on left
Premature Thelarche

- Isolated breast development (unilateral or bilateral)
  - Typically not beyond Tanner stage 3
- Absence of other secondary sexual characteristics
- No growth acceleration
- Typically occurs before age 2 years, resolves by age 3 years
Delayed Puberty

• Girls
  • No breast development by age 12 years
  • No menarche by age 16 years or 5 years after thelarche

• Boys
  • No testicular enlargement by age 14 years
Delayed Puberty

- Hypogonadotrophic Hypogonadism
- Primary Gonadal Failure
- Constitutional delay (benign variant)
Hypogonadotropic Hypogonadism

Causes:
- Brain tumor
- Infiltrative diseases
- Genetics
Causes:
- Chemotherapy
- Radiation
- Chromosomal abnormalities (XO, XXY)
- Other genetic factors
Delayed Puberty: Evaluation

- History - history of radiation/chemotherapy, sense of smell, family history, growth pattern, BMI
- Physical exam
Delayed Puberty: Evaluation

- Laboratory evaluation: LH, FSH, estradiol/testosterone
  - Morning labs
  - +/- Karyotype
- TSH, Prolactin
- Bone age X-ray
- Imaging – brain MRI (hypogonadotrophic hypogonadism)
Treatment

• Pubertal induction
  ▫ Estradiol – transdermal, pills
  ▫ Testosterone – IM (SC) injections, gel
Primary amenorrhea in a 16 year old female

- Reports adult body odor, pubic hair and axillary hair at 12 years; breast development at 14 years
- No history of vaginal bleeding
- Previously healthy, negative review of systems
Primary amenorrhea

- Tanner 1 breast
- GU: Tanner 5 pubic hair, normal external female genitalia, nonestrogenized vaginal mucosa
- Extremities: short 4<sup>th</sup>/5<sup>th</sup> metacarpals, scant axillary hair (1-2 hairs noted)
Primary amenorrhea

- Urine pregnancy: negative
- LH: 28.7 mIU/mL (0.4-11.7)
- FSH: 107.1 mIU/mL (1-9.2)
- Estradiol: 1.8 pg/ml (34-170)
- Normal thyroid, prolactin
- Karyotype: 45 XO
- Bone age 13 years
Genetic Mutations Associated with POI

New mutations being identified

<table>
<thead>
<tr>
<th>Estimated frequency in POI</th>
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<tbody>
<tr>
<td>X chromosome defects</td>
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<tr>
<td>Turner's syndrome and related defects</td>
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<tr>
<td>Triple X syndrome</td>
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<td>Fragile X syndrome (FMR1 premutation)</td>
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<td>DIAPH2 disruption (translocation)</td>
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<td>BMP15 variants</td>
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<td>PGRMC1 variants</td>
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<td>Autosomal defects</td>
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<tr>
<td>Complex diseases</td>
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<td>Galactosemia (GALT)</td>
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<td>BPES (FOXL2)</td>
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<td>APECED (AIRE)</td>
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<td>Mitochondrial diseases (POLG)</td>
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<td>Demirhan syndrome (BMPR1B)</td>
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<td>PHP1a (GNAS)</td>
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<td>Ovarioleucodystrophy (EIF2B)</td>
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<td>Ataxia telangiectasia (ATM)</td>
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<td>Perrault syndrome (HSD17B4, HARS2, CLPP, LARS2, C100orf2)</td>
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<td>Premature aging syndromes:</td>
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<td>Bloom syndrome (BLM)</td>
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<td>Werner syndrome (WRN)</td>
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<td>GAPO disease (ANTXR1)</td>
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<td>Isolated disease</td>
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<tr>
<td>FSH/LH resistance (FSHR and LHCGR)</td>
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<tr>
<td>INHA variants</td>
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<td>GDF9 variants</td>
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<td>FOXL2 variants</td>
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<td>FOXO3 variants</td>
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<td>NOBOX variants</td>
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<td>FIGLA variants</td>
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<tr>
<td>NR5A1 variants</td>
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<td>LHX8 variants</td>
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<tr>
<td>DNA replication/meiosis and DNA repair genes variants (DMC1, MSH4, MSH5, SPO11, STAG3, SMC1β, REC8, POI1B, HFM1, MCM8, MCM9, SYCE1, PSMC3IP, NUP107, FANCA, FANCC, FANCG)</td>
</tr>
</tbody>
</table>

FSH, follicle-stimulating hormone; LH, luteinizing hormone; POI, primary ovarian insufficiency.

a Refer to specific article on this same issue.

b 1% in Indian and 2% in Chinese women, respectively.

