PRECOCIOUS PUBERTY

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PRECOCIOUS PUBERTY

WHAT IS PRECOCIOUS PUBERTY?

- Early onset of puberty before 8 years of age in girls
  9 Y in boys
- Difficult to ascertain the early age limit because
  - A -15% of black girls
    - 5% of white girls
    } Breast development at 7 Y of age without associated early menarche
  - B -17.7% of black girls
    -2.8 % of white girls
    } Pubic hair development at 7 Y of age
- Most cases of PP are 2ry to idiopathic premature maturation of the HPO axis with Gn RH release

PRECOCIOUS PUBERTY

WHAT ARE THE ABNORMALITIES IN THE PROCESS OF SEXUAL MATURATION?

1-Precocious puberty

2-Delayed puberty

3-Dissencronous (eg. Physical changes are not followed by menarche after an appropriate interval)

4-Heterosexual changes

5-Timing of progression of pubertal changes

PRECOCIOUS PUBERTY

WHAT ARE THE TYPES OF PRECOCIOUS PUBERTY?

1- Central / true precocious puberty

2-Peripheral /GnRH independent precocious puberty

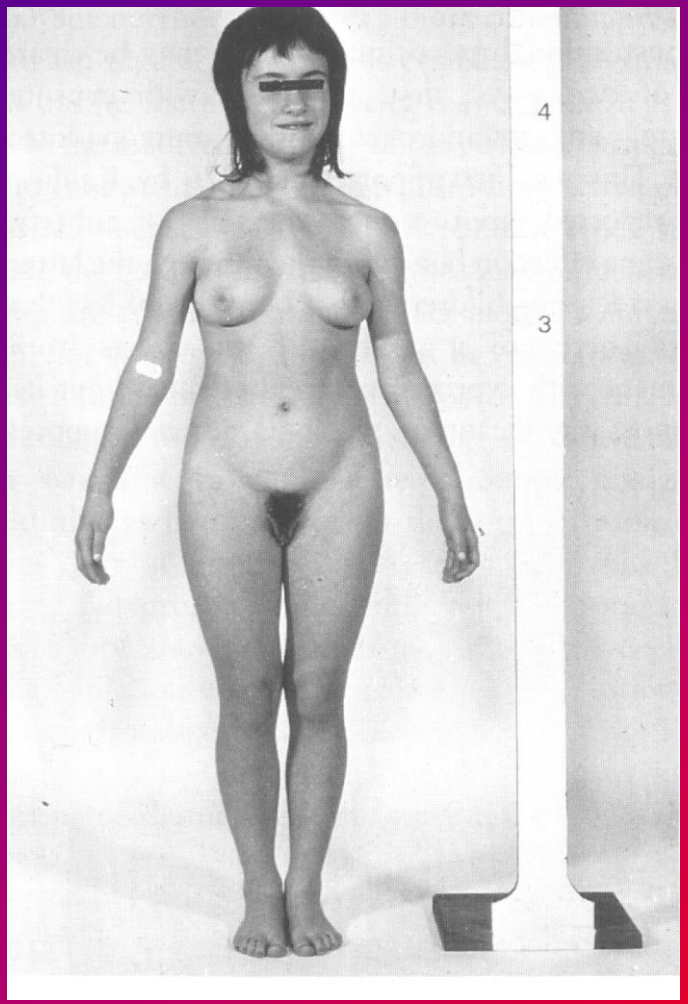
3-Incomplete precocious puberty

CENTRAL PRECOCIOUS PUBERTY

- CPP is physiologically normal pubertal development that occur at an early age
- GnRH dependent

  ↑ GnRH pulses ⇨ ↑ gonadotropins ⇨ ↑↑ ovarian estrogen production & eventual ovulation
- It follows the pattern of pubertal changes that occur in normal puberty
- More common in girls than boys

A 7 Y OLD CHILD WITH CPP



CAUSES OF CPP

1-Idiopathic ----- 80-90%

2-CNS tumors

a-Hypothalamic hamartomas

- A congenital malformation
- The most common type of CNS tumor that cause CPP
- Size & shape do not change significantly over time
- May be associated with seizures (the intrahypothalamic type)
- Rapidly progressing CPP in a child < 2 Y suggest this Dx
- GnRH Rx is satisfactory & safe

b-Optic glyomas

c-Craniopharyngioma

d-Dysgerminoma

e-Epindymoma

f-ganglioneuroma

CAUSES OF CPP

3-CNS dysfunction

a-Space occupying lesion eg. Arachnoid cyst

b-Hydrocephalus

c-Irradiation

d-Trauma

e-Infection

f-Septooptic dysplasia (congenital)

g-Excessive exposure to sex steroids (congenital adrenal hyperplasia)

PERIPHERAL PRECOCIOUS PUBERTY
PPP / Pseudo PP

- GnRH independent
- Due to inappropriate sex hormone secretion or exposure to exogenous sex steroids
- LH & FSH levels are low prepubertal , while estrogen ↑↑
- May present with some or all of the physical changes of puberty

