

# Puberty - Early Normal and Abnormal Development

Paul Hofman 2009

# Case Scenario 1

6 year old girl with 1 year hx of breast development.  
Otherwise well with no past hx of note.

O/E she has

Tanner 2-3 breast development

Tanner 1 pubic hair

Height on 90th%ile

Does this patient have precocious puberty?

# Definitions

Precocious puberty - < 8.5 years girls  
< 9.5 years boys

A symptom NOT a diagnosis

Major medical complication is short stature

# Definitions

First signs of puberty

girls - breast development/ growth spurt

boys - testicular growth ( $> 4\text{ml}$ )  
(growth spurt late)

# Definitions

Oestrogen action = Breast Development

Androgen action = Pubic hair, acne, body odour,  
axillary hair, hirsutism, genital enlargement

# Definition

Normal Puberty -

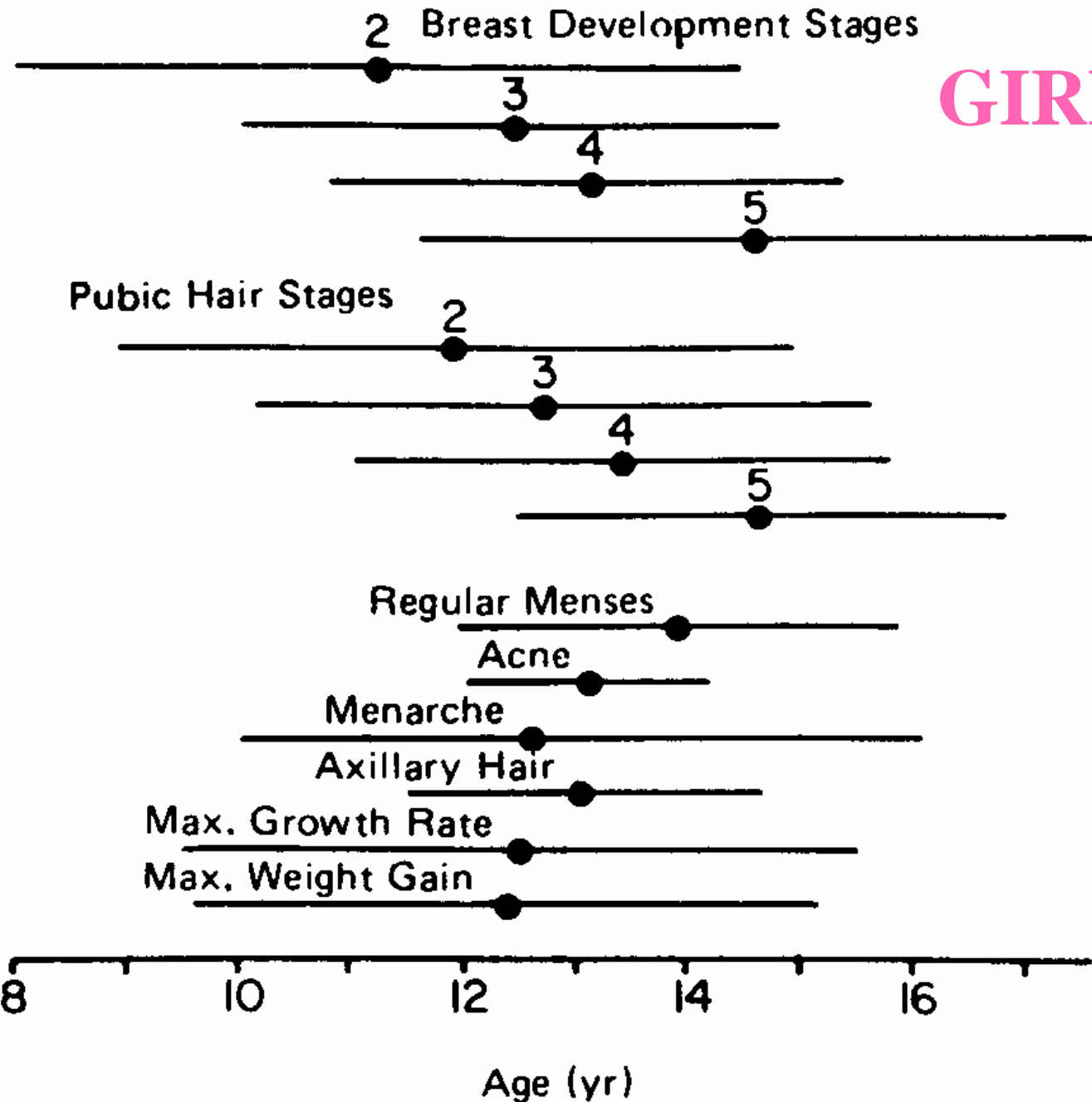
Central activation of the H-P-Gonadal axis

