Professor

Paul Hofman

Paediatrician Endocrinologist

Liggins Institute, The University of Auckland,
Starship Children Hospital, Auckland

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14:00 - 14:55 WS #108: Common pubertal variants – how to distinguish from true pathology

15:05 - 16:00 WS #119: Common pubertal variants – how to distinguish from true pathology (Repeated)

Puberty - Early Normal and Abnormal Development

Paul Hofman 2016

And for about eleven years Mr and Mrs Hormone slept peacefully inside her, until her body clock woke them up! This made them very grumpy!

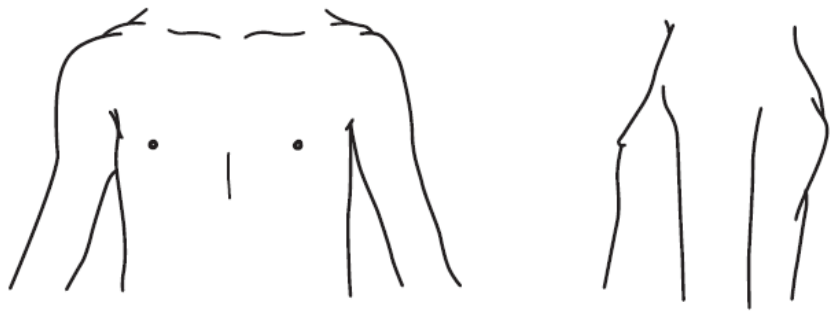
Case Scenario 1

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

