# PRECOCIOUS PUBERTY AND SECONDARY AMENORRHEA

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- **Dr. Lawrence** has not received payment or funding from any organizations supporting this program or whose product(s) are being discussed in this program.
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# 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

# Practice Question for iClickr

## What is your practice profile?

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

# NORMAL PUBERTY

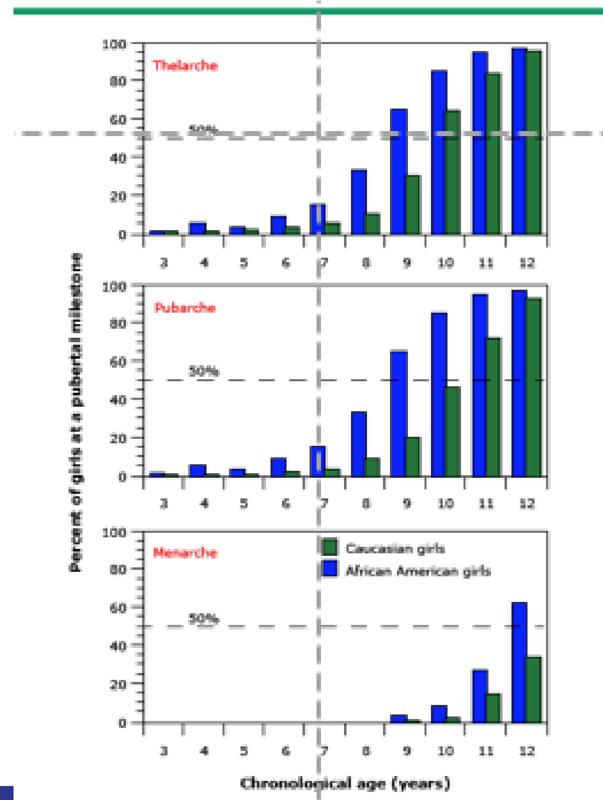
# Normal timing of Puberty

Girls: 8-13 years

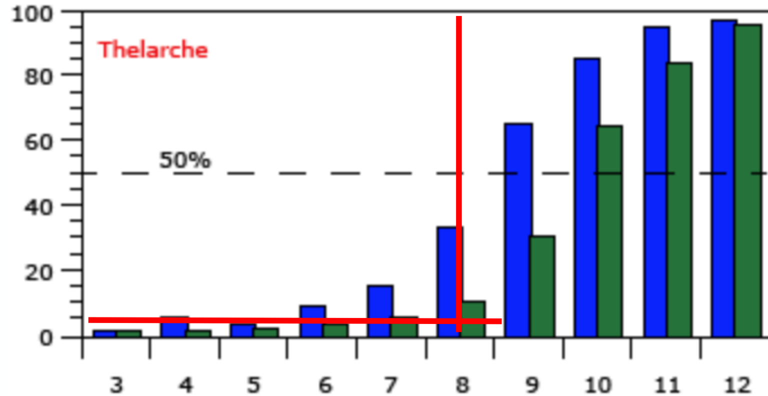
Boys: 9-14 years

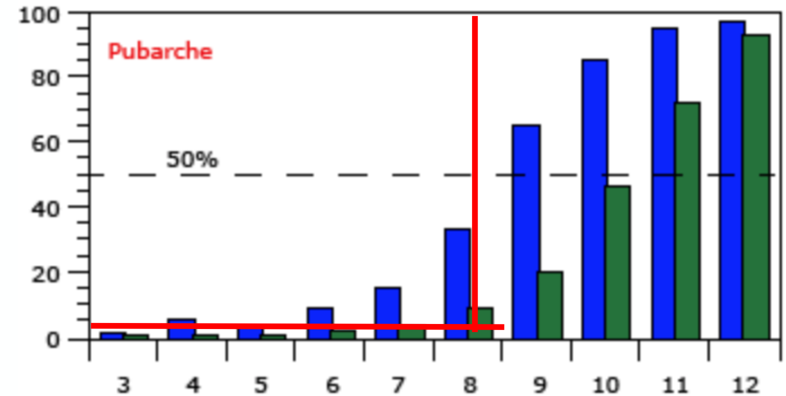
Time to redefine?

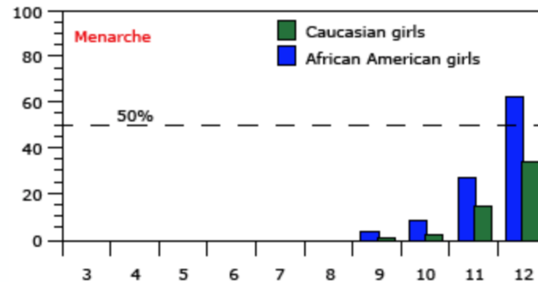
# Timing of puberty of girls in US



# Timing of puberty of girls in US

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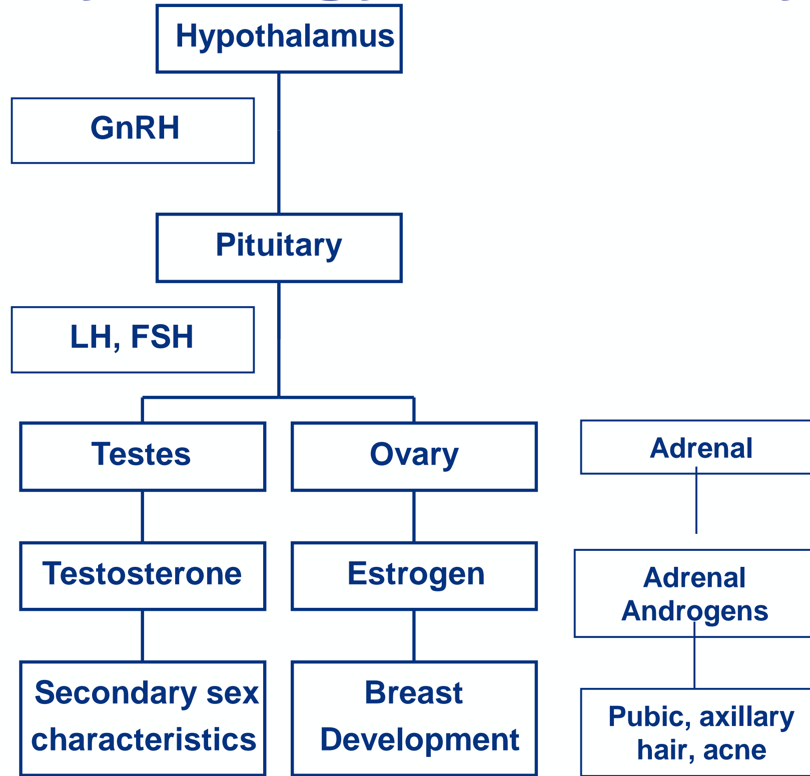
*Herman-Giddens et al, Pediatrics 1997; 99:505.*

# Physiology of Puberty



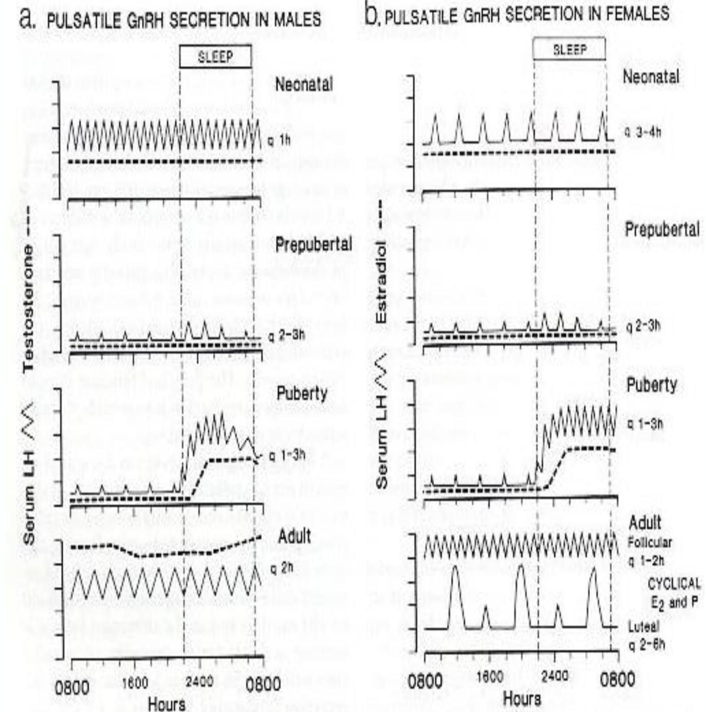
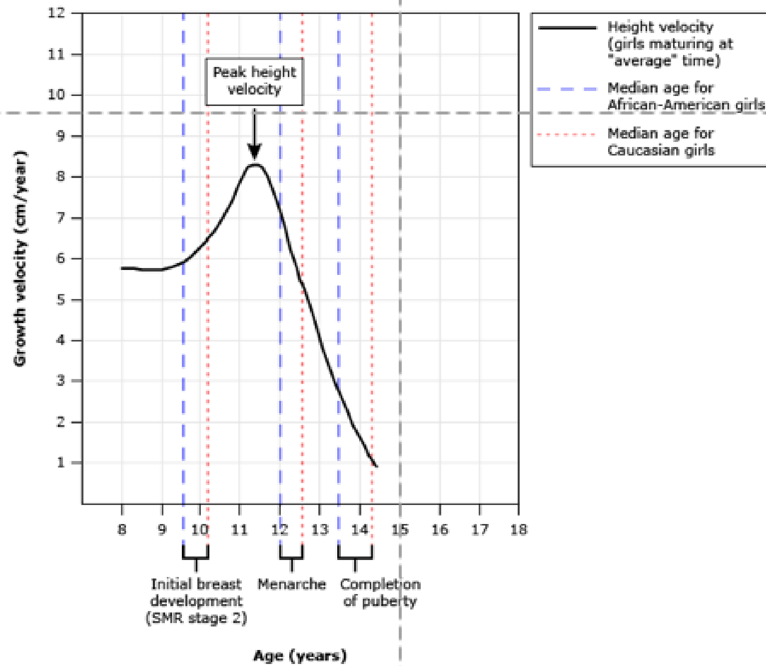
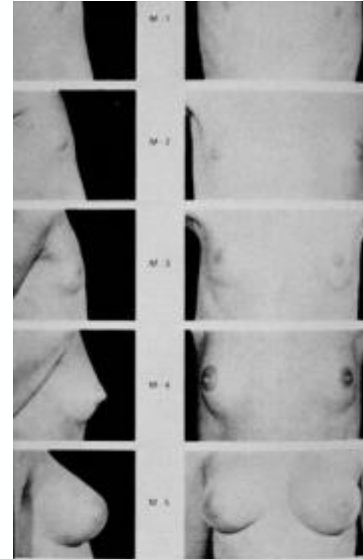
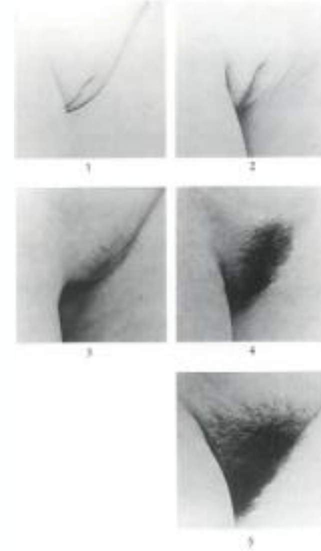