*Progressive sequential* changes

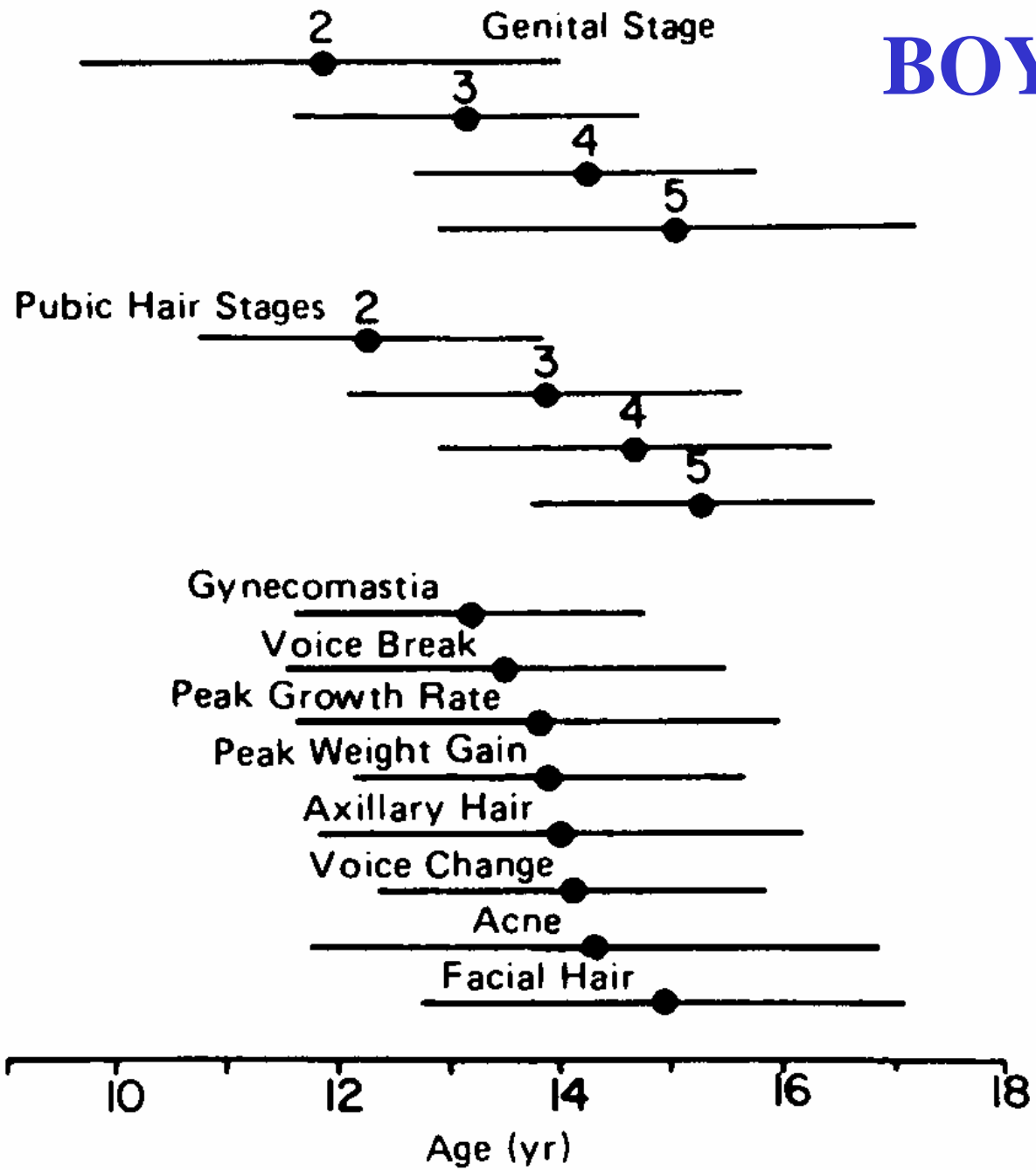
Appropriate rate (over 3-4 years)

