Assessing Early or Delayed Puberty – When to Worry

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Conflict of Interest Declaration

• Currently or recently participating in clinical trials supported by:
  1. Sanofi – Type 1 diabetes
  2. NIH, JDRF – Type 1 diabetes
  3. CIHR – Type 2 diabetes in youth
  4. Health Canada – Environmental contaminants and puberty timing
Objectives

• Review normal patterns of pubertal development
• Distinguish between normal variants and pathological puberty presentations
• Know initial investigations and when to refer patients with variants of pubertal development.
Definitions

• Thelarche
  onset of breast development
  Tanner 2 -
  “Button” under areola

Heralds onset of TRUE puberty

https://mybodyandhowitcancreatelifecamille.weebly.com/
Definitions

- Adrenarche
  - onset of pubic hair
  - axillary hair
  - body odour

Independent of GnRH

https://mybodyandhowitcancreatelifecamille.weebly.com/
Definitions

- **Gonadarche**
  - Onset of testicular or ovarian growth and hormone production
- **Menarche**
  - Onset of menses

https://mybodyandhowitcancreatelife.camille.weebly.com/
Normal Pubertal Timing

- **Girls**
  - Onset age 8-13 yrs
  - African Canadian girls onset from age 7 may be normal (up to 20% of African American girls)
  - No menarche by 4 years after breast buds or age 16 is delayed

- **Boys**
  - Onset 9-14 yrs
  - Testicular volume at onset $\geq$ 4mL (2.5 cm long); average age 11.5 years
  - Testes <4 mL at age 14 is delayed
Usual Sequence of Pubertal Events - Girls

Thelarche is first sign of puberty in 85% of girls.

Thelarche to menarche – average - 2.3 years

From Handbook of Normal Physical Measurements (Tanner)
Sequence of Pubertal Events – In Boys

Key point:
• First sign = Testicular enlargement
• growth acceleration begins later

From Handbook of Normal Physical Measurements (Tanner)
Females

Males

From Handbook of Normal Physical Measurements (Tanner)
# Normal Growth Rates

<table>
<thead>
<tr>
<th>Age</th>
<th>Girls</th>
<th>Boys</th>
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<tbody>
<tr>
<td>Age 2 (Average)</td>
<td>8-10 cm/year</td>
<td>8-10 cm/year</td>
</tr>
<tr>
<td>Age 5- pubertgy (minimum)</td>
<td>5 cm/year</td>
<td>5 cm/year</td>
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<tr>
<td>Pubertal Growth Spurt</td>
<td>8 cm/yr Tanner 2-3</td>
<td>9 cm/yr Tanner 3-4</td>
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<tr>
<td>Age 16</td>
<td>0 cm/year</td>
<td>2 cm/year</td>
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From Age 2 - puberty – any statural growth not parallel to the 50th percentile requires assessment
7 year old Girl with Early Development

• Mom very concerned as child in grade 2
  – “How could she handle menstrual periods?”
  – “I’m not ready for this!”

• Approach
  – Series of questions

Munro Ferguson c1997
Is this adrenarche alone or true puberty?

History and physical

• Adrenarche
  – Sexual hair, acne, adult type body odour
  – Normal growth rate, if benign
  – Lack of signs of true puberty

• True Puberty
  – Breast development, maturation of genitalia, menses in girls
  – Testicular enlargement in boys
  – Accelerated growth rate
Is this a Normal Variant or is it Pathological?

CLUES

• Gender – boys more often pathological
• Pace of change – faster more often pathological
• Age – younger more likely pathological
• Virilization in a girl - clitoromegaly
Scenario 1 – 7 year old girl

- Mom reports adult type body odour x 6 months, pubic hair x 3 month

- On exam
  - Height 90th %ile (same as at age 5), Weight 90th %ile
  - No breast buds, no axillary hair, normal immature genitalia
  - 5-10 course, straight pubic hairs on mons pubis
Reassuring Features - Scenario 1

- Pace slow
- Age close to 8 years
- Female
- Isolated Adrenarche
- Likely Benign Premature Adrenarche
Scenario 2 - 7 year old boy

- Mom reports adult type body odour x few weeks, pubic hair x 1 month, significant acne for past month

- On exam
  - Height 90\textsuperscript{th} %ile (was 75\textsuperscript{th} at age 5), Weight 90\textsuperscript{th} %ile
  - Acne on face and back, small amount axillary hair, testes immature (<2.5 cm in length)
  - Moderate amount course, curly pubic hair on scrotum and around base of phallus
Adrenarche – Benign or Not?