CAUSES

A-Exogenous sex steroids or gonadotropins

B-Abnormal secretion of gonadotropins (rare)
eg. Tumors secreting hCG (teratoma)

CAUSES OF PPP

C-Functioning ovarian tumors UNCOMMON

- Granulosa cell
- Granulosa-thica cell

} 70% present with PP

- Mixed germ cell → usually benign

- Present with rapid progression of breast development , vaginal bleeding & abdominal pain
- Palpable mass & dulling of vaginal mucosa
- Estradiol level excessively elevated
- U/S, CT, MRI, are helpful in confirming the Dx
- Rx ⇨ Excision ⇨ regression of 2ry sexual chct

- Malignant ovarian trs are responsible for 2-3% of all cases of precocious pseudopuberty (PPP) in girls.
- The most common are the granulosa cell tumors

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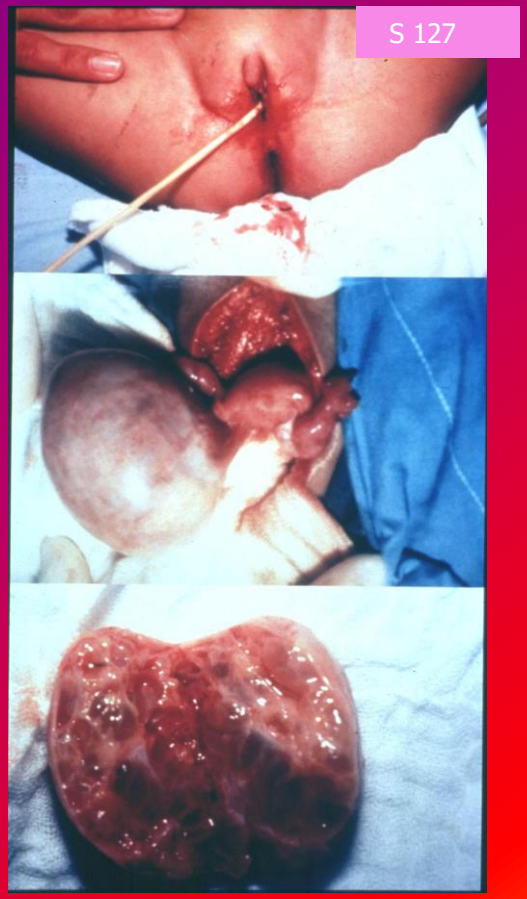

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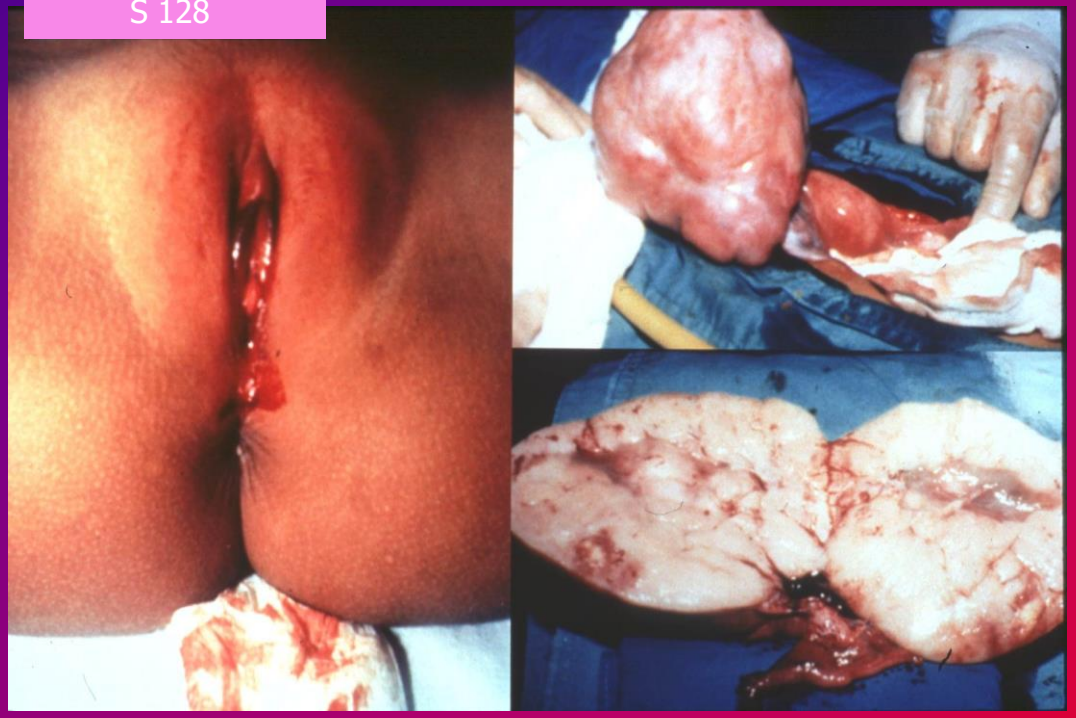