FIGURE 5.2 — Schematic representation of serum LH and sex steroid secretory patterns in (a) males and (b) females throughout human sexual maturation.

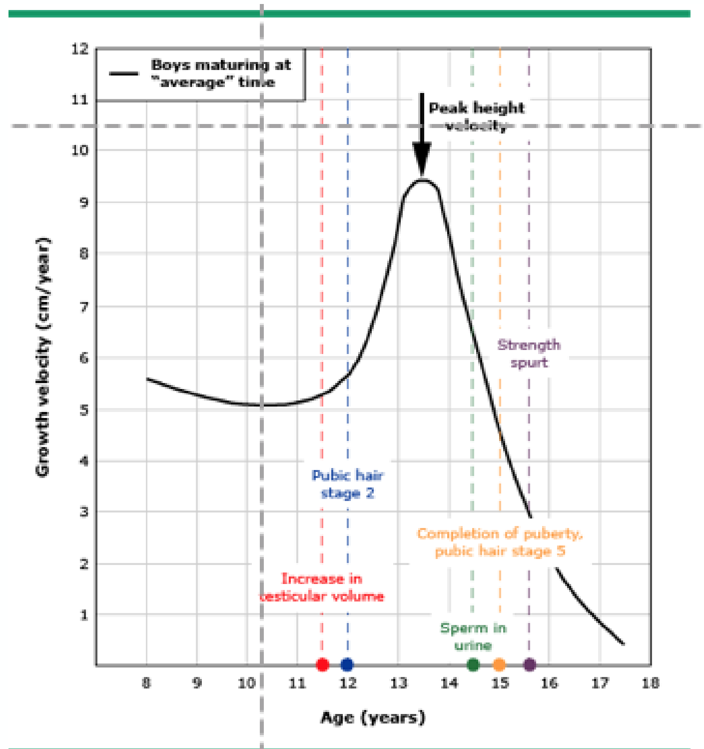
# Sequence of puberty in girls

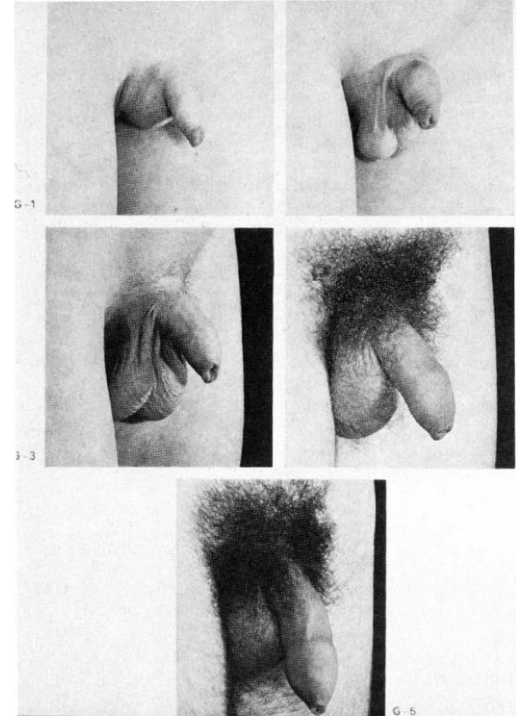


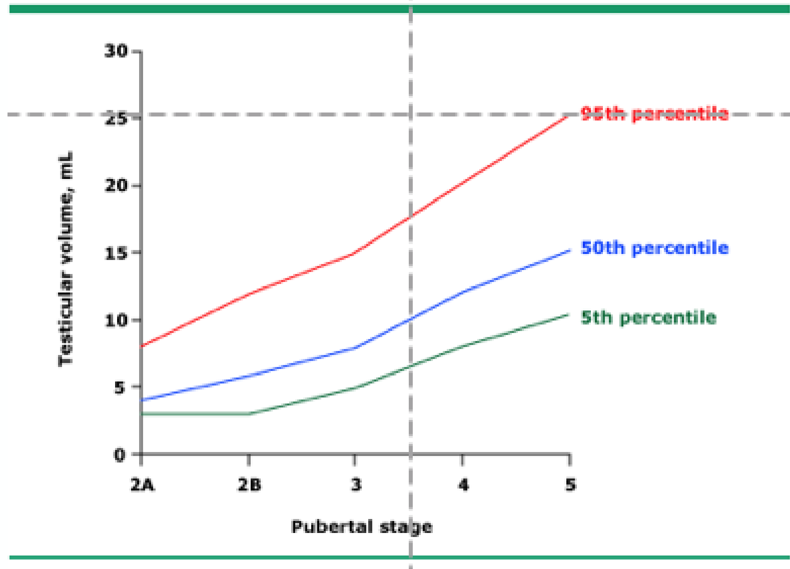


# Sequence of puberty in boys



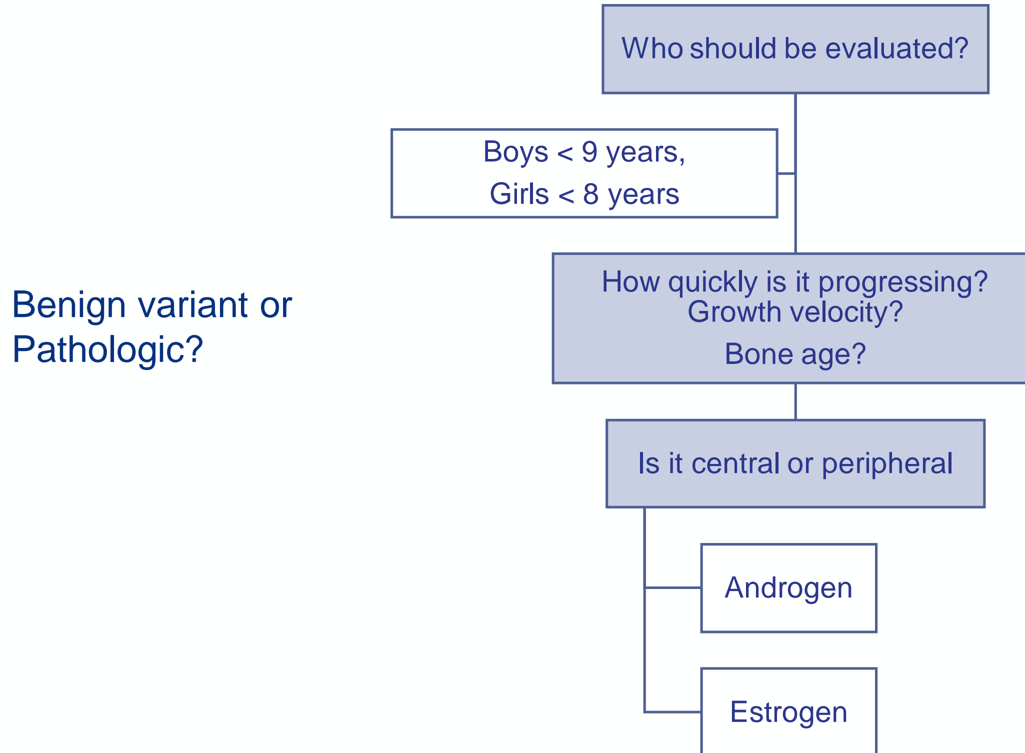
# Testicular volume

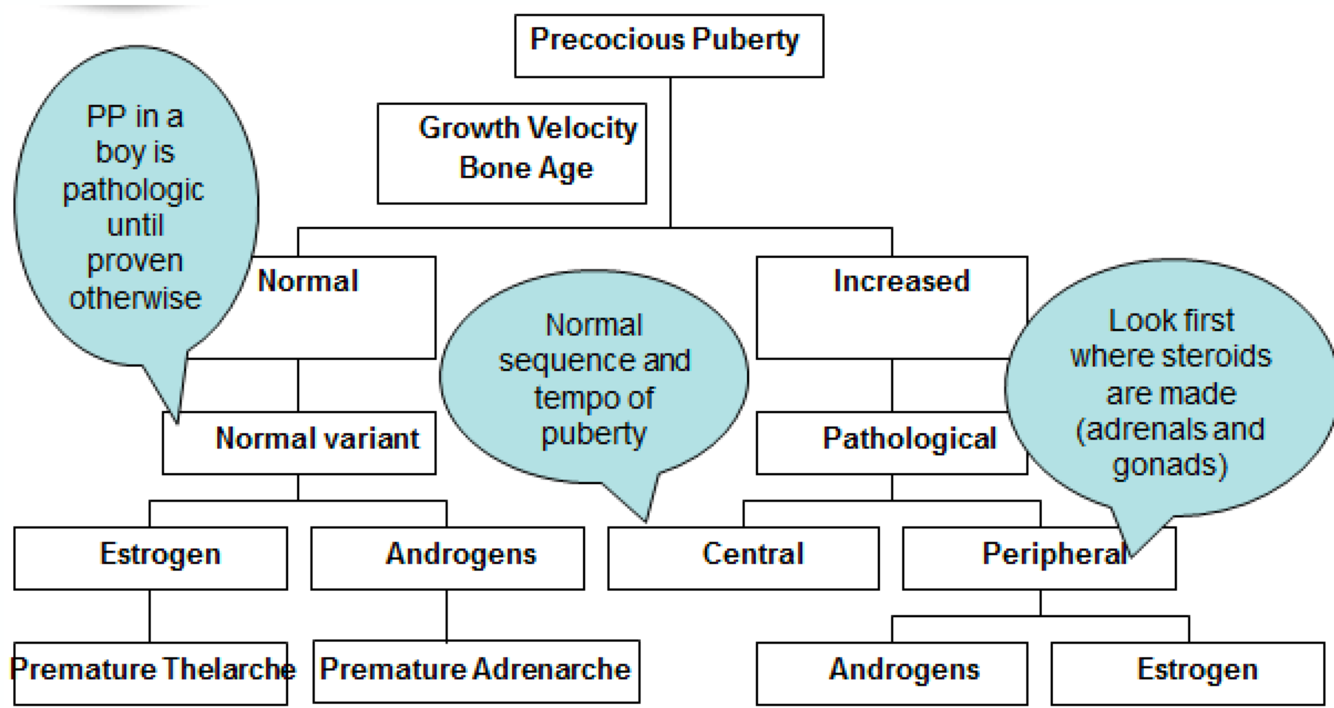


# PRECOCIOUS PUBERTY

# General approach to early puberty

Benign variant or Pathologic?



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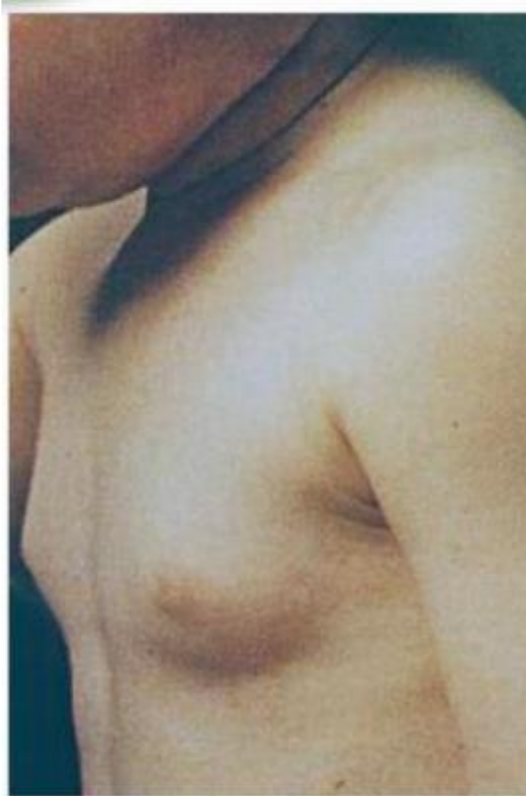