**Benign**
- Gradual slow change
- General physical normal
- Genitalia normal for age
- Normal growth rate, but often tall
- Bone age mildly advanced
- Small increase in adrenal hormones
- Onset after age 5
- More common in girls

**Concerning**
- Rapid changes
- Cushingoid features
- Clitoromegaly girls, maturing phallus boys
- Rapid growth rate
- Bone age significantly advanced (>2 SD)
- High adrenal hormones
- Onset prior to age 5
- Boys
Plan?

- Scenario 1 - Suspected benign premature adrenarche
  - Reassess in 3-4 months for rates of progression and of growth
  - May screen with DHEAS and bone age
  - Ask parents to alert you if rapid changes
  - Reassure parents that this condition not linked to early menarche/true puberty
Plan?

• Scenario 2 – Features of concern
  – Bone age
  – DHEAS, testosterone and 17-alpha hydroxyprogesterone
  – Early referral to pediatrics/endocrinology
If it is not benign?

Tumour
- Should be rapid onset/progression
- Bone age, growth may not yet be advanced

• Adrenal tumour
  - High adrenal steroids (DHEAS)

• Ovarian tumour
  - High testosterone, androstenedione (ovarian steroids)
If it is not benign?

- Congenital adrenal hyperplasia
  - Advanced bone age, accelerated growth
  - May have onset before age 5
  - 17 alpha hydroxy-progesterone elevated

- Would be simple virilising or late-onset form
Concern for Tumour

• First step is to document abnormal androgen production

• Next step imaging
  – Adrenal tumour – MRI or CT
    • Usually use MRI to avoid radiation exposure of CT
  – Ovarian tumour
    • Pelvic Ultrasound
Girl age 18 months with precocious adrenarche and slightly enlarged clitoris

1) high DHEAS and Testosterone indicate adrenal abnormality

2) normal 17 OH Progesterone ruled out congenital adrenal hyperplasia

Tumor
4 - Isolated Pubic Hair of Infancy

- 7 month old infant, healthy
- Parents noted few coarse pubic hairs 6 weeks ago
  - On Scrotum (males); Labia or mons (females)
  - No progression, no other signs of puberty
- No hormonal exposures
- Normal growth trajectory
- Normal physical aside from pubic hair
Isolated Pubic Hair of Infancy

• Lab – testosterone, DHEAS, 17 OH progesterone – normal

• Course – Resolves by ~ age 12 months

• Abnormal, but benign
  – Not known to be associated with any other issues
  – Possibly related to mini-puberty of infancy
Scenario 5

- 7 year old girl with recent onset of breast buds, moodier recently, otherwise well
- One of tallest in class
- Mother’s menarche age 10 years
- On exam
  - Height 90th %ile, Weight 97%ile
  - Normal neurological exam
  - Tanner 2 breast buds
  - Few fine pubic hairs
  - Genitalia – small thin labia minora, thin, glistening red mucosa
Female Tanner Staging:

- Tanner 2 is just a small breast bud, under areola
- Tanner 3 is more, beyond areola
- As soon as a girl progresses to Stage Tanner 2, growth acceleration begins
True Puberty - Normal Variant or Pathological?