Turner Syndrome

- Complete or partial loss of one X chromosome
- 4-5% of all cases of POI
- 90% of women with TS demonstrate POI
- Other features can include:
  - Short stature
  - Aortic coarctation, bicuspid Ao valve
  - Broad neck and chest
  - Wide carrying angle
  - Multiple nevi

Fragile X

- Fragile X gene (*FMR1*) is located on the X chromosome at Xq27.3
- Mutation consists of an unstable CGG repeat in the 5’ untranslated region of the FMR1 gene
  - Normal is <40-44 repeats
  - Pre-mutation is 55-200 repeats
  - Fragile X syndrome is >200 repeats
- Abnormal expansion silences gene

Fragile X Premutation

- Of women with POI, *FMR1* premutation accounts for:
  - 3.2% of isolated cases
  - 11.5% of familial cases
- Of women with *FMR1* premutation
  - 15-24% have POI
- Women with premutation have an increased risk of having a child with fragile X syndrome

Genetic

- 4-31% of women with POI had one or more affected family members with POI
- Maternal transmission most frequent

Rosetti, Clinical Genetics 2017
16 year old female with POI due to Turner syndrome

- Pubertal induction initiated with transdermal estradiol
- Screening for renal disease, cardiac disease, dyslipidemia, diabetes mellitus, hearing loss
  - All negative
7 year old boy with early puberty

- 7 year 11 month old boy referred for early puberty
- Body odor since age 6 years, pubic hair since age 6 years 6 months, also with acne
- “Has always been larger than peers”
- PMH asthma, otherwise healthy
- No family history of early puberty
Early puberty
Early puberty

Height Velocity-for-age Percentiles (Boys, 2.5 to 17.5 years)
7 year old with early puberty

- **GU**: 8-10 cc testicles bilaterally, Tanner 3 pubic hair

**Labs: (done in afternoon)**
- LH 1.1 mIU/ml (pre-pubertal <0.2)
- FSH 2.48 mIU/ml
- Total Testosterone 26 ng/dl (pre-pubertal <30)
- TSH, HCG, 17-OHP normal
Brain MRI
7 year old with early puberty

MRI:
• 2cm optic glioma at the chiasm with hydrocephalus

Bone age X-ray
• Advanced at 10-11 years
7 year old with early puberty

Clinical course:

- Treated with chemotherapy x 12 months with good response
- Hydrocephalus compensated and stable
- Normal height prediction based on bone age X-ray, family chose not to pursue treatment for central precocious puberty
5 year old girl with early puberty

- 5 year 9 month old girl with breast development
- Started 4 months ago (5 years 5 months old) and progressed very slowly
- Pubic hair since 5 years 2 months, also progressed slowly
- Body odor since 5 years 8 months

- Premature - 35 weeks, induced for placental insufficiency, BW 4 lb 11 oz, no complications after birth
- No known hormonal exposures
- Family history negative for early puberty, maternal menarche age 12 years
5 year old girl with early puberty
5 year old girl with early puberty

- Chest: Tanner stage 3 breasts
- GU: Tanner stage 3 pubic hair

**Labs**
- Estradiol 38 pg/ml (pre-pubertal <15)
- LH 0.822 mIU/ml (pre-pubertal <0.2)
- FSH 5.3 mIU/ml
- TSH, Prolactin, DHEAS, 17-OHP, and testosterone normal
- Brain MRI normal

**Central Precocious Puberty**

**Idiopathic**
5 year old girl with early puberty

- Diagnosis: Idiopathic central precocious puberty
- Treatment: Histrelin implant
Pubertal assessment

• Tanner staging at every well child check
• Girls 8-12/13 years
• Boys 9-14 years
• Tempo

• Gonadarche vs Adrenarche
  ▫ Gonadarche: LH, FSH, Estradiol/testosterone
  ▫ Adrenarche: 17OHP, DHEAS, testosterone
  ▫ Morning labs
"At your age, Tommy, a boy’s body goes through changes that are not always easy to understand."