PRECOCIOUS PUBERTY AND SECONDARY AMENORRHEA

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• No specific products will be discussed in this program.
Objectives

Recognize when early puberty is a variant of normal and when to worry

Apply an algorithm to help investigate and manage a patient presenting with precocious puberty

Formulate a management plan to investigate and manage patients presenting with (primary or) secondary amenorrhea
What is your practice profile?

A. Resident or student
B. Family physician
C. Pediatrician
D. Nurse / Nurse practitioner
E. Other
NORMAL PUBERTY

“I’ve had to reprogram my voice recognition software six times — I hate puberty!”
Normal timing of Puberty

Girls: 8-13 years
Boys: 9-14 years

Time to redefine?
Timing of puberty of girls in US
Timing of puberty of girls in US

Herman-Giddens et al, Pediatrics 1997; 99:505.
Physiology of Puberty

Hypothalamus
  - GnRH
  - Pituitary
    - LH, FSH
    - Testes
      - Testosterone
      - Secondary sex characteristics
        - Breast Development
    - Ovary
      - Estrogen
      - Adrenal
        - Adrenal Androgens
  - Adrenal
    - Pubic, axillary hair, acne

Figure 5.2 — Schematic representation of serum LH and sex steroid secretion patterns in (a) males and (b) females throughout human sexual maturation.
Sequence of puberty in girls

- Initial breast development (SMR stage 2)
- Menarche
- Completion of puberty

- Height velocity (girls maturing at "average" time)
- Median age for African-American girls
- Median age for Caucasian girls

Age (years)

Growth velocity (cm/year)

Peak height velocity
Sequence of puberty in boys
Testicular volume

Testicular volume in each pubertal stage

Testicular volume, mL

Pubertal stage

5th percentile

50th percentile

95th percentile

2A  2B  3  4  5
PRECOCIOUS PUBERTY
General approach to early puberty

Who should be evaluated?

- Boys < 9 years,
- Girls < 8 years

How quickly is it progressing?
- Growth velocity?
- Bone age?

Is it central or peripheral

- Androgen
- Estrogen

Benign variant or pathologic?
Precocious Puberty

Growth Velocity
Bone Age

Normal

Normal variant

Normal sequence and tempo of puberty

Estrogen

Premature Thelarche

Androgens

Premature Adrenarche

Increased

Pathological

Central

Androgens

Peripheral

Estrogen

Look first where steroids are made (adrenals and gonads)

PP in a boy is pathologic until proven otherwise
Case 1

Are you worried?

A. Yes

B. No
Case 2

What is the MOST likely diagnosis?

A. Adrenal tumor
B. Congenital adrenal hyperplasia
C. Benign premature adrenarche
D. Central precocious puberty
Other benign variants

• Pubic hair of infancy
• Benign prepubertal vaginal bleeding
• Non-progressive or intermittently progressive precocious puberty
Case 3

What is the MOST likely cause of her precocious puberty?

A. McCune Albright Syndrome
B. Adrenal adenoma
C. Central precocious puberty
D. Ovarian cyst/tumour
E. Profound hypothyroidism
Case 3b
What investigation would best confirm diagnosis of CPP?

A. Baseline LH and FSH
B. Estradiol level
C. MRI of hypothalamus/pituitary
D. Pelvic ultrasound
E. LHRH stimulation test
Screening investigations: baseline LH, FSH, E2

• LH - ultrasensitive assay (≤0.1 IU/L)
  — LH < 0.2 IU/L. - peripheral PP or benign variant
  — LH > 0.2-0.3 IU/L. (assay dependent) suggestive of CPP
  — Beware of interpreting in girls less than 2 (minipuberty)

• FSH
  — limited utility to distinguish CPP and benign variants
  — Tend to be suppressed in peripheral PP

• Estrogen/ testosterone
  — If very high with suppressed LH, FSH = Peripheral PP
  — Need sensitive assays to identify pubertal levels at the low end
Next steps:

• GnRH stimulation test
  — Can distinguish CPP from benign variant
  — Also indicated for discordant clinical/biochemical picture (LH < 0.3 with ongoing pubertal progression)