Reassuring Features

• Otherwise well with normal neuro exam
• Recent onset – no evidence for rapid pace
• Female
• Family history of early menarche
• Age close to “normal” cutpoint of 8 years
Scenario 6

- 7.2 year old girl with onset of breast development 3 mos ago, moodier recently
- History of hydrocephalus with VP shunt
- Recent growth spurt, no longer one of shortest in class
- Mother’s menarche age 12.5 years
Scenario 6

- On exam
  - Ht 50\textsuperscript{th} percentile, Weight 75\textsuperscript{th} percentile
  - Unchanged neurological exam
  - Tanner 3 breast development, areola dark and thickened
  - Tanner 2 pubic hair
  - Genitalia appear mature
    - Labia minora prominent
    - Mucosa dull pale pink, thicker
    - Leukorrhea present
Features Raising Concern

- History of neurological disease
- Recent onset but relatively advanced
  - pace appears rapid
- Younger age
- Family history not positive for early puberty
Investigation of Precocious Puberty

- Suspected normal variant
  - Consider bone age
  - Follow for rate of progression, growth rate & bone age
- If concerning features may also obtain
  - Estradiol/testosterone for gonadal activity
  - LH for pituitary activity (only helpful if high)
  - Pelvic ultrasound – uterine size, presence of endometrial echo, ovarian size for estrogen effect
When to Refer

- White girls < age 8 years
- African descent girls < age 7
  EXCEPT if isolated premature thelarche in age < 3

Girls with breast development after age 7 with:
  - Unusually rapid progression (Bone age > 2 years ahead and low predicted adult height for family)
  - CNS findings – new or chronic
  - Significant anticipated or evident psychosocial effects
  - Short(er) stature
Factors in Decision to Treat

• What is the predicted adult height?
  – May be short as bone maturation is advanced by early puberty, stop growing sooner

• Psychosocial considerations
  – Menses
  – Emotional/behavioural issues
  – Developmental maturity of girl

• Treatment with GnRH agonist IM q 3-4 weeks usually given in family physician’s office
Benign Premature Thelarche

Age 3 - breast development noted since infancy, size seems to fluctuate; no recent growth spurt

Isolated breast buds
Immature nipples
Immature genitalia
Bone Age Normal*
LH very low
Pelvic U/S normal (little cysts seen in little ovaries)

* Follow-up and Bone Age only investigation needed
Central Precocious Puberty (gonadotropin dependent)

Age 3 years - rapid onset of breast development with growth spurt

Nipples pigmented & thickened
Perineum mature with leukorrhea
Rapid growth
U/S uterus enlarged for age
LH and Estradiol high; DHEAS normal
Precocious Puberty in Boys

- Onset before age 9 years
- Is uncommon and pathological (tumour) until proven otherwise
- Refer promptly for endocrine assessment
7 year old boy with breast development

- Parents noted breast changes in past 2 months, first on left and now both sides
- Otherwise well
- No medications, no estrogen preparations in the house
7 year old boy with breast development

Physical Exam

Ht 75\textsuperscript{th} \%ile; Weight 50\textsuperscript{th} \%ile;
BMI 25-50\textsuperscript{th} \%ile
Normal general examination
No acne, no pubic or axillary hair
Tanner 1 genitalia; testes 2 mL bilateral
Tanner 3 breast changes
– 3-4 cm diameter
Concerning or Not?

• Prepubertal gynecomastia is pathological until proven otherwise
  – Need to rule out tumour
  – Refer to endocrinology
  – However, most often no cause is found

• Work-up
  – Estradiol, early am testosterone, LH
  – Beta HCG
  – DHEAS
  – Consider testicular ultrasound
Further History

- Using tea tree oil daily shampoo and mouth wash
- Stopped and gynecomastia resolved
- Similar effects can be seen with lavender oil

- If no exposures and normal hormonal work-up, observation and reassessment if progression
Gynecomastia

- 14 year old boy, concerned regarding breast changes in past 6 months
  - Won’t swim, unwilling to change for gym
- Sometimes tender, no discharge
- Pubertal signs and growth spurt noted recently
- Past history: Overweight
- No medications, performance enhancing drugs or cannabis use
- No Family history of gynecomastia
Gynecomastia

• Examination
  – Height 50\textsuperscript{th} percentile
  – Weight 97\textsuperscript{th} percentile
  – BMI 97\textsuperscript{th} percentile
• Breast tissue – glandular 3.5 cm in diameter, bilateral, overlying adipose tissue make it prominent
• Tanner stage 3 Pubic hair, testes 10 mL (mid puberty)
Likely Diagnosis and Prognosis?