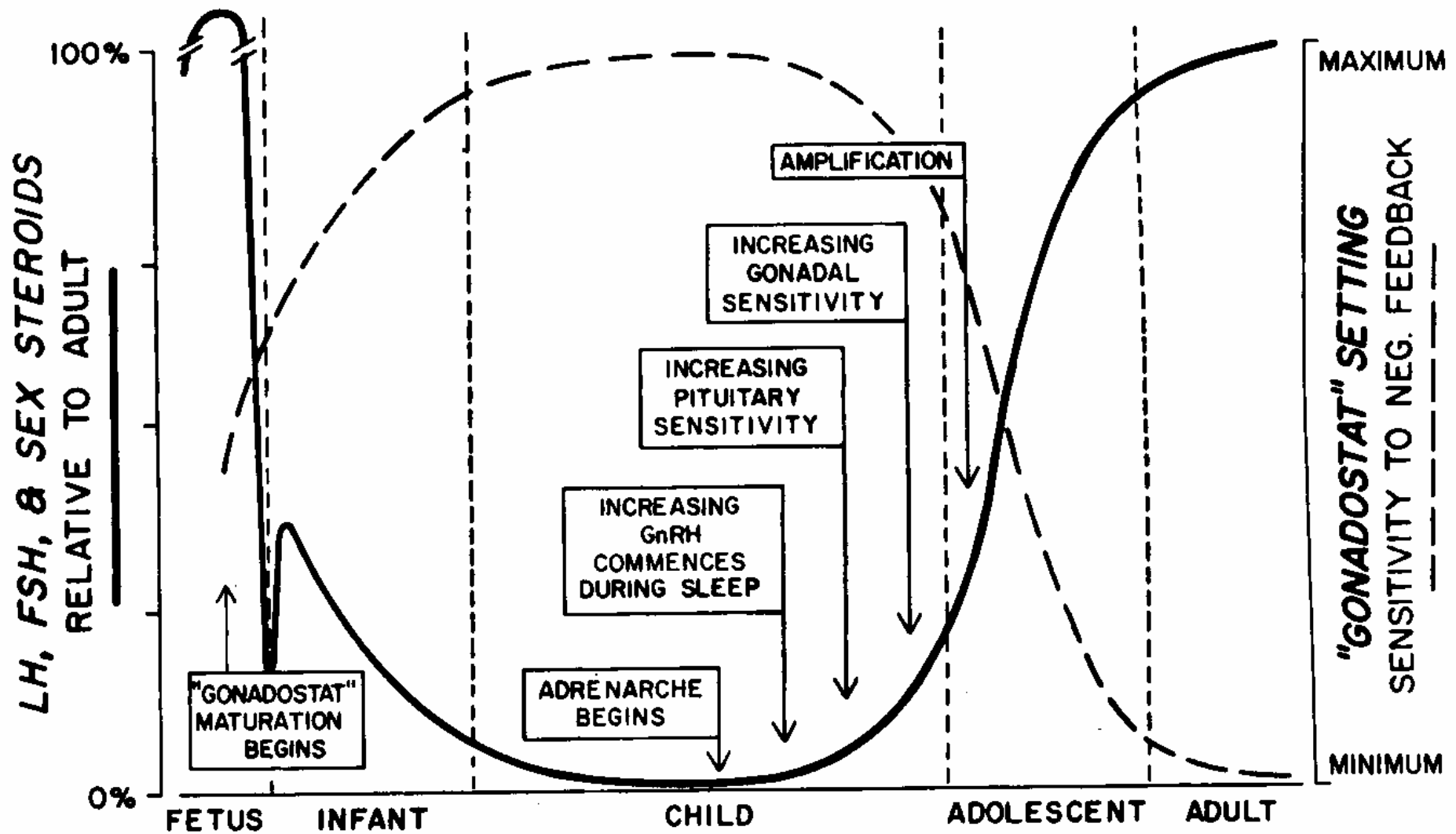
**Sustained, ongoing sex steroid action**

