Better Late Than Never

Evaluation of delayed puberty in primary care

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What’s puberty?

- Hormonal and body changes of the transition from childhood to sexual maturity, fertility, end of growth.
- Most of the physical changes are effects of androgens or estrogens
- From start to finish, it takes about 5 years in girls, 6 in boys.
Tanner Stages: Males

**Tanner 1:**
Pubic Hair: None
Testes: <2.5cm (<3mL)

**Tanner 2:**
PH: Scanty, Long, Slightly pigmented
Testes: 2.5-3.2cm (>4mL)

**Tanner 3:**
PH: Beginning to curl, small amount
Testes: 3.3-4cm (>10mL)

**Tanner 4:**
PH: Coarse, curly, adult male distribution
Testes: 4.1-4.5cm (>16mL)

**Tanner 5:**
PH spread to medial surface of thigh
Testes: >4.5cm (25mL or larger)

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Relationship of Pubertal Milestones

- **Height spurt**
- **Penis**
- **Testis**
- **Pubic hair**

Age (years)

- Apex strength spurt
- 10½ -16
- 11 -14½
- 13½ -17
- 10 -13½
- 10 -15
- 14½ -18
- 14 -18
What’s normal?

- In boys
  - Testicular enlargement 11.5y (9.5-13.5y)
  - Pubic hair 12y (10-14y)
  - Growth spurt 12.5-15y
  - Completion of growth 17.5

Tanner Stages: Females

<table>
<thead>
<tr>
<th>Tanner 1:</th>
<th>Tanner 2:</th>
<th>Tanner 3:</th>
<th>Tanner 4:</th>
<th>Tanner 5:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubic Hair None</td>
<td>PH: Scanty, Long, Slightly pigmented, located at medial surface of labia</td>
<td>PH: Beginning to curl, increasing amount</td>
<td>PH: Coarse, curly, adult female distribution</td>
<td>PH spread to medial surface of thigh</td>
</tr>
<tr>
<td>Breasts: None</td>
<td>Breasts: Breast bud elevated as small mound</td>
<td>Breasts: Mound and areola enlarged, no contour demarcation</td>
<td>Breasts: Areola and papilla form 2nd mound</td>
<td>Breasts: Mature nipple, areola part of general breast</td>
</tr>
</tbody>
</table>
Relationship of Pubertal Milestones

What’s normal?

- In girls
  - Thelarche 10y5m (8y-13y)
  - Pubarche 11y (8.5-13.5y)
  - Growth spurt 10-12.5y
  - Menarche 12.5y (10.5-14.5)
  - Adult height reached 14.5y
Two parallel hormonal processes: gonadal and adrenal

- **Gonadal maturation (gonadarche)**
  - Release of hypothalamic suppression allows pulsed GnRH to stimulate the pituitary
  - Pituitary LH & FSH signal the gonads to start making sex hormones

- **Adrenal maturation (adrenarche)**
  - Histological changes in zona reticularis
  - Adrenal androgen precursors rise: DHEAS, Androstenedione
  - Physical effects include body odor, pubic hair, acne
  - In about 30% of females begins prior to gonadarche

**Adrenarche isn’t the important part of puberty**

- Pubic hair, acne, axillary hair don’t count
- Neither do moodiness or abdominal discomfort
- Breast development in girls, testicular enlargement in boys, are the clearest that centrally directed, gonadal puberty is underway
2 Quick Slides on Adrenarche

- DHEA-S or Androstenedione higher than age, lower than adult (usually Tanner 2 level)
- LH, FSH, estradiol, or testosterone all normal
- BA up to 2 yrs advanced
- Associated with IUGR
- Associated with obesity, future PCOS

Primary Care Management of Premature Adrenarche

- Recheck progress in 6 mos: may have increased pubic hair up to stage 3, a little acne, some axillary hair, body odor.
- No growth acceleration, breast budding, phallic enlargement or testicular enlargement should occur
- No treatment for adrenarche, but watch for PCOS as girls pass menarche
Overview