- Typical adolescent gynecomastia
  - Reassurance is all that is required
  - Likely to resolve over 1-2 years
  - Overweight may contribute so lifestyle counselling appropriate
  - Substances (androgens, cannabis) discussion
  - Return if does not resolve
Likely Diagnosis and Prognosis?

• Atypical features
  – Present beyond age 17 or longer than 2 years
  – Size > 4cm
  – Consider referral
  – Laboratory tests as per prepubertal plus karyotype for 46XXY
  – If persists surgery is an option
Pubertal Delay

Munro Ferguson c1997
Scenario 7

- 14.5 year old boy height and weight below the 3rd percentile
- Always small but difference more recently
- Normal physical exam
- Tanner 1 for pubertal development
- Positive family history (father was a late bloomer, now 5’11)
Male pubertal staging: Measuring testicular volume is important

- The first sign of puberty is a minimal enlargement of the testes from 2mL to 4mL
- But the growth acceleration of puberty does not begin until Stage Tanner 3, when testes are 8 to 10 mL
Puberty starts at 4mL = 2.5 cm in length.
Management of Constitutional Delay

• Reassurance
  – Discuss future growth potential (delayed bone age)

• Some boys remain very distressed
  – Refer for assessment of option of short course of testosterone
  – Must be sure there is no growth hormone deficiency or other disorder
  – Testosterone 50-100 mg IM x 4-6 months will give some virilization and may “kick start” puberty
    • Does not effect final adult height
Scenario 8

- 16 year old female with primary amenorrhea
- Thelarche age 14, but minimal change since
- No leukorrhea or menses
- No concerns re: excess body hair or acne
- No galactorrhea
- No growth spurt noted
- Well, but past medical history of chronic otitis media and needed myringotomy tubes
- Activity level and diet normal
Scenario 8

- Mother’s menarche – age 11
- Father’s puberty consistent with peers
- On exam
  - Height – 4’9 <3rd%ile – Height age 11 years
  - Weight 60 kg – 50-75%ile
  - BMI – 28.5 – 97th %ile
  - Breasts, small Tanner 2
  - Pubic hair Tanner 2
Key Investigations

Delayed puberty in girls/Primary Amenorrhea
- Genetic and Congenital problems are higher on list

- Pregnancy test
- LH, FSH
- Pelvic ultrasound
- Prolactin, TSH, androgens
Gonadal Axis

Hypothalamus

Pituitary

Gonads

- Estrogen
- Testosterone

Pulsatile GnRH → LH, FSH → Gonads

Feedback loop: Estrogen, Testosterone
Hypergonadotrophic Hypogonadism

- LH  30.9 IU/L  (<8.4)
- FSH  109.0 IU/L  (15)
- Pelvic ultrasound – Ovaries not seen, uterus tiny

Diagnosis – Ovarian Failure

What now?
Causes of Hypergonadotrophic Hypogonadism

- Chromosomal
  - Females – Turner syndrome 45XO
  - Males – Klinefelters syndrome 47XXY
- Genetic – LH or FSH receptor defect, galactosemia
  - Autoimmune disease
- Gonadal damage/destruction
  - Chemotherapy, radiotherapy, infection (mumps orchitis/oophoritis)
Scenario 8 - Results

- Karyotype 45 X, all cells
- Turner syndrome causing primary hypogonadism

- Clues
  - Lack of puberty or partial puberty
  - Recurrent Otitis media
  - Short stature
  - Some dysmorphic features, but often subtle
Turner syndrome: Useful signs

- *Hands* for puffy fingers and *nails* which are buried partially with prominent pericuticular tissue
- *Short wide neck*; not necessarily webbed; *low posterior hair line*
- *Ears* prominent, posteriorly rotated
- *Ptosis* (subtle)
- *Multiple nevi*

**Karyotype short girls**

Twins (identical) mosaic xo/xx
Estrogen/Progesterone Replacement

• Different from HRT of menopause
  – Physiologic replacement
  – Important for feminization, bone health, sexual function, possible future IVF etc.