# Case 1

Are you worried?

A. Yes

B. No



# Case 2

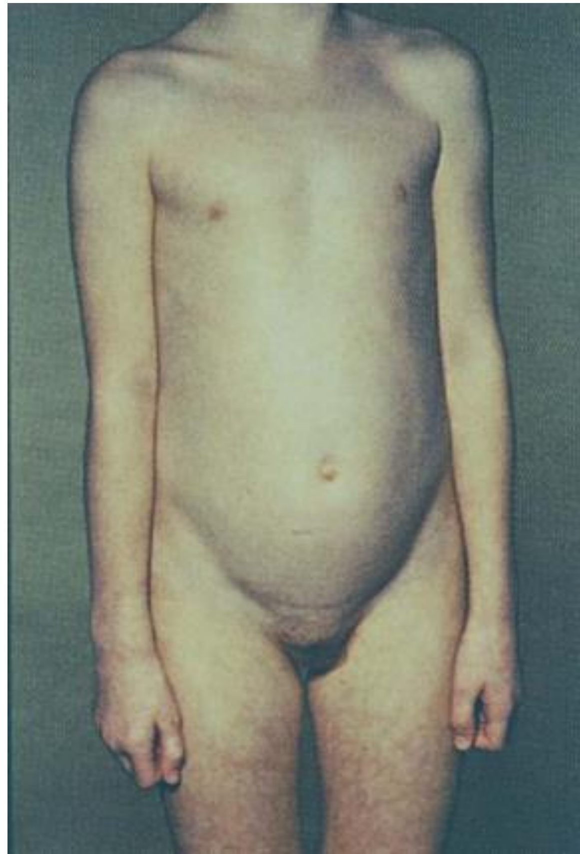
What is the MOST likely diagnosis?

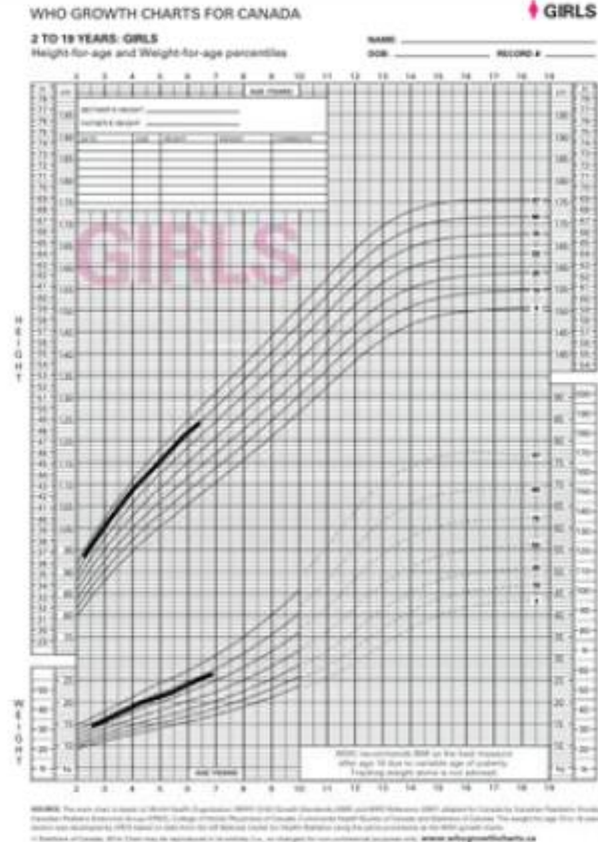
A. Adrenal tumor

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?

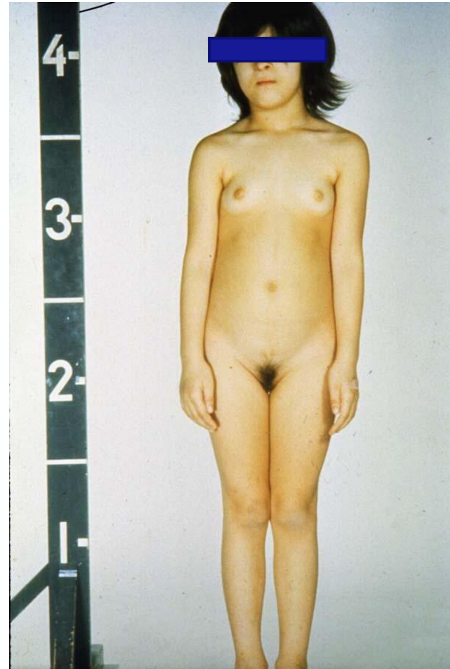
A. Baseline LH and FSH

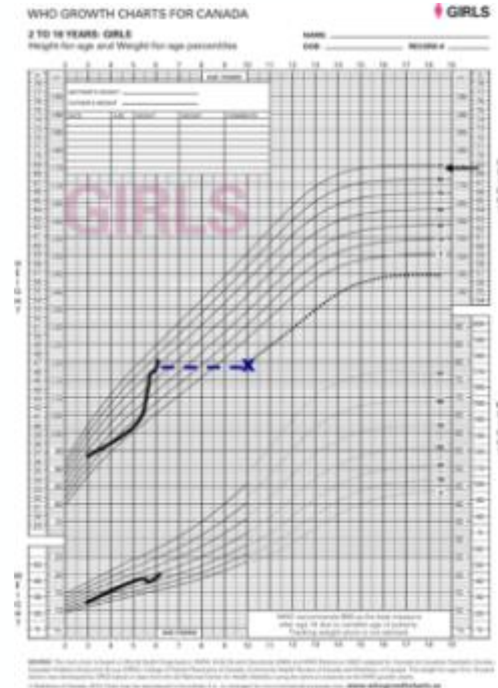
B. Estradiol level

C. MRI of hypothalamus/pituitary

D. Pelvic ultrasound

E. LHRH stimulation test



# Screening investigations: baseline LH, FSH, E2

- LH - ultrasensitive assay ($\leq$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