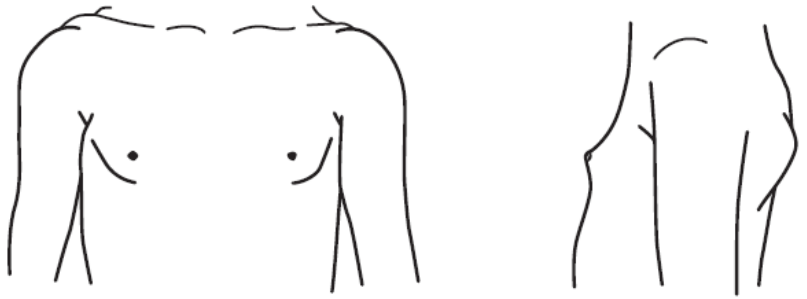
O/E she has

- Tanner 2-3 breast development
- Tanner 1 pubic hair
- Height on 90th%ile

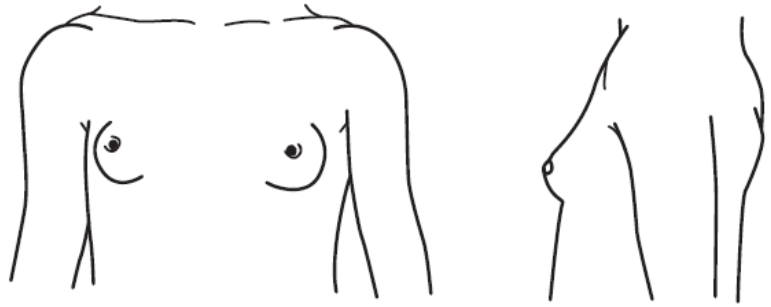
Breast Development Stages



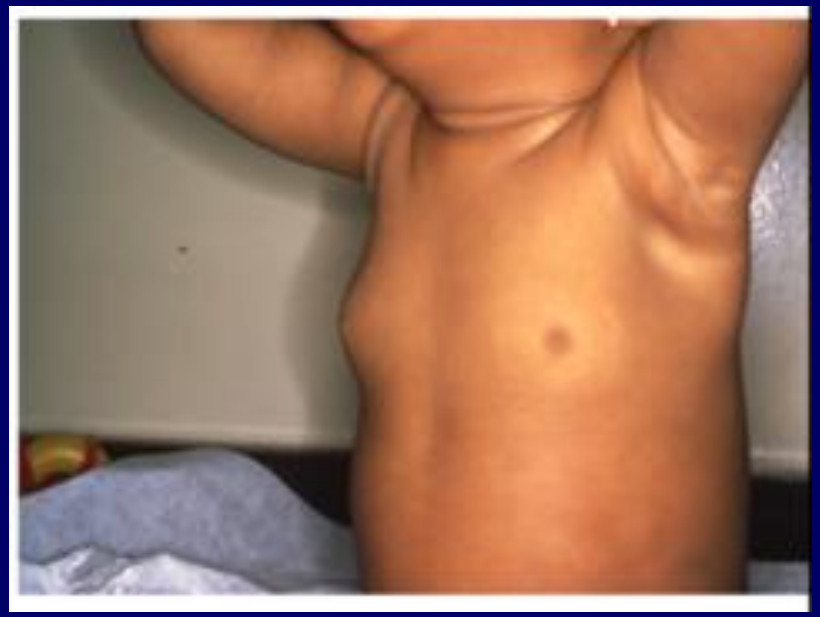
Stage 1. Prepubertal



Stage 2. Elevation of breasts and papilla



Stage 3. Further elevation and areola but no separation of contours



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 (> 3ml)
(growth spurt late)

Definitions

Oestrogen action = Breast Development

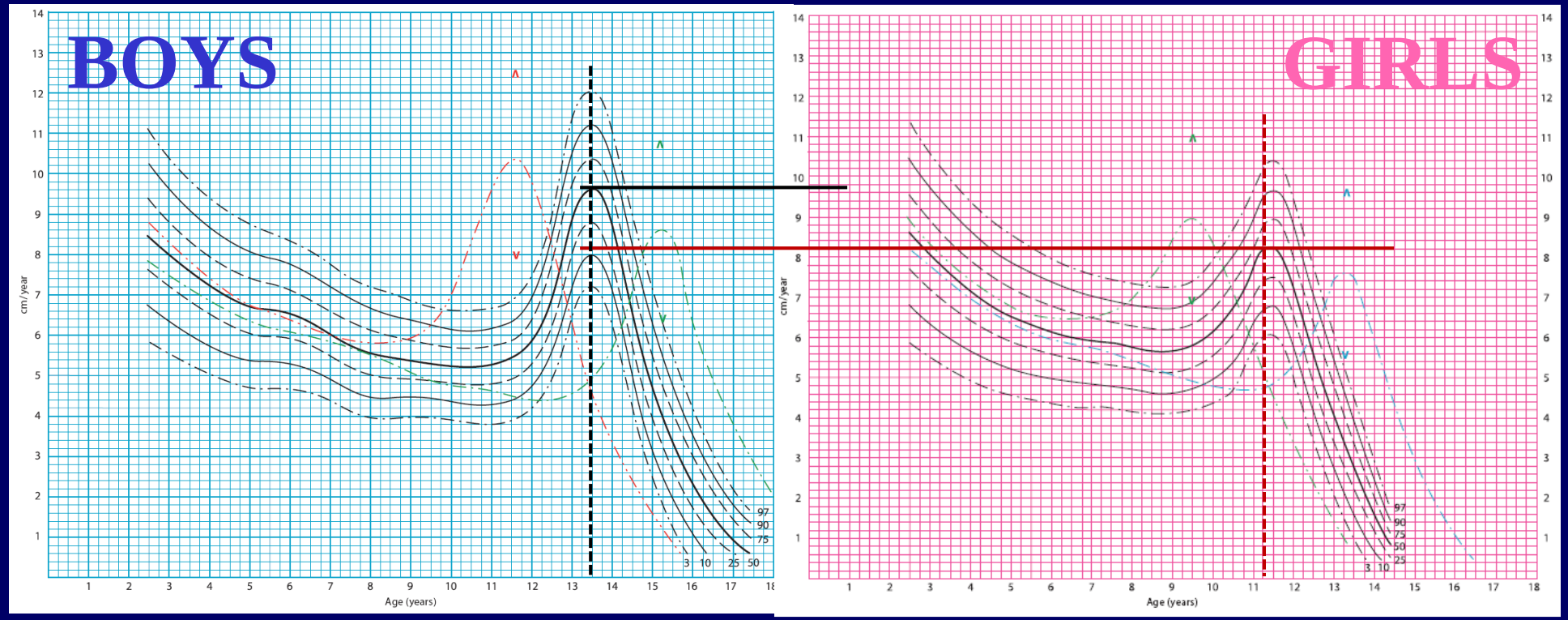
Androgen action = Pubic hair, acne, body odour, axillary hair, hirsutism, genital enlargement