• Interpretation:
  — Peak LH > 3.3-5 mIU/L is pubertal
  — Peak LH/FSH ratio typically higher in CPP (>0.66)
  — Stimulated E or T (but measured at 24 h so not practical)

Caution when interpreting < 2 years of age
Next steps

• Androgens to distinguish peripheral PP and benign variant
  • DHEAS > 3.7 umol/L or testosterone > 1.2 nmol/L

• Other biochemical tests
  • hCG in boys
  • TSH

• If confirm CPP, consider MRI particularly for girls < 6 yrs of age or rapidly progressive puberty
Central Precocious Puberty
Treatment of CPP with Lupron
Case 4

6 year old twins, one with growth acceleration, advanced bone age, testes 4 Ml. What is the MOST likely diagnosis?

A. Congenital adrenal hyperplasia
B. Central precocious puberty
C. Adrenal tumour
D. hCG secreting tumour
E. Benign premature adrenarche
Approach to Early Puberty in Boys

Bone age, GV

- Normal
  - Normal Variant
    - Androgens
      - Premature Adrenarche
    - Central
      - Testes ≥ 4ml
  
- Increased
  - Pathological
    - Peripheral
      - Androgens
        - Testes Adrenal Other
      - Estrogen
        - Testes Adrenal Other
Case 5

A 5 year old girl presents with a 2 month history of breast development & a 5 day history of vaginal bleeding.
Case 5

What is the MOST likely cause of her precocious puberty?

A. Vaginal foreign body
B. Adrenal adenoma
C. Central precocious puberty
D. Ovarian cyst/tumor
E. Profound hypothyroidism
Case 5

What is the MOST likely cause of her precocious puberty?

A. Vaginal foreign body
B. Adrenal adenoma
C. Central precocious puberty
D. Ovarian cyst/tumor
E. Profound hypothyroidism
Approach to Early Puberty in Girls

Bone age, GV

Normal

Increased

Normal Variant

Pathological

Estrogen

Androgens

Central

Peripheral

Premature Thelarche

Premature Adrenarche

Estrogen +/- androgens

Estrogen

Ovary Adrenal Other

Androgens

Ovary Adrenal Other
Case 6

What is the single MOST helpful test you should order to confirm the most likely diagnosis?

A. 17 hydroxyprogesterone
B. Testo profile
C. DHEAS
D. LH, FSH (baseline and stimulated)
E. US of abdo and testes
CAH

6.5 Schematic representation of the common form of congenital adrenal hyperplasia, 21-hydroxylase deficiency.
Classical CAH
Girl with Simple Virilizing CAH

Late onset CAH
CAH - Management

+/- Hydrocortisone
+/- Fludrocortisone
+/- NaCL

Glucocorticoid treatment DOES NOT mimic physiologic secretion
Summary:

- Clinical evaluation for girls < 8 and boys < 9
- 3 main categories are
  - Central precocious puberty
  - Peripheral precocious puberty
  - Benign variants
- Pathology more likely with
  - Girls < 6, any boy
  - Not following the usual sequence and tempo of puberty
- Initial investigations: LH, FSH, E/T
Approach to Early Puberty in Boys

Less likely to be benign variant in boys than girls

Estrogen: evaluate for pathologic cause

Bone age, GV

Normal

Increased

Normal Variant

Testicular size is key to Dx

Pathological

Androgenic

Premature Adrenarche

Testes > 4ml

Androgens

Testes Adrenal Other

Peripheral

Estrogen

Testes Adrenal Other
Approach to Early Puberty in Girls

Bone age, GV

- Normal
  - Onset typically around 6-7 years, normal growth, BA. Risk of PCOS, Ins Resistance
  - Premature Thelarche
  - Premature Adrenarche

- Increased
  - Altered tempo, early menarche
  - Estrogen +/- androgens
  - Estrogen
  - Androgens

- Pathological
  - Especially if Adrenarche <6 y, rapid progression, isolated androgens

Other
SECONDARY AMENORRHEA
Major causes of secondary amenorrhea

• Pregnancy
• Hypothalamic functional
• Hypogonadism
  — Hypogonadotropin (hypothalamic or pituitary lesion)
  — Hypergonadotropin (ovarian failure)
• Suppressed by other hormones
  — Prolactin
  — Excess androgens
• Other hormone abnormalities
  — Hypo or hyperthyroidism