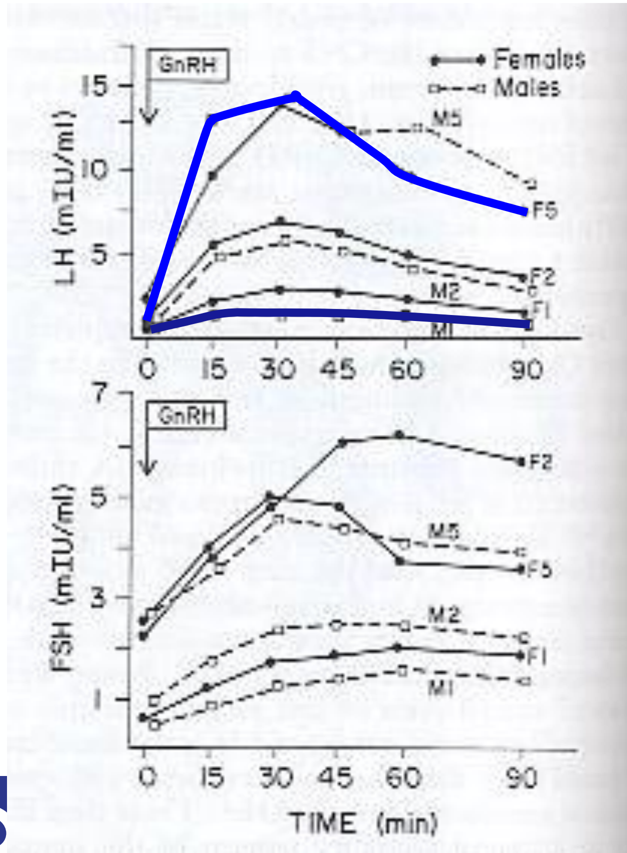
# Next steps

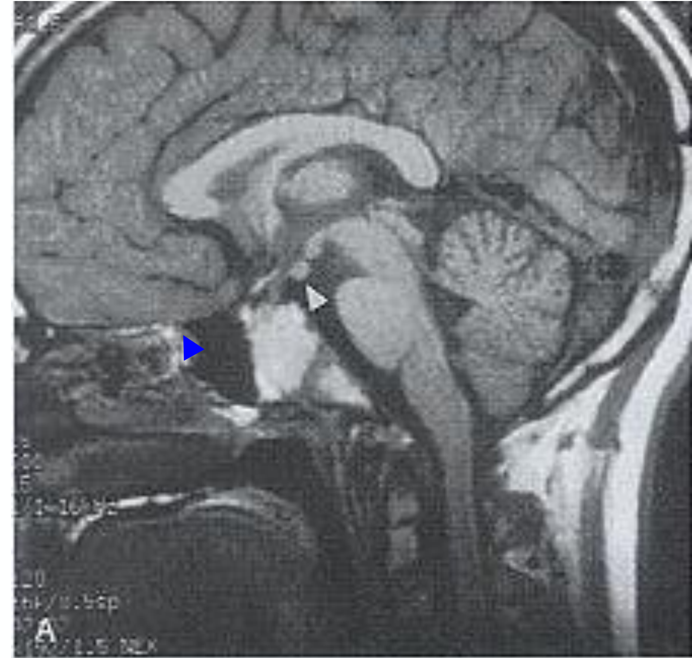
- Androgens to distinguish peripheral PP and benign variant
  - DHEAS $> 3.7$ umol/L or testosterone $> 1.2$ nmol/L

- Other biochemical tests
  - hCG in boys
  - TSH

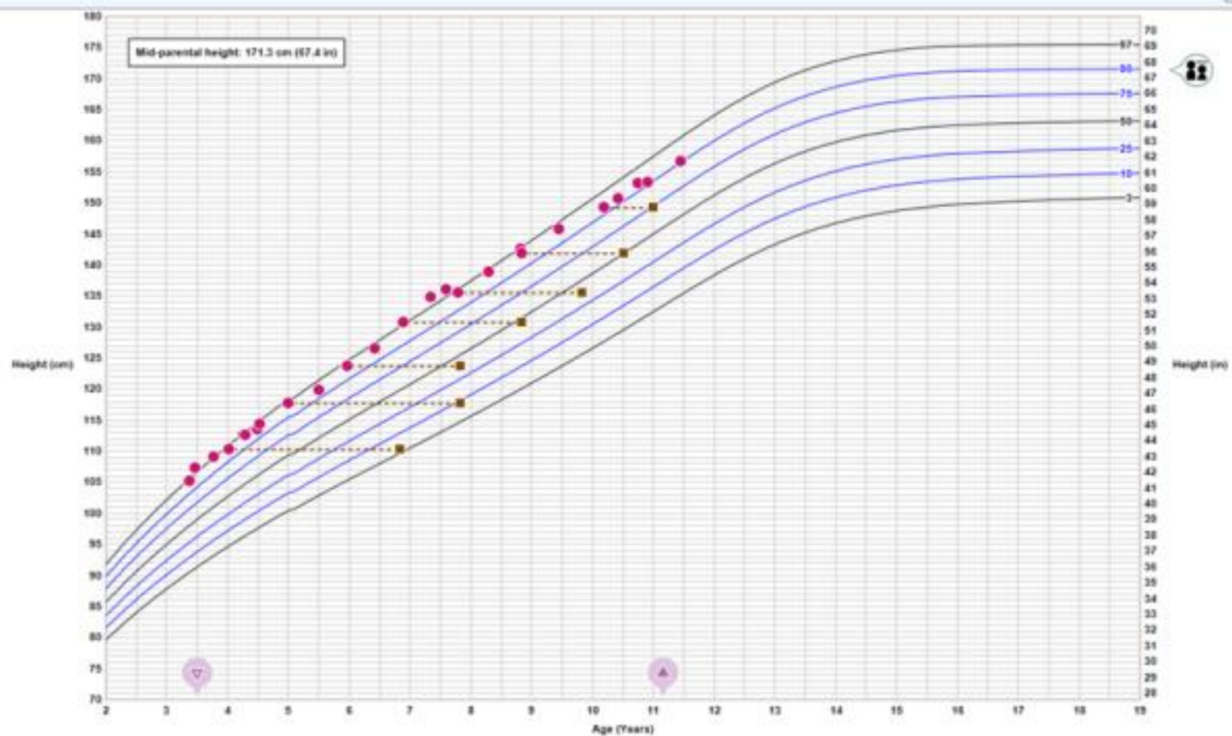
- If confirm CPP, consider MRI particularly for girls $< 6$ yers of age or rapidly progressive puberty

# Central Precocious Puberty



# Treatment of CPP with Lupron

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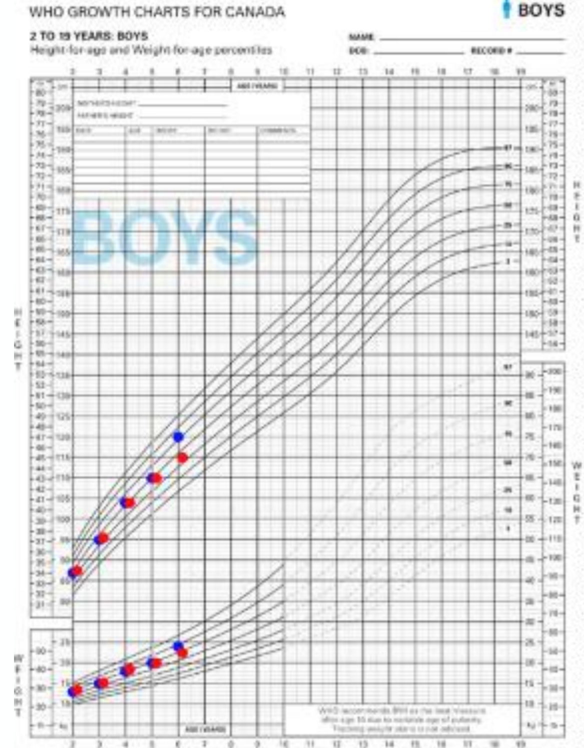
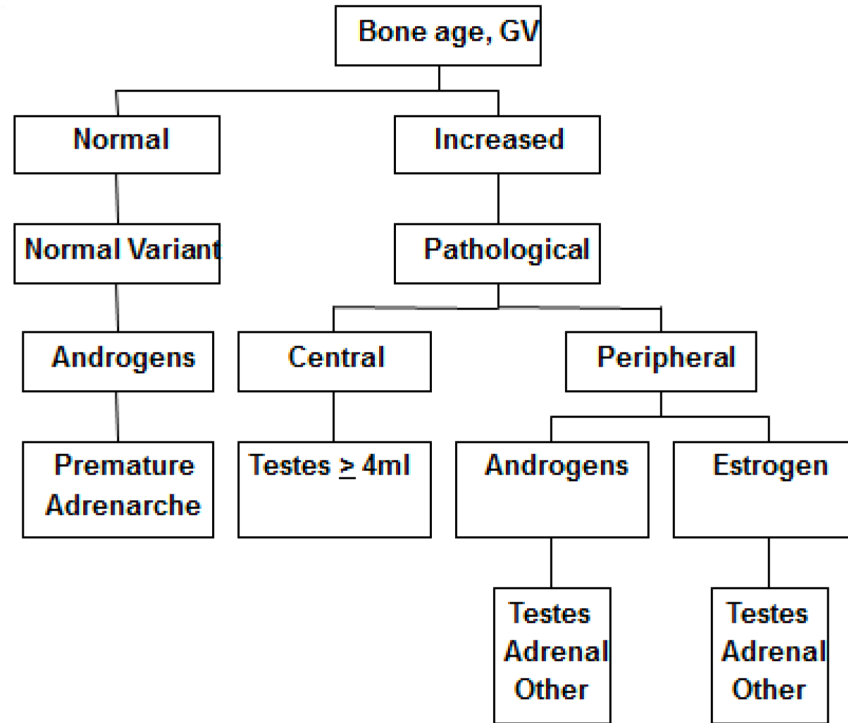
# Case 4

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



# Case 5

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

WHO GROWTH CHARTS FOR CANADA

GIRLS

2 TO 19 YEARS: GIRLS
Height-for-age and Weight-for-age percentiles

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# 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

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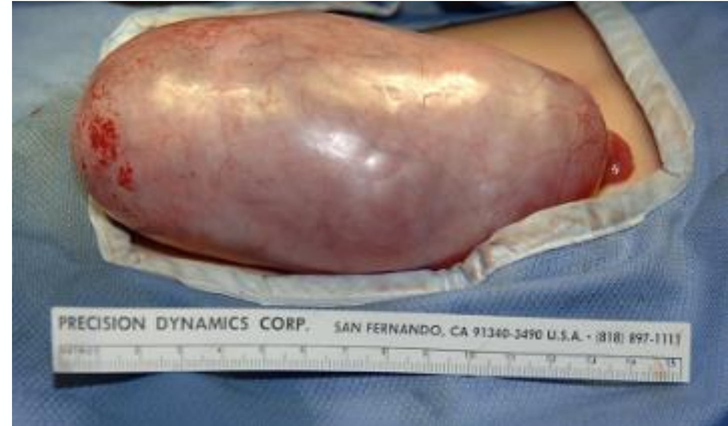