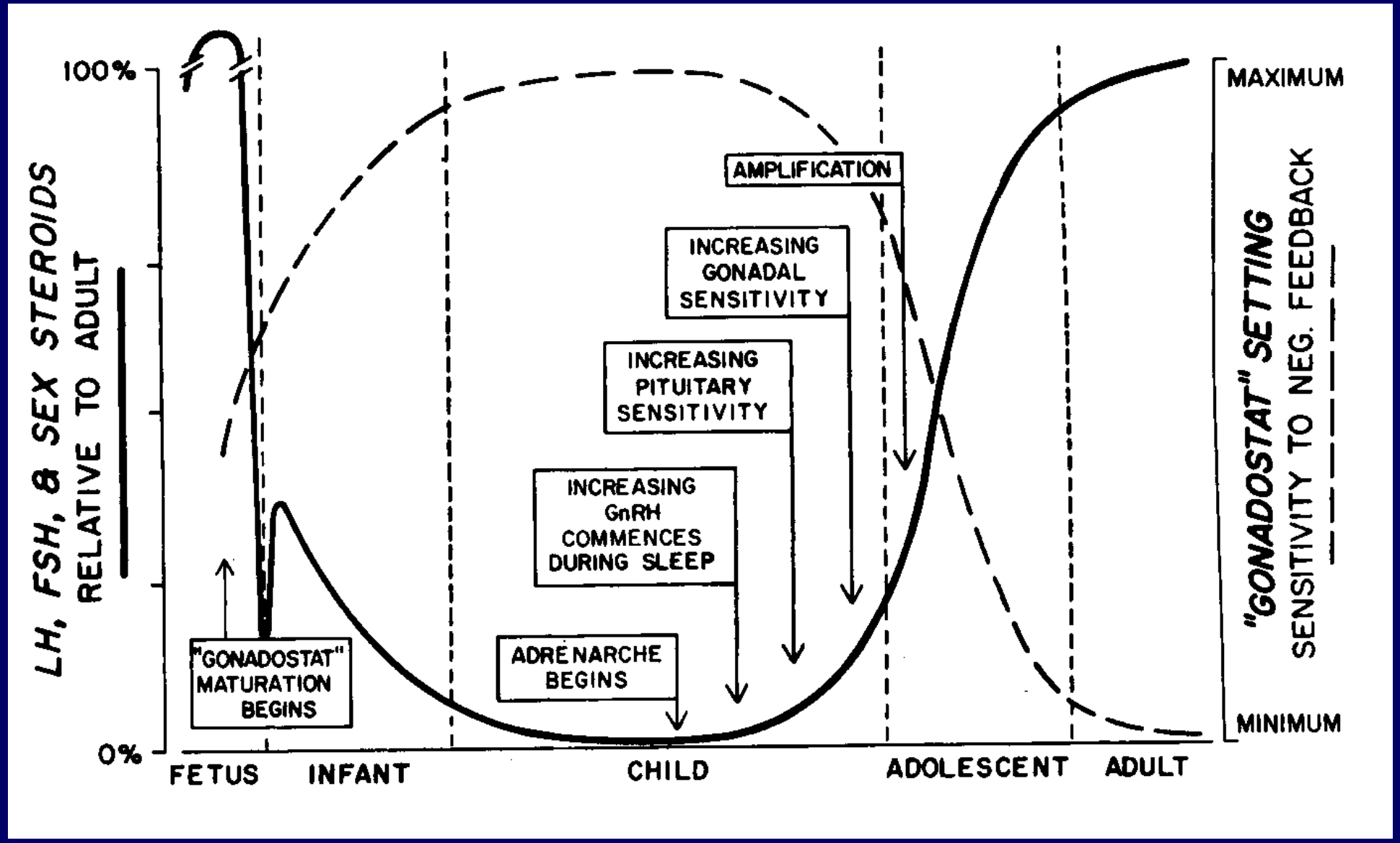
Definition

Normal Puberty -

- Central activation of the H-P-Gonadal axis
- ***Progressive sequential*** changes
- Appropriate rate (over 3-4 years)

Sustained, ongoing sex steroid action


BOYS
GIRLS
cm/year
Age (years)
97
90
75
50
25
10
3


100%
0%
LH, FSH, & SEX STEROIDS
RELATIVE TO ADULT
"GONADOSTAT" MATURATION BEGINS
ADRENARCHE BEGINS
INCREASING GnRH COMMENCES DURING SLEEP
INCREASING PITUITARY SENSITIVITY
INCREASING GONADAL SENSITIVITY
AMPLIFICATION
FETUS
INFANT
CHILD
ADOLESCENT
ADULT
MAXIMUM
MINIMUM
"GONADOSTAT" SETTING
SENSITIVITY TO NEG. FEEDBACK

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

Usually Unhelpful and 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

Endogenous

Central
GnRH dependent

- Trauma
- CNS inection
- CNS tumour
- Radiotherapy
- Spina bifida
- Hydocephalus
- Hamartoma

Peripheral
GnRH independent

- Ovarian
- Adrenal
- McCune Albright Syn.
- Hypothyroidism

Exogenous

- O/C
- HRT
- E2 creams
- Lavender and Tea Tree oils
- Soy?
- ‘Natural remedies’