<table>
<thead>
<tr>
<th>Girls</th>
<th>Pubertal Sign</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thelarche (breast buds)</td>
<td>First Physical Sign</td>
<td>Increased testicular volume (4 mL)</td>
</tr>
<tr>
<td>10.5-11 yrs</td>
<td>Mean Age of Onset</td>
<td>11.5 yrs</td>
</tr>
<tr>
<td>Follows by few months, but may precede (10%)</td>
<td>Pubarche</td>
<td>Follows by few months, but may precede (10%)</td>
</tr>
<tr>
<td>2 yrs after thelarche</td>
<td>Menarche</td>
<td>N/A</td>
</tr>
<tr>
<td>Coincides with thelarche</td>
<td>Growth spur</td>
<td>Gradual acceleration, noticeable by 2nd yr</td>
</tr>
<tr>
<td>4 yrs after thelarche, 2 yrs after menarche</td>
<td>Peak height</td>
<td>6 yrs from onset</td>
</tr>
</tbody>
</table>

What’s late?

- In girls
  - No breast development by 13
  - No menarche by 3 years after breast development (or by 16)

- In boys
  - No testicular enlargement by 14
Sometimes late is late and sometimes it’s hypogonadism...

- No recommended age of evaluation cleanly separates pathologic from physiologic delay
  - Likelihood of hypogonadism rises with duration of delay

- Other clues may suggest hypogonadism
  - Discordance of development (in physiologic delay, all aspects of physical maturation are concordant)
  - Physical or historical evidence of conditions associated with hypogonadism
Examples of Discordance

- A 12 year old girl with PH3 but B1
- A 13 year old boy with PH3 but 3 cc testes
- How do you express this in your documentation?

Examples of Evidence Suggesting Hypogonadism

- Extreme shortness, poor growth velocity
- Bone marrow transplant, head irradiation
- Extreme tallness
- Hypoplastic genitalia or undescended testes
- Abnormal cognitive or social function
...And Even if it’s Not Hypogonadism, Delay Might Not Be Healthy

- Undernutrition/Poor Absorption
  - Eating disorder
  - Inflammatory bowel disease, celiac disease
  - Stimulant induced anorexia

- Chronic illness
  - Poorly controlled diabetes, chronic renal failure, cystic fibrosis, chronic inflammation etc, etc

- Other hormone imbalance
  - Hypothyroidism, Growth Hormone Deficiency, Cushing syndrome, PCOS

Questions to Ask Yourself (and the patient) During Evaluation of Delayed Puberty

- Growth pattern
  - Height unusually tall or short for family
  - Current velocity, is it appropriate for Tanner Stage

- Nutritional state, body image, dietary intake

- Level of physical activity, training
Questions to Ask Yourself (and the patient) During Evaluation of Delayed Puberty

- Past medical history
  - Diseases or treatments associated with gonadal or pituitary damage
- Review of systems
  - Bowel, respiratory, behavioral symptoms
- Physical examination
  - Dysmorphic features, chronic systemic illness, fat stores
  - Inventory of androgen and estrogen effects on exam
    - Concordant or Discordance?

Where to Start with the Work-up?

- Bone age
- Basic screening tests: CBC, CMP, urinalysis, ESR, TSH
- LH, FSH (time of day and assay matters!)
- Other tests as indicated by specific findings (e.g., karyotype, celiac screen, sweat test, other nutritional tests, growth factors)
This evidence should suggest tentative diagnostic category

- Probable constitutional delay
- Probable pathologic delay due to systemic disease or malnutrition
- Probable gonadotropin deficiency (LH or FSH deficiency)
- Probable primary hypogonadism (gonadal failure)

Initial categories:

**Probable Constitutional Delay**

- Apparently healthy by history, review of systems, exam, screening labs
- Normal nutritional status and growth velocity for Tanner Stage
- Child seems like a healthy, but younger child
- Family history may be positive for parental delay
- All aspects of physical maturation concordant
- LH, FSH not elevated (prepubertal or early pubertal)
- Bone age will be delayed

*Note: gonadotropin deficiency is not excluded*
Constitutional delay

- All aspects of physical & hormonal maturation must be concordant, younger than age
- Mgmt: reassurance, prediction of onset of puberty (bone age helpful)
- If puberty doesn’t occur as expected, refer
- We may offer several months of low dose testosterone or estrogen, which will often induce puberty
- No simple test distinguishes constitutional delay from gonadotropin deficiency

Initial categories:

Probable Pathologic Delay

- History, ROS, nutritional state, exam and/or screening tests suggest chronic illness, undernutrition, or some other endocrine disorder is impeding normal puberty
- LH, FSH not elevated (prepubertal or early pubertal)
- Bone age usually delayed

Pursue the clues. The delayed puberty is probably not the child’s most important problem.
Initial categories:

Probable Gonadotropin Deficiency

- Other pituitary deficiencies
- Growth worse than delay pattern
- Head radiation, trauma, tumor, surgery
- Hyposmia or anosmia
- Physical features of hypothalamic syndrome
  - Prader-Willi, etc.
- Bone age > 12 in girls, >14 in boys
- Hypoplastic genitalia, undescended testes
- LH, FSH low or in appropriately normal
- Discordant PH and breasts/testes

Initial categories:

Probable Primary Hypogonadism

- History, review of systems, or exam may suggest a specific syndrome diagnosis
  - Dysmorphisms
- Discordant PH and breasts/testes
- LH, FSH elevated
- Bone age may or may not be delayed
- Karyotype indicated if history doesn’t contain obvious cause of damage to gonads
Case Presentation

- 18-year-old male presents for evaluation of small testicular volume and gynecomastia noted at recent WCC
- Patient states he first noted gynecomastia approx 2 years ago
- Notes onset of pubic and axillary hair development at 13 years of age
- Can’t recall onset of testicular or phallus enlargement
- Rarely has spontaneous nocturnal/morning erections
- Able to obtain, but not maintain erection during masturbation

Case continued

- PMH, PSH, Fam Hx unremarkable
- Denies use of dietary supplements, marijuana, testosterone, or other substances
Physical Exam

- Ht 74 inches (95%), Wt 183lbs (88%), BMI 70%
- Chest: bilateral, Tanner 2 gynecomastia
- GU: left testis 5mL, right testis 8mL, Tanner 5 PH, moderate axillary hair, pubertal phallus, scant facial hair

What To Do Next?

- Is this patient’s exam normal?
- What is your differential diagnosis?
- What would you do next?
Klinefelter syndrome

- XXY, Hypergonadotropic Hypogonadism
- Common: 1 in 1000, but commonly missed
- Hypogonadism may be partial or subtle
- Tall stature in most, even in childhood
- Pubic hair develops but testes remain small
- By late teens some develop characteristic eunuchoid habitus (poorly muscled, long limbs, gynecomastia)

Klinefelter syndrome

- Developmental delay is mild but most have social and academic problems
- Small risk of germ cell tumor, breast cancers
- Spermatogenesis is more likely to be impaired than hormone production
  - Can be eligible for sperm banking if diagnosed early
- Benefits from testosterone replacement
Turner syndrome

- 45,X but many variant partial X deletions
- Growth failure begins in infancy, worsens in mid-childhood and again in early teens
  - Growth hormone helps and is FDA approved
- Most have recurrent ear infections
- Most have some subtle dysmorphic features
Turner Syndrome and Hollywood: Linda Hunt (NCIS)
Turner syndrome

- Check out the AAP Guidelines for Health Management of Turner Syndrome
- Many other organ systems can be affected
- Management:
  - Growth hormone
  - Estrogen for puberty
  - Check for other associated problems

Questions?