WHO GROWTH CHARTS FOR CANADA

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2 TO 19 YEARS: GIRLS

Height-for-age and Weight-for-age percentiles

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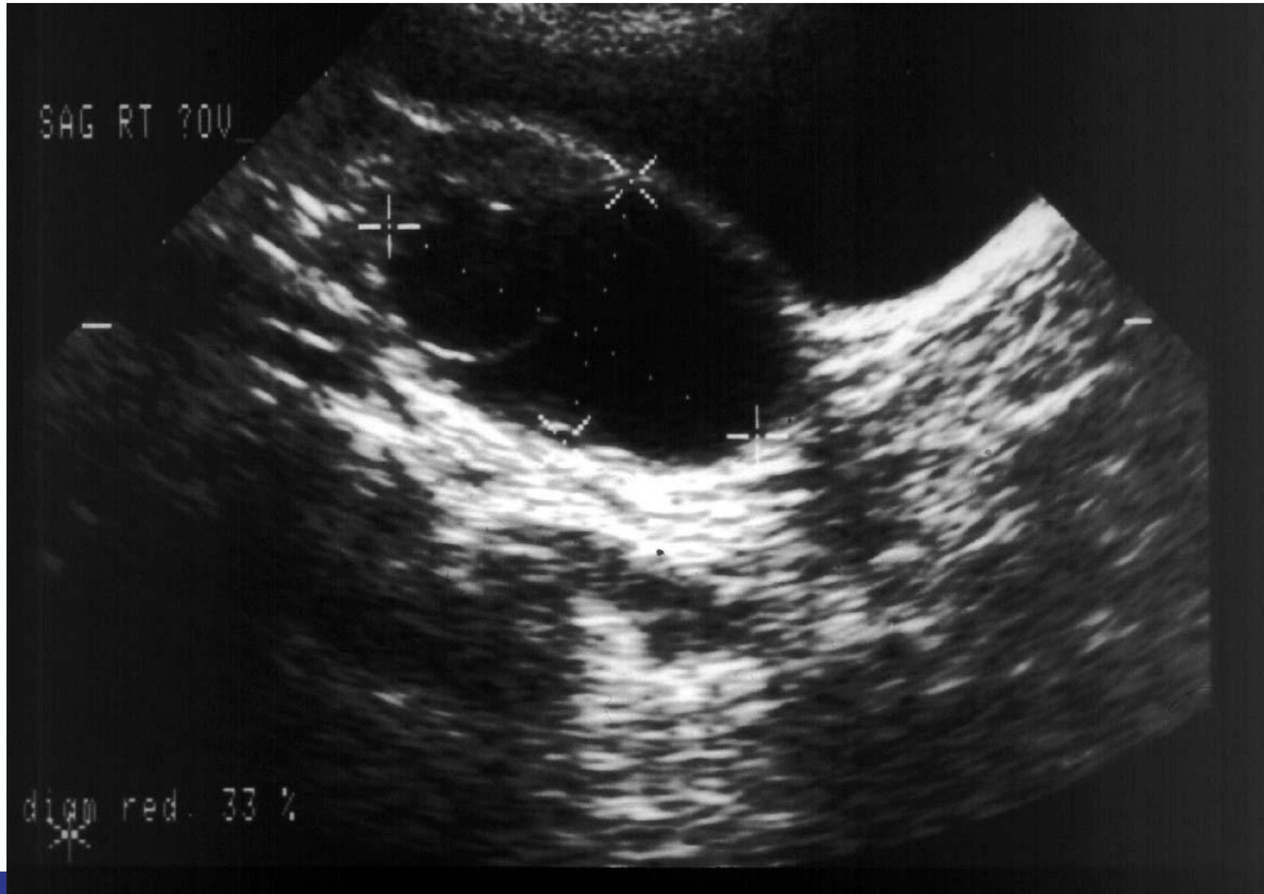


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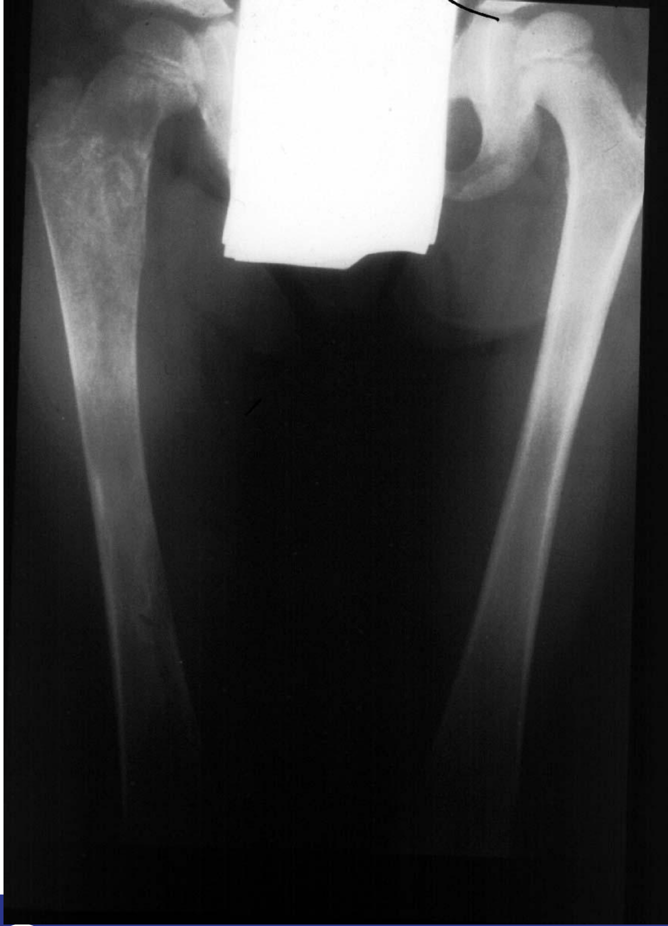
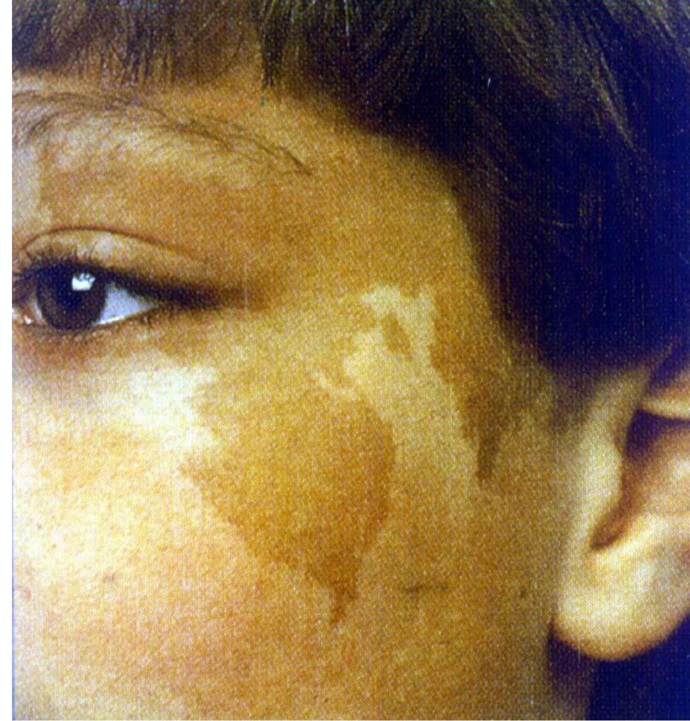
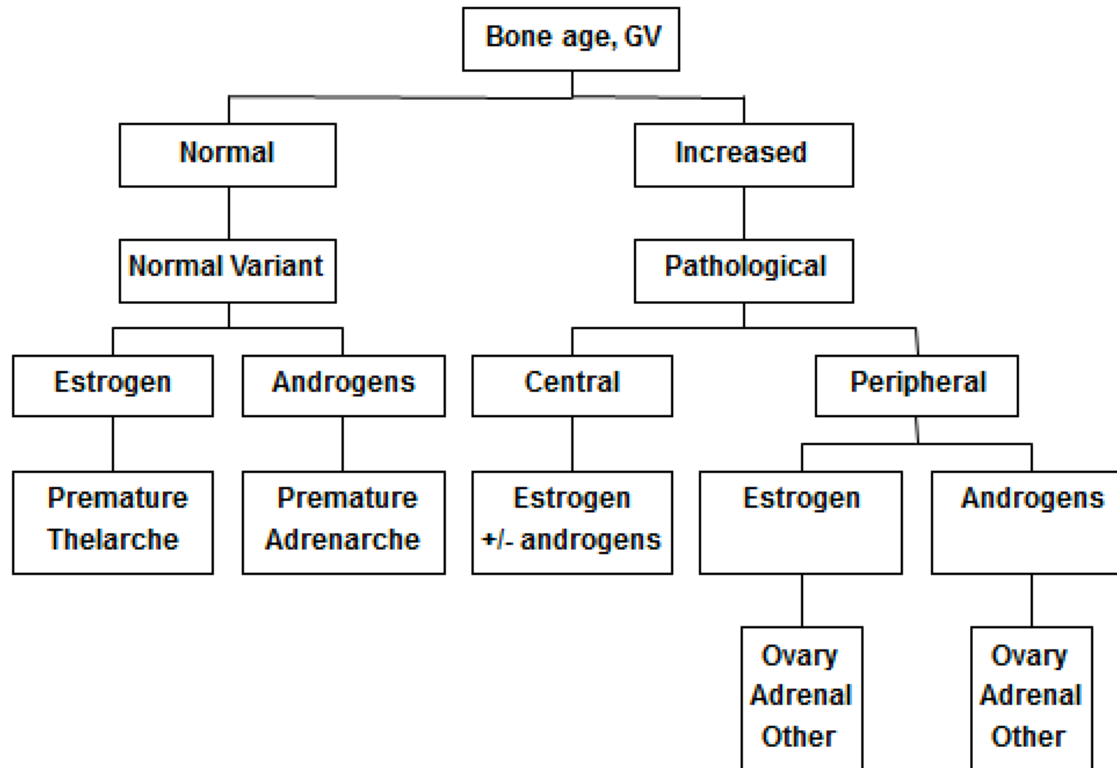