# GIRLS



# BOYS





# Signs of sustained sex steroid effect

Growth	height velocity height compared to mid parental height
Breasts	progressive development
Introitus	pink-red epithelium pre oestrogen white-pink with sustained oestrogen exposure (cornification of epithelium)

# Investigations for sustained sex steroid effect

**Bone Age** (X-ray L hand and wrist)

**USS pelvis** Uterine size/ volume, sometimes useful  
info on ovaries.

## *Unhelpful/ Useless/ Uninterpretable tests*

FSH and LH

Testosterone

Oestradiol (the assay is less sensitive than the  
bioassay of growth and breast development)

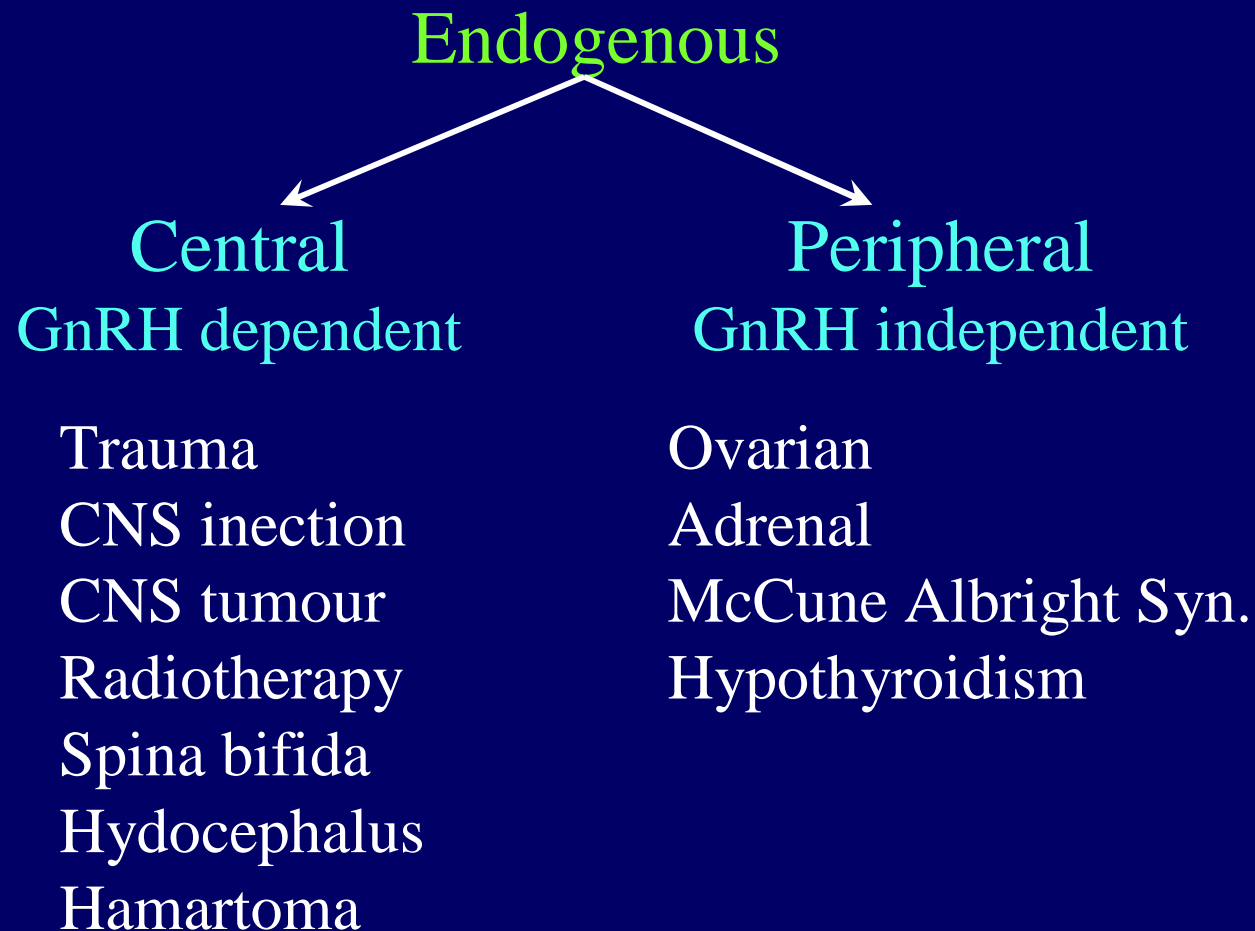
# Case Scenario 1

Midparental Height	25th%ile
Introitus	white-pink colour
Bone Age	10 years (CA 6 years)