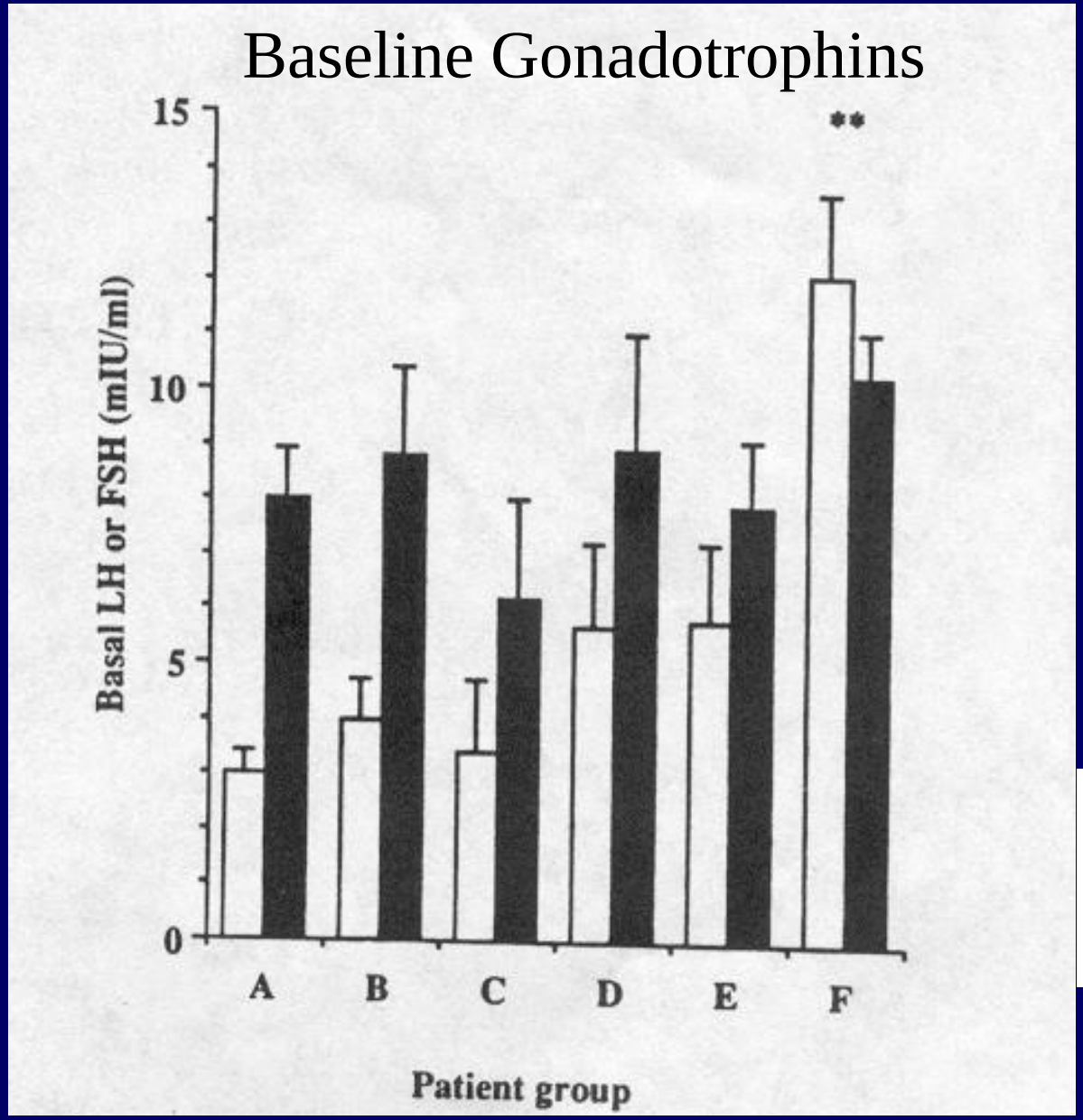
Diagnosis

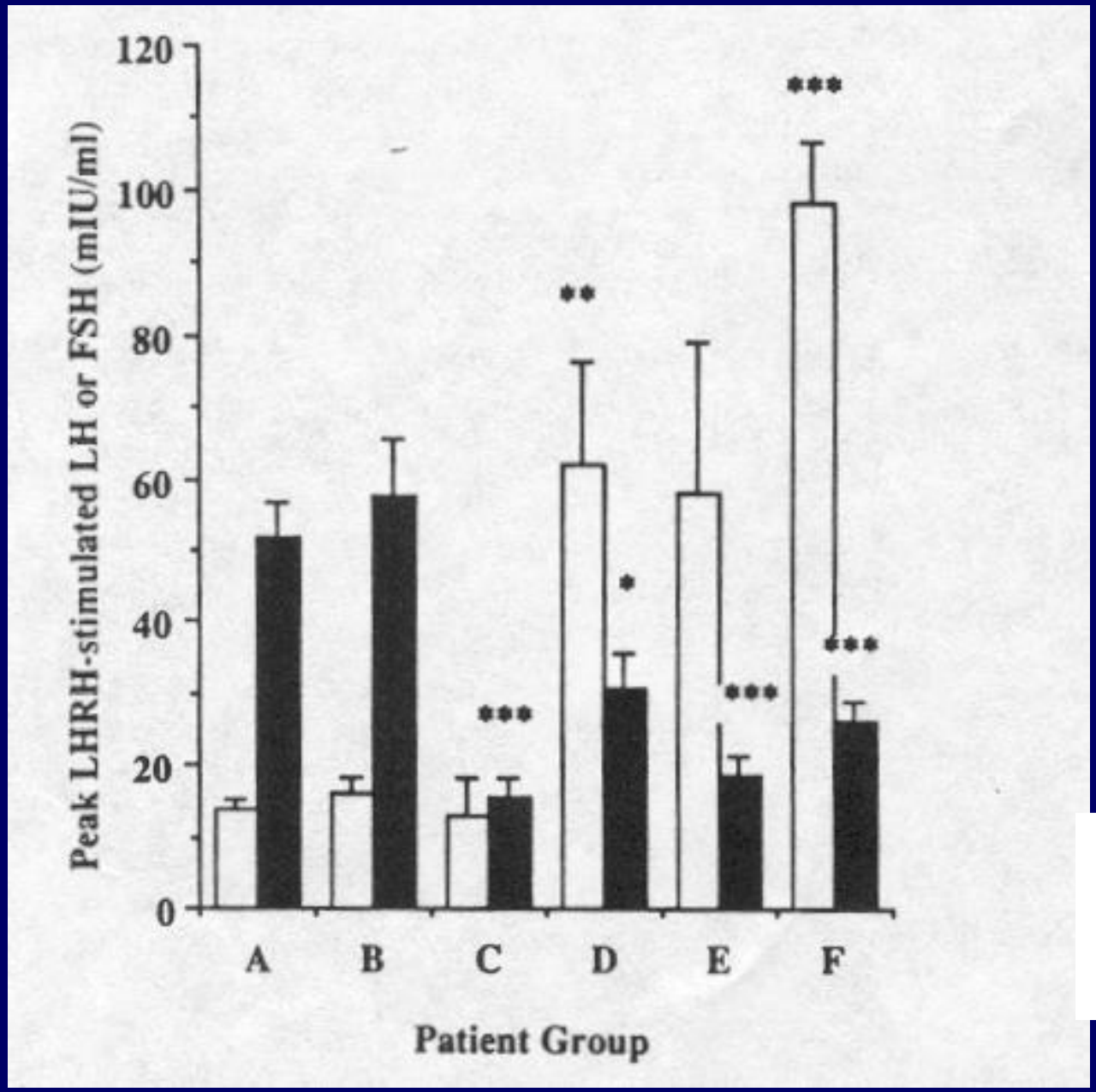
When are further investigations required?

• If there is evidence of significant and/or sustained sex steroid exposure (increase height velocity, advanced bone age, progressive clinical pubertal changes) the distinction between true central and peripheral precocious puberty needs to be made.

• This can be most reliably done using the GnRH stimulation test.

Baseline Gonadotrophins




120
100
80
60
40
20
0
Peak LHRH-stimulated LH or FSH (mIU/ml)
A
B
C
D
E
F
Patient Group
***
**
*
***
***
***
FSH
LH

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 = 90th%ile
- BA = 6 years

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

Differential Dx

Premature Thelarche

Endogenous (early)

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

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
- Prepubertal (usually late childhood)
  - Aromatase overactivity
- Pubertal
  - 50-75% of pubertal boys (possibly more)
  - Often looks worse with obesity (with increased aromatisation).
  - Unless severe resolves in late puberty.
  - If structural breast changes have occurred the gynaecomastia won’t resolve.

Differential Diagnosis

Pathological

- Drugs
  - Marijuana
  - Antiandrogens (spironololactone)
  - Oestrogens
  - Dopamine antagonists
  - H2 antagonists …..
- Tumour associated
  - **hCG or LH secreting tumour**
  - Oestrogen secreting tumour
- Miscellaneous (Klinefelters, hypothyroidism, androgen insensitivity syndrome)
- Familial (X-linked recessive of 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 (androstenedione, testosterone and DHEAS)*

Treatment Options

- **Surgical -** if extreme or prolonged

- **Medical** (treat underlying condition/ remove offending medication or drugs)
  - **Block 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 comedomes.

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 ≤ 3ml
Pubertal	testis ≥ 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 comedomes.