# Approach to Early Puberty in Girls



# Case 6

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

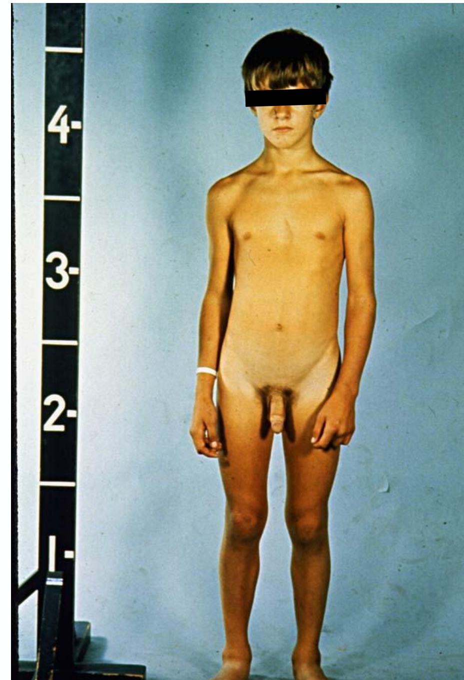
A. 17 hydroxyprogesterone

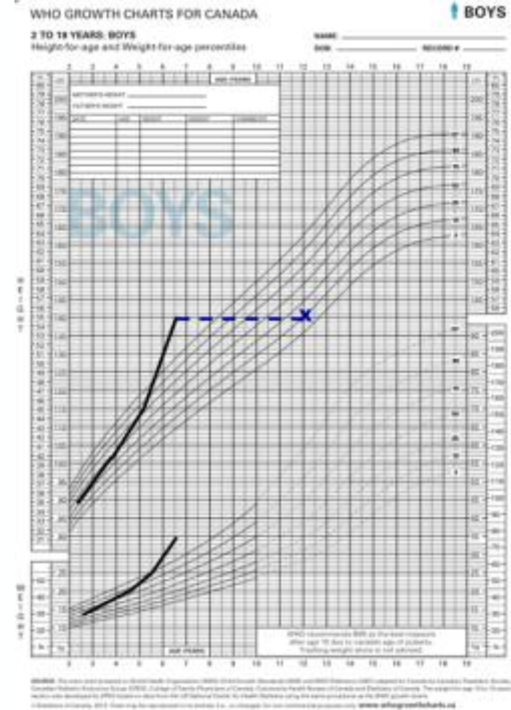
B. Testo profile

C. DHEAS

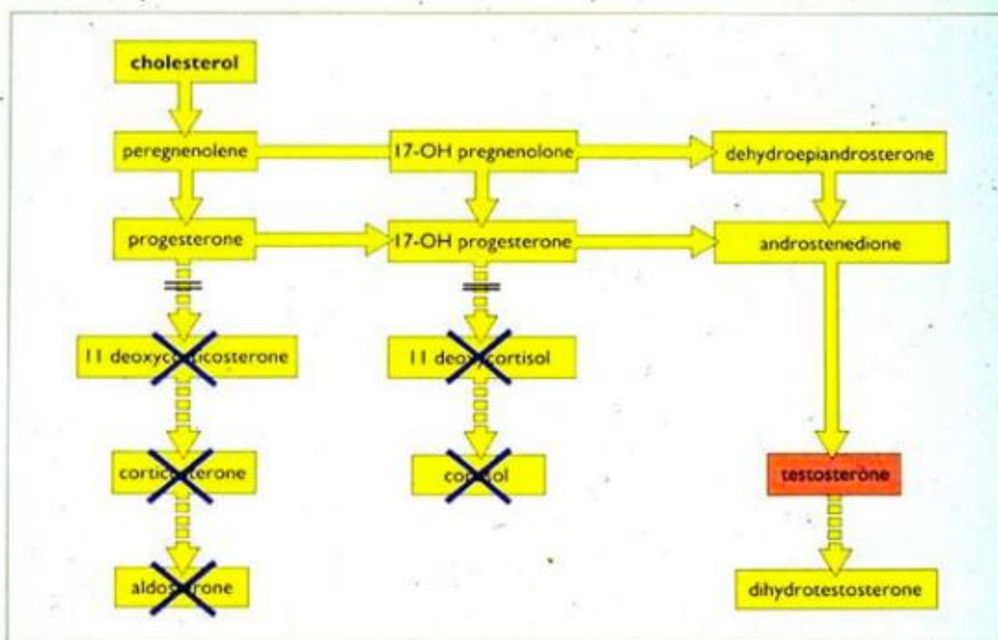
D. LH,FSH (baseline and stimulated)

E. US of abdo and testes

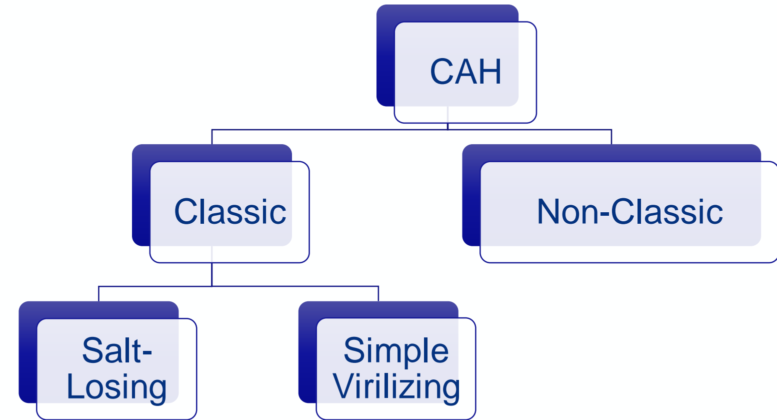


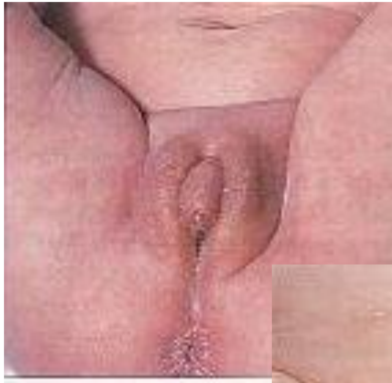
# CAH

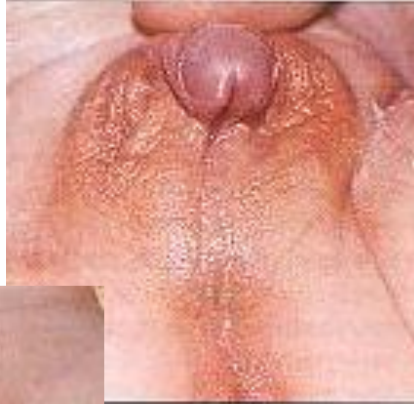


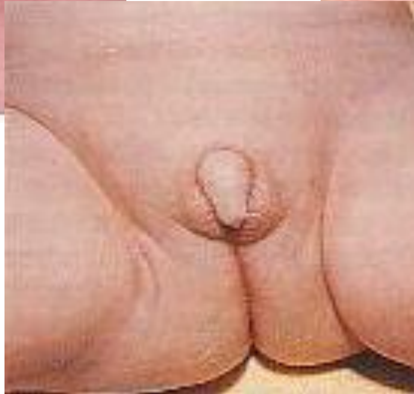
6.5 Schematic representation of the common form of congenital adrenal hyperplasia, 21-hydroxylase deficiency.