Interpretation - Highly suggestive of sustained oestrogen exposure/ action.

Warrants urgent paediatric endocrine referral.

# Differential Dx



## Exogenous

O/C

HRT

E2 creams

Soy?

‘Natural remedies’

## Case scenario 2

6 year old girl with 1 year hx of breast development.  
Otherwise well with no past hx of note

O/E she has

Tanner 2-3 breast development

Tanner 1 pubic hair

Height on 90th%ile

Mid parental height = 90<sup>th</sup>%ile

BA = 6 years

Summary – No evidence of sustained or progressive  
sex steroid excess.

# Differential Dx

## Premature Thelarche

### Endogenous (early)

```
graph TD; A[Endogenous (early)] --> B[Central GnRH dependent]; A --> C[Peripheral GnRH independent];
```

Central  
GnRH dependent

Trauma  
CNS inection  
CNS tumour  
Radiotherapy  
Spina bifida  
Hydocephalus  
Hamartoma

Peripheral  
GnRH independent

Adrenal  
McCune Albright Syn.  
Hypothyroidism

### Exogenous

O/C  
HRT  
E2 creams  
Soy?  
'Natural remedies'

# Premature Thelarche

- common
- variable breast development
- usually 1-4 years age
- no height velocity acceleration
- BA=CA
- No pubertal progression

# Diagnosis of isolated breast development

## *When is referral required?*

If there is no evidence of sustained sex steroid exposure based on physical exam, growth data, or bone age close observation (initially 3 monthly) is appropriate.

If there are signs of progressive oestrogen exposure urgent referral to paediatric endocrinology is appropriate

## Boobs or Bust?

What about breast development in boys?

### Case Scenario 3

- 14 year old boy presents with Tanner 3 breast development of ~12 months duration.
- Distressed by this – never goes swimming.
- In puberty: Tanner 3 genitalia and pubic hair and 10 ml testis.

# Differential Diagnosis

## Non Pathological Gynaecomastia

- Neonatal
- Pubertal
  - 50-75% of pubertal boys (possibly more)
  - Often looks worse with obesity (as well as increased aromatisation).
  - Unless severe resolves in late puberty.
  - If structural breast changes have occurred the gynaecomastia may not resolve.

# Differential Diagnosis

## Pathological

- Drugs
  - Marijuana
  - Antiandrogens
  - Oestrogens
  - Dopamine antagonists
  - H2 antagonists etc.
- Tumour associated
  - **hCG or LH secreting tumour**
  - Oestrogen secreting tumour
- Miscellaneous (Klinefelters, hypothyroidism, androgen insensitivity syndrome)
- Familial (X-linked recessive or sex limited dominant e.g. Tutankanum)

# What history is relevant?

- Are they in puberty?
- Are they fat?
- Medications/ drug abuse
- Evidence for elevated prolactin levels (nipple discharge)
- Is there any evidence/hx suggestive of hypogonadism
- Any evidence of an underlying endocrinopathy
- Family history of gynaecomastia.
- History of systemic illness ( eg renal, hepatic etc.)