• Combined estrogen and progesterone
  – Begin with small doses estrogen only
  – Transdermal estrogen is preferred
  – After ~ 2 years of estrogen
    • Estrogen with prometrium monthly or every 3 month - orally or transdermal patch
    • Some prefer Oral contraceptive pill
Testosterone Replacement

• Usual
  – Intramuscular injection 50 mg q 4 weeks to begin
  – Adult dose 200 mg q 2-3 weeks

• Options
  – Transdermal daily
    • Patch - frequent skin irritation
    • Gel - need to avoid skin to skin contact with females and children for 6 hours, then shower
  – If fertility desired – intermittent GnRH analogues or gonadotropins are future possibility
Case 9

- 15 year old male, concerned re: lack of puberty
- No medical problems, no complaints
- Cross country runner
- Was average height until past 3 years, now shorter than many of peers
- Normal sense of smell
- Family history - unavailable - adopted
Case 9

- Height 10-25%ile, Weight 5%ile
- General exam normal
- Tanner 2 - pubic hair
- Tanner 1 - genitalia, testes 3 mL
Investigations

- LH, FSH, testosterone
- Prolactin
- TSH
- Screen for chronic disease
- Bone age
Investigations

- LH <0.2 IU/L (<11)
- FSH 1.6 IU/L (<15)
- TSH 3.3 mIU/L (0.4-5.5)
- Free T4 13.2 pmol/L (8-22)
- Prolactin 20 mcg/L (6-24)
- Testosterone 2.4 nmol/L (<2.5, prepubertal)
- CBC, ESR, Creatinine, TTG, Albumin - normal
What is differential?

- Hypothalamic hypogonadism
  - Functional – Exercise, anorexia
  - Genetic – Kallman’s
  - Anatomic – pituitary tumour, infiltration

- Normal Variation
  - Bone age should be delayed
  - Use for height prediction helpful

Chronic Illness – keep it in the back of your mind
In Endocrine Clinic

• GnRH test would be performed
• If pubertal pattern (good LH response) then suggests normal variant and puberty likely to progress soon
• If minimal response – cannot distinguish between functional, constitutional, and genetic causes
GnRH stimulation test

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<tr>
<th>Time</th>
<th>LH</th>
<th>FSH</th>
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<tbody>
<tr>
<td>0'</td>
<td>0.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Give GnRH IV</td>
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<td></td>
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<tr>
<td>40'</td>
<td>9</td>
<td>3.2</td>
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LH rises above 8

Shows pituitary response to GnRH
So puberty likely to progress over next year
# GnRH Stimulation Test

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<tbody>
<tr>
<td>0'</td>
<td>&lt; 0.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Give GnRH via and IV</td>
<td></td>
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</tr>
<tr>
<td>40'</td>
<td>1.1</td>
<td>3.0</td>
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LH and FSH do not respond to GnRH

Could be constitutional delay

OR Could be hypogonadotropin hypogonadism

2011-2012
Options?

- Observation
- Stimulation test not likely helpful
  - If delayed puberty or central hypogonadism may have poor response
  - Neuroimaging if worried about anatomic cause
- Calculate predicted height based on bone age
- Short course low dose testosterone
  - 4-6 months then reassess
Age 16 returns - testicular volume 6-8 mL

Diagnosis - Extreme of constitutional delay of puberty
About Testosterone Levels

- Lab reports give adult range 8-30
- May also say <2.5 nmol/L prepubertal
- Don’t give ranges for pubertal boys
- Basically anything between is normal
- Working to remedy this with the labs but it is slow
Key Points – Pubertal Delay

Gonadotropin levels (LH, FSH) help to narrow the differential diagnosis

• Remember to measure prolactin, even without galactorrhea

• PREGNANCY test in females is useful even with primary amenorrhea

• Sometimes time is the only thing that brings an answer
Take Home Messages

- Rapid referral of boys with precocious puberty is indicated
- In girls, assess pace, family history and exam findings
  - Refer all under 7 and between 7 and 8 with concerning features
- Delayed puberty is common in boys – look for features of constitutional delay (family history, normal growth rate, slim boy)
- Screen delayed puberty with LH and FSH if not clearly constitutional, as this guides investigation