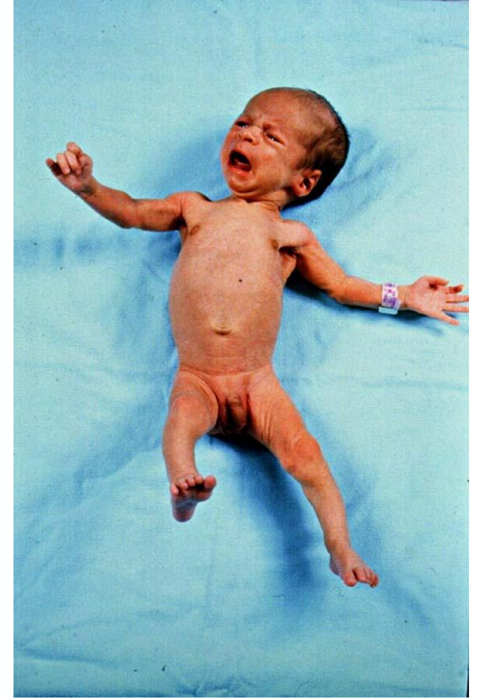


# Classical CAH

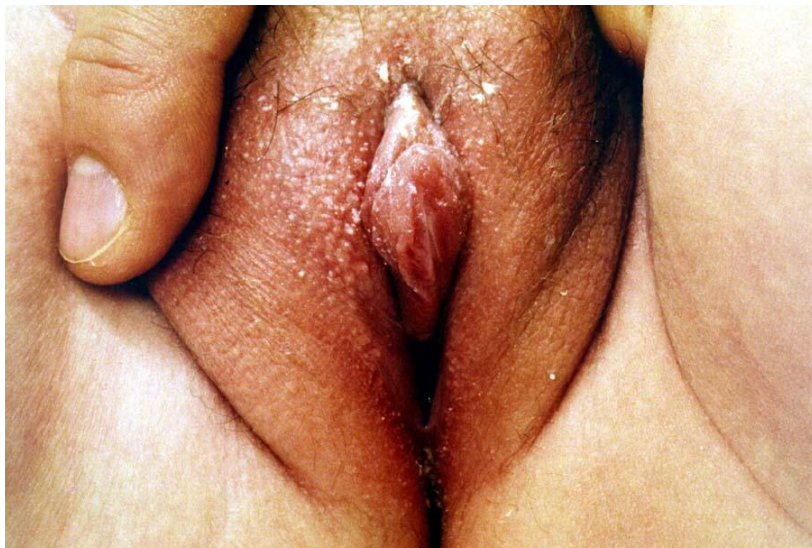




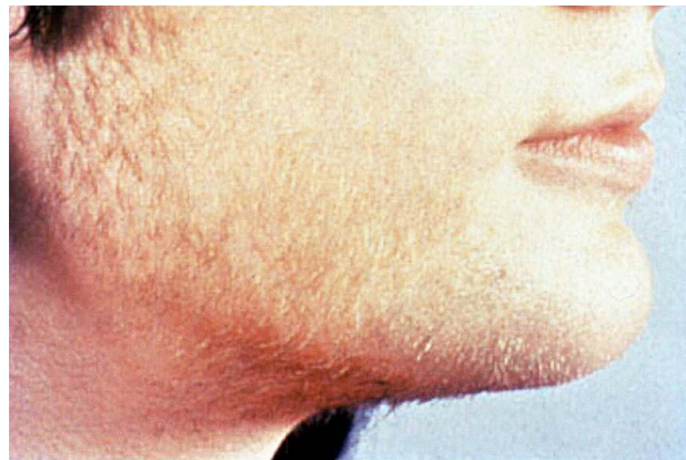




## Girl with Simple Virilizing CAH

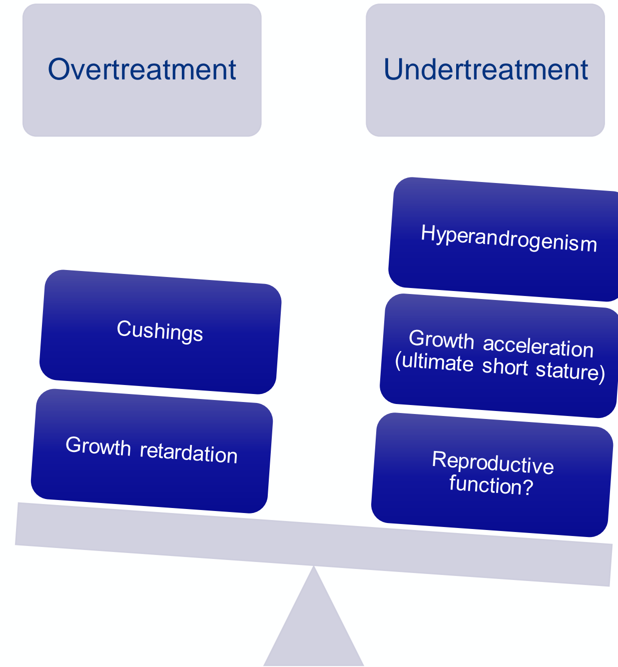


## Late onset CAH



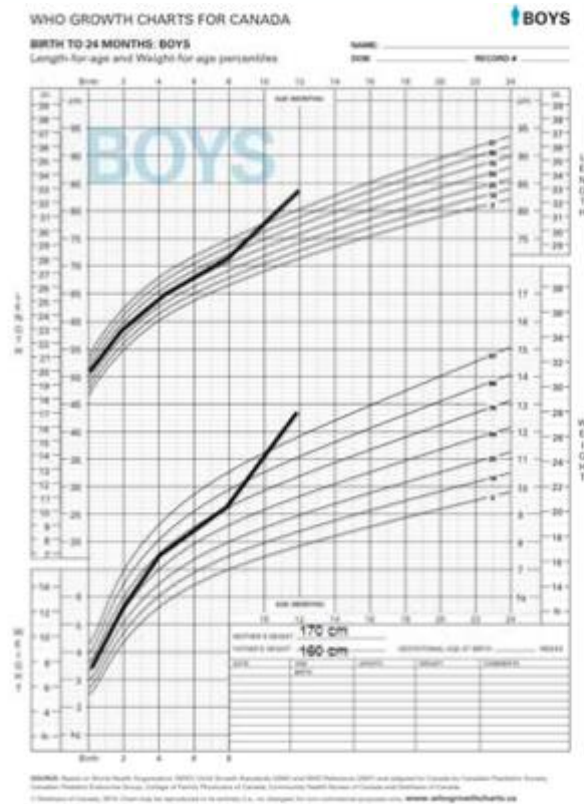
# CAH - Management

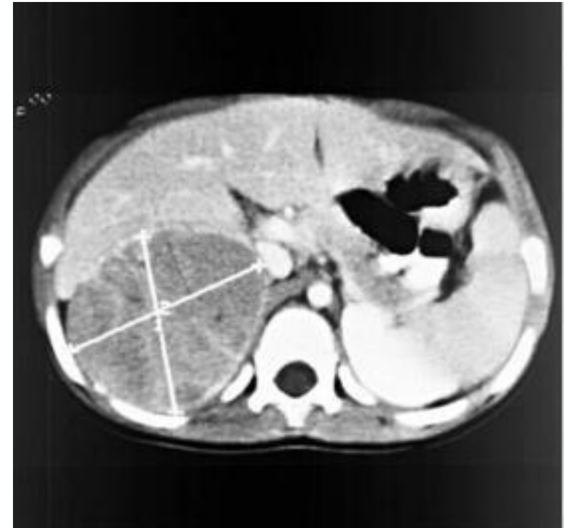
+/- Hydrocortisone
+/- Fludrocortisone
+/- NaCL




Glucocorticoid treatment DOES NOT mimic physiologic secretion

# Case 7

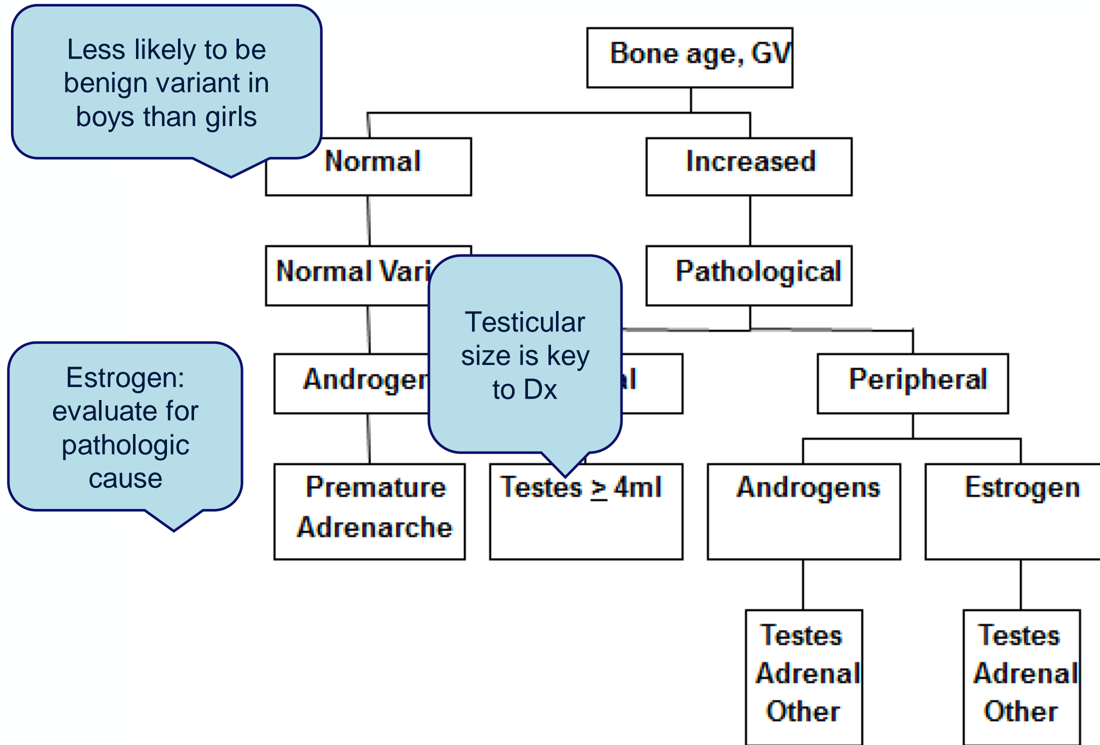


# Summary:

- 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

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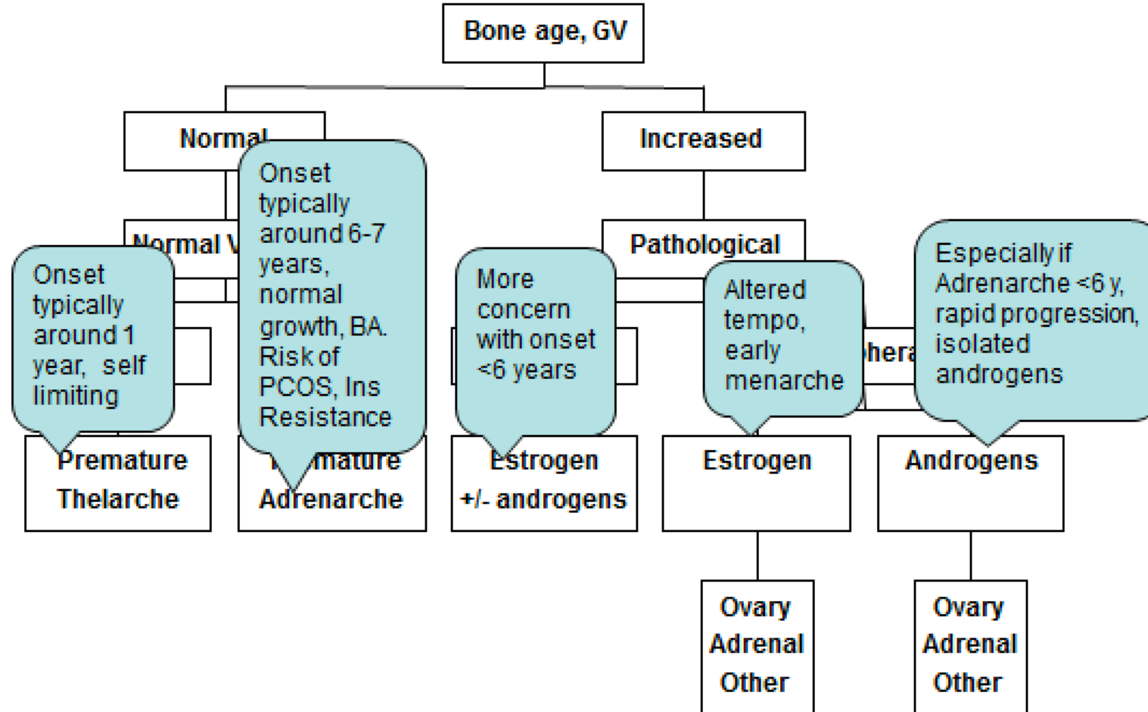
# Approach to Early Puberty in Girls