# Relevant exam findings

- Breast(s) size and consistency(firm/soft)
- Nipple discharge
- Testis size/asymmetry
- Evidence of chronic illness
- Abdo - masses (adrenal/liver)
- Thyroid

# What investigations are appropriate?

- Investigations depend on the presentation. Minimal workup is needed for the obese adolescent male with gynaecomastia. It can often be difficult to tell whether there is real breast tissue there!
- But investigate more fully if the boy is
  - prepubertal
  - stuttering puberty
  - thin (at least not obese)
  - breast development is marked

# Investigations

- hCG (*tumour*)
- Karyotype (*Klinefelters*)
- Liver/renal (*evidence of chronic illness*)
- TFTs (*signs of hypo/hypothyroidism*)
- Basal Gonadotropins (LH and FSH)  
(*Klinefelters, primary hypogonadism*)
- *Prolactin*
- *Oestradiol*
- *Androgens*

# Treatment Options

- **Surgical** - if extreme or prolonged
- **Medical** (treat underlying condition/ remove offending medication or drugs)
  - **Decrease Oestrogen**
    - *Tamoxifen- selective estrogen receptor modulator (SERM)*  
*Dose 20mg daily – usually need for 1-2 years.*

# Case Scenario 4- Premature Pubarche

6 year old boy presents with 23 pubic hairs!

Hairs present for 2-3 months and slowly increasing in no.

Some body odor and a few comedones.

# Pubic versus Vellous Hair

- Pubic hair is dark, thick and curly
- Vellous hair is fine and down like. It can be dark and quite long in certain ethnic groups (eg Mediterranean, Indian, Polynesian)

# Further work up

Growth      height 75th %ile

                 height velocity 95th%ile

Skin            Not pigmented, oily

Testis         1ml bilaterally (pea sized)

Bone Age        10 years

# Early androgen signs

- pubic hair
- increasing genital size
- body odour
- acne and oily skin

# Early pubertal changes in boys

Gonadal examination makes the assessment of male puberty easier!

Prepubertal                      testis  $\leq$  3ml

Pubertal                              testis  $\geq$  4 ml

Increasing testicular size *almost always* indicates a central cause.

Prepubertal testis indicates a peripheral cause (almost always adrenal)

# Case Scenario - Summary

Evidence of sustained sex steroid with increased growth and advanced bone age.

Prepubertal testis size indicates a peripheral cause.

Warrants urgent referral to a paediatric endocrinologist

# Differential Dx

## Endogenous

### **Gonadal**

Androgen secreting tumour

### **Adrenal**

Congenital adrenal hyperplasia

Androgen secreting tumour

hCG secreting tumour

## Exogenous (rare)

Anabolic steroids

# Futher tests

Abdo (adrenal) and gonadal USS - may need CT

## Androgen profile

Androstenedione

Testosterone/ free testosterone

Dehydroepiandrosterone (DHEA)

17 OH progesterone (*for CAH*)

Sex hormone binding globulin (SHBG)

# Case Scenario 5

6 year old boy presents with 23 pubic hairs!

Hairs present for 2-3 months and slowly increasing in no.

Some body odour and a few comedones.