• bHCG
• LH, FSH
• Estradiol
• Prolactin
• Testosterone (if ssx), 17OHP
• TSH (FreeT4)
# Interpretation of initial investigations

<table>
<thead>
<tr>
<th>Labs</th>
<th>Diagnosis</th>
<th>Next steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>High FSH, Low E2</td>
<td>Primary ovarian failure</td>
<td>Karyotype/microarray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fragile X premutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autoantibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Hx of chemo/radiation)</td>
</tr>
<tr>
<td>Normal or low FSH</td>
<td>Hypothalamic/ pituitary cause</td>
<td>Look for etiology, chronic disease</td>
</tr>
<tr>
<td></td>
<td>(tend to have lower LH, and E2)</td>
<td>Unexplained/ headaches etc - MRI</td>
</tr>
<tr>
<td></td>
<td>PCOS</td>
<td>Androgen levels</td>
</tr>
<tr>
<td></td>
<td>(tend to have LH&gt;FSH, E2, ssx)</td>
<td></td>
</tr>
<tr>
<td>Elevated prolactin</td>
<td>&lt; 50 likely stress related</td>
<td>Confirm elevation</td>
</tr>
<tr>
<td></td>
<td>Medication, hypothyroidism</td>
<td>Consider MRI</td>
</tr>
<tr>
<td></td>
<td>Pituitary adenoma</td>
<td></td>
</tr>
</tbody>
</table>
## Interpretation of Initial Investigations

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<tr>
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</thead>
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<tr>
<td>Elevated androgens</td>
<td>PPCOS</td>
<td>Karyotype/microarray</td>
</tr>
<tr>
<td></td>
<td>Late onset CAH, Adrenal tumour (T &gt; 5.2 mmol/L, DHEAS &gt; 18.9 umol/L)</td>
<td>Fragile X premutation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autoantibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Hx of chemo/radiation)</td>
</tr>
<tr>
<td>TSH abnormal</td>
<td>Hypo or Hyper thyroidism</td>
<td></td>
</tr>
<tr>
<td>All normal</td>
<td>Evaluate estrogen status with provera challenge 10 mg x 10 days</td>
<td></td>
</tr>
</tbody>
</table>
Primary Amenorrhea

• Definition:
  — Absence of menarche by age 15 years and the presence of normal growth and secondary sexual characteristics
  — Absence of menarche with no pubertal signs by age 13 years is an indication for evaluation

• Are there signs of puberty? If so, when did they start?
• Family history of puberty
Primary amenorrhea

- 20%. Hypogonadotrophic hypogonadism (including functional hypothalamic amenorrhea
- 5% pituitary disorder

5% other – AIS, CAH, PCOS

- 50%. Genetic – gonadal dysgenesis

- 15%. Mullerian agenesis
- 5% Vaginal septum
No pubertal signs

- Gonadal dysgenesis (Turner syndrome)
- Other DSD
- Physiologic delay of puberty (CDGP, systemic illness, weight loss…)
- Hypopituitarism
With pubertal signs

• Breasts < 2 years – likely constitutional delay

• Breasts > 2 years
  — Mullerian agenesis
  — PCOS
  — Anorexia
  — Much less commonly
    • Pituitary disorders
    • Other endocrinopathies
    • DSD such as androgen insensitivity syndrome
    • POI
    • Imperforate hymen
Approach to primary amenorrhea

Clinical assessment
- hCG, FSH, TSH, Prolactin
- Ultrasound

Uterus present
- FSH
  - High
    - Turner syndrome
      - or
        - (46,XY gonadal dysgenesis, 46,XX primary ovarian insufficiency)
  - Normal or low

Uterus absent
- 46,XX
  - Mullerian agenesis
- 46, XY
  - DSD (AIS, other)
  - Hypopituitarism
  - Outflow tract obstruction
Summary of approach to amenorrhea

• History –
  — puberty and growth history. (and family history)
  — general health, weight, exercise
  — Signs of excess prolactin (galactorrhea)
  — Signs of excess androgens

• Physical
  — Height, stigmata of Turner syndrome
  — Tanner staging and genital exam
  — Virilization
  — Galactorrhea