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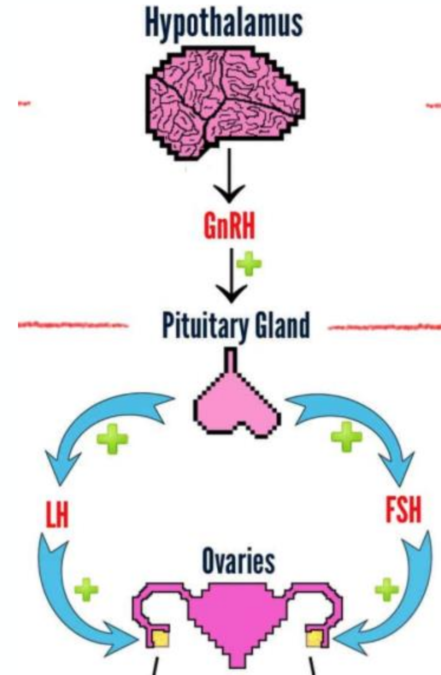
# SECONDARY AMENORRHEA



# Major causes of secondary amenorrhea

- Pregnancy
- Hypothalamic functional
- Hypogonadism
  - Hypogonadotropic (hypothalamic or pituitary lesion)
  - Hypergonadotropic (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)

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# Interpretation of initial investigations

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

# Interpretation of Initial Investigations

| Labs | Diagnosis | Next steps |
|---|---|---|
| Elevated androgens | PPCOS<br>Late onset CAH,<br>Adrenal tumour (T > 5.2 mmol/L, DHEAS > 18.9 umol/L) | Karyotype/microarray<br>Fragile X premutation<br>Autoantibodies<br>(Hx of chemo/radiation) |
| TSH abnormal | Hypo or Hyper thyroidism | |
| All normal | | Evaluate estrogen status with provera challenge 10 mg x 10 days |

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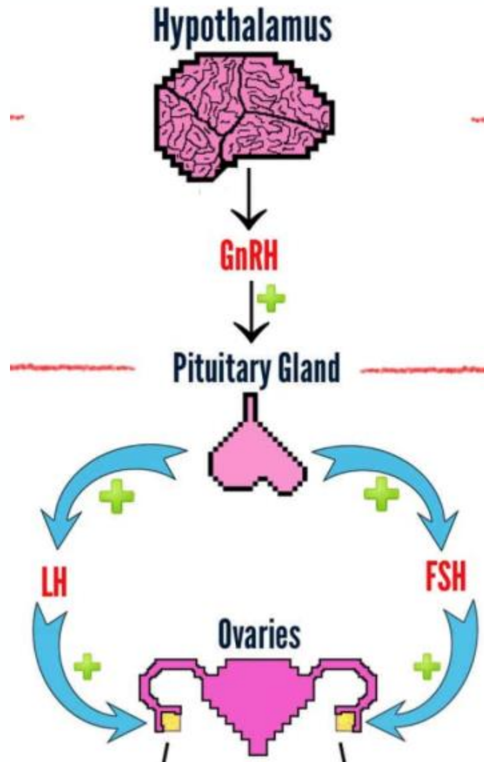
# Primary Amenorrhea

- Definition:
  - —Absence of menarche by age 15 years I 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%. Hypogonadotropic hypogonadism (including functional hypothalamic amenorrhea
5% pituitary disorder

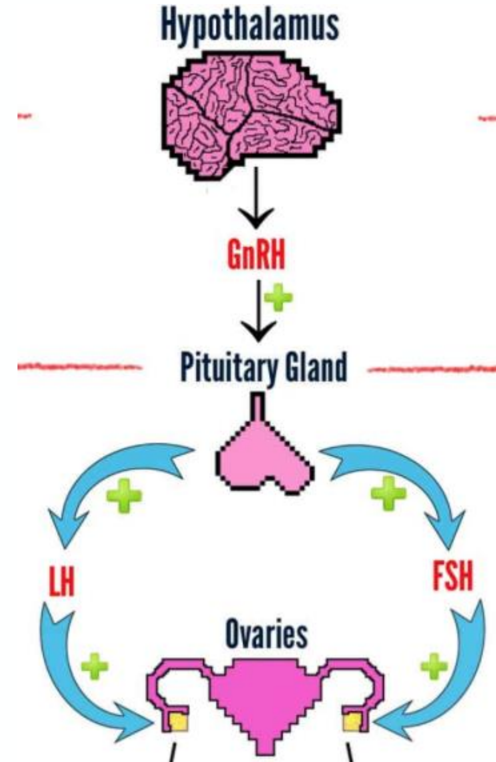
5% other – AIS, CAH, PCOS

50%. Genetic – gonadal dysgenesis

15%. Mullerian agenesis
5% Vaginal septum

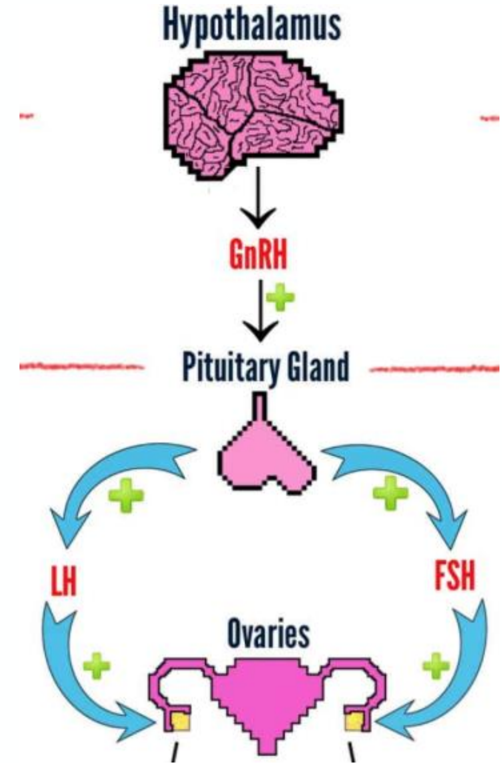
# No pubertal signs

- 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

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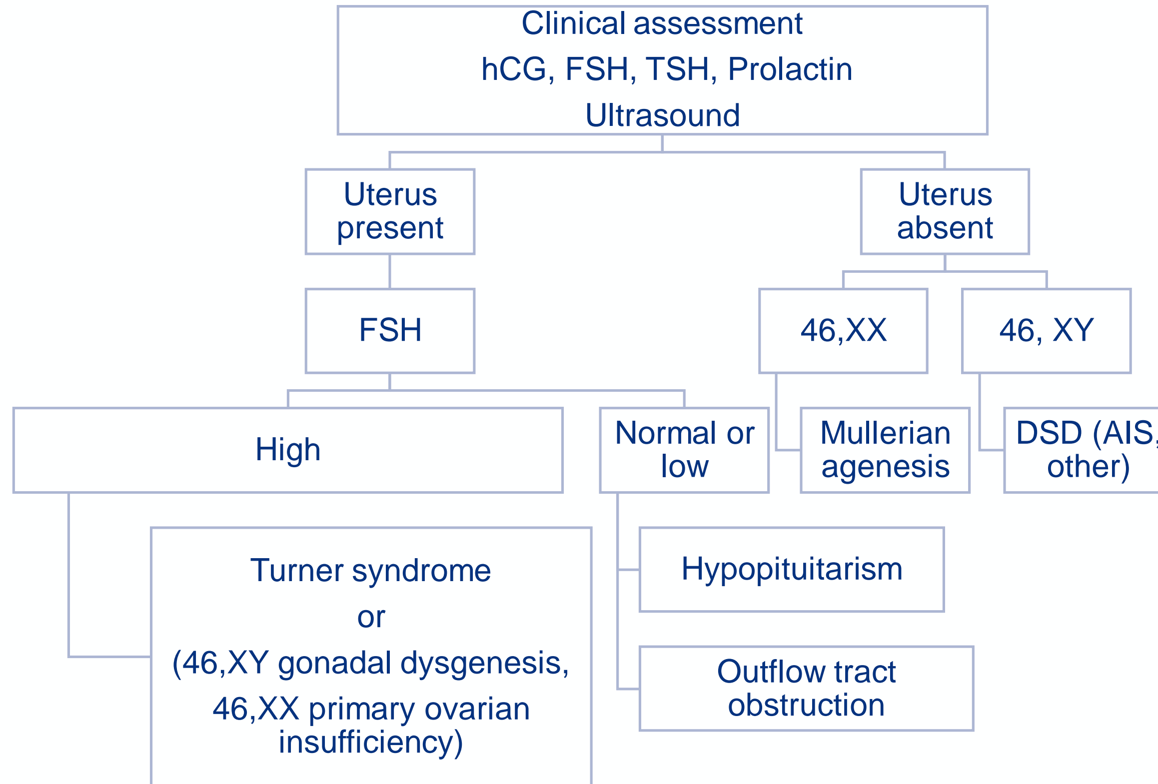
# Approach to primary amenorrhea

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# 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