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)

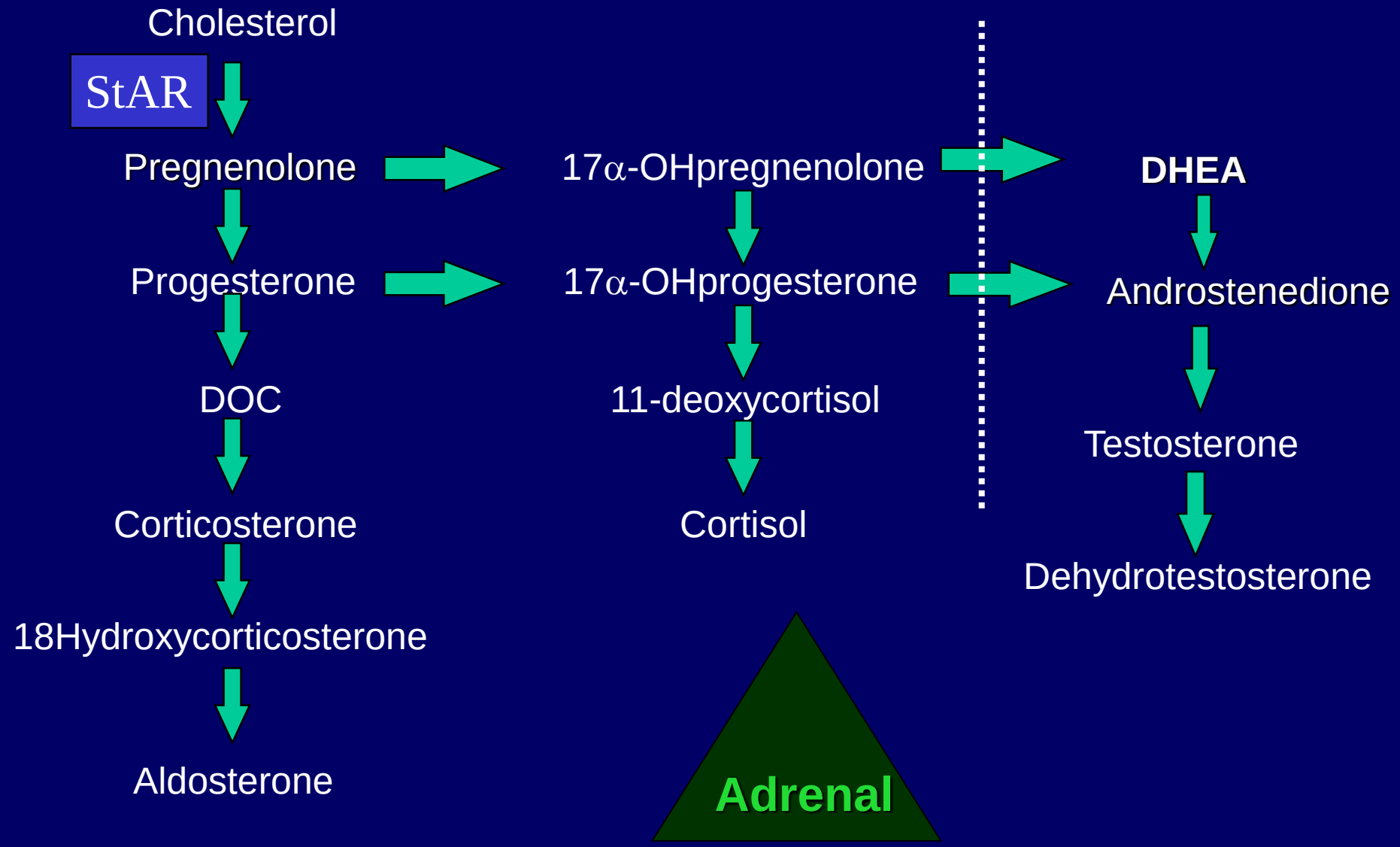
PREMATURE ADRENARCHE most likely

- 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 or minimal 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

Steroid Biosynthesis



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.