Height velocity 50th%ile, Height 50th%ile

Bone Age = 7 years

testis < 1ml bilaterally

# Assessment and Differential Dx

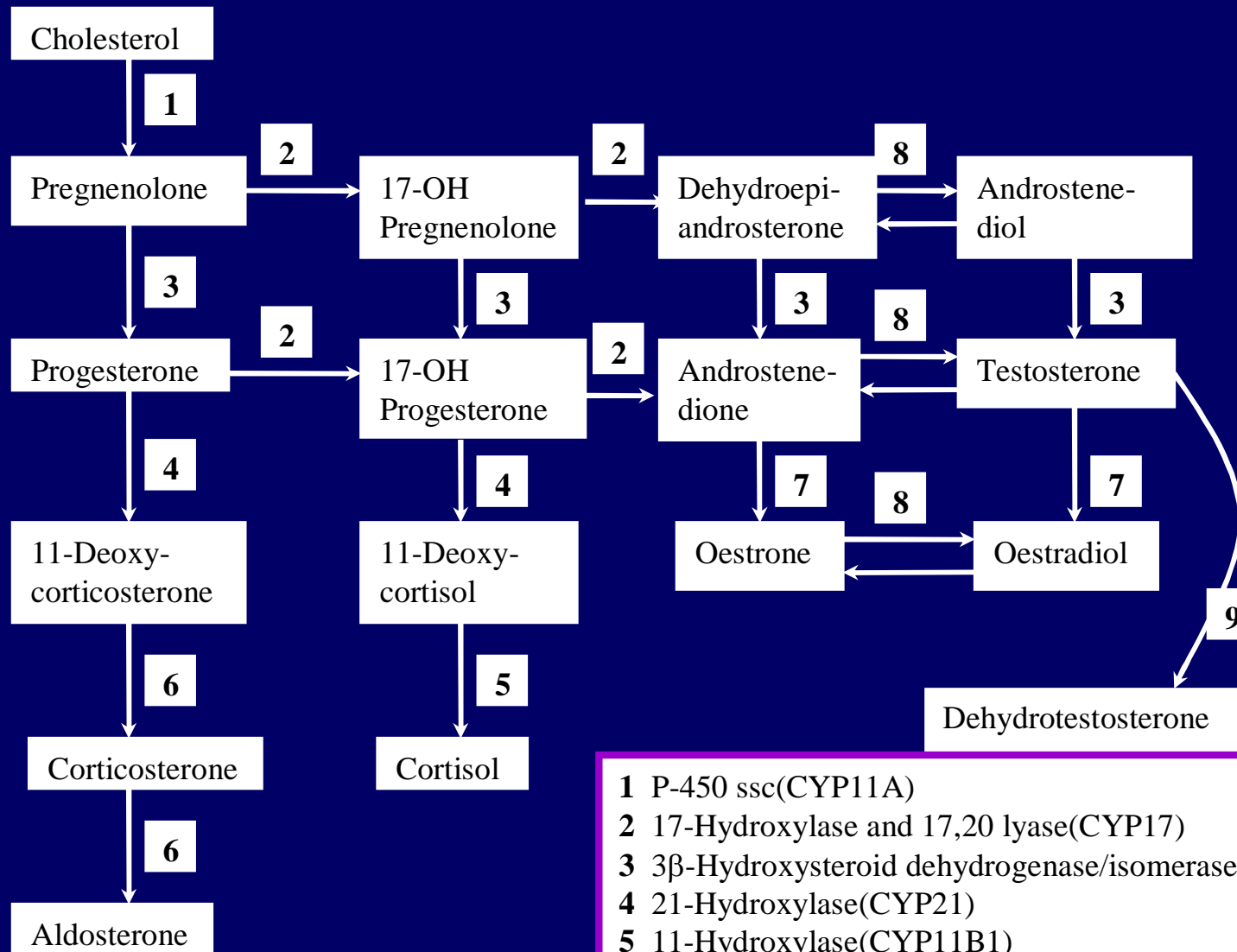
No evidence of sustained sex steroid effect (normal height velocity and bone age)

**PREMATURE ADRENARCHE** most likely

Commonest cause of premature pubarche  
occurs generally in mid childhood

# Adrenarche

- maturational increase in adrenal 17-ketosteroids
- results in increased DHEA (into pubertal range)
- no change in levels of other adrenal androgens
- none to small increase in growth velocity
- no advancement of bone age
- Usually the cause of early virilisation in boys and girls ie pubic hair development
- Biochemically present 1-2 years before pubarche



- 1 P-450 ssc(CYP11A)
- 2 17-Hydroxylase and 17,20 lyase(CYP17)
- 3 3β-Hydroxysteroid dehydrogenase/isomerase(HSD3B2)
- 4 21-Hydroxylase(CYP21)
- 5 11-Hydroxylase(CYP11B1)
- 6 Aldosterone synthetase(CYP11B2)
- 7 Aromatase
- 8 17β-Hydroxysteroid dehydrogenase
- 9 5α reductase

# Management of premature pubarche

If there is no evidence for ongoing androgen exposure (ie growth acceleration, advanced bone age or ongoing virilisation) the diagnosis is likely premature adrenarche.

Observation for 1-2 years (4-6 monthly) to ensure no pubertal progression.

Underlying organic pathology (eg tumour or CAH) needs appropriate tx.

# Summary

- The assessment of early puberty is mainly clinical and auxological.
- A bone age is the only mandatory initial investigation.
- Sex steroids levels (with the exception of 17 hydroxy progesterone) are generally unhelpful and do not assist in the diagnosis.
- Precocious puberty is a symptom not a diagnosis.
- A GnRH stimulation test will reliably define those in true central precocious puberty.
- Treatment largely depends on the degree of final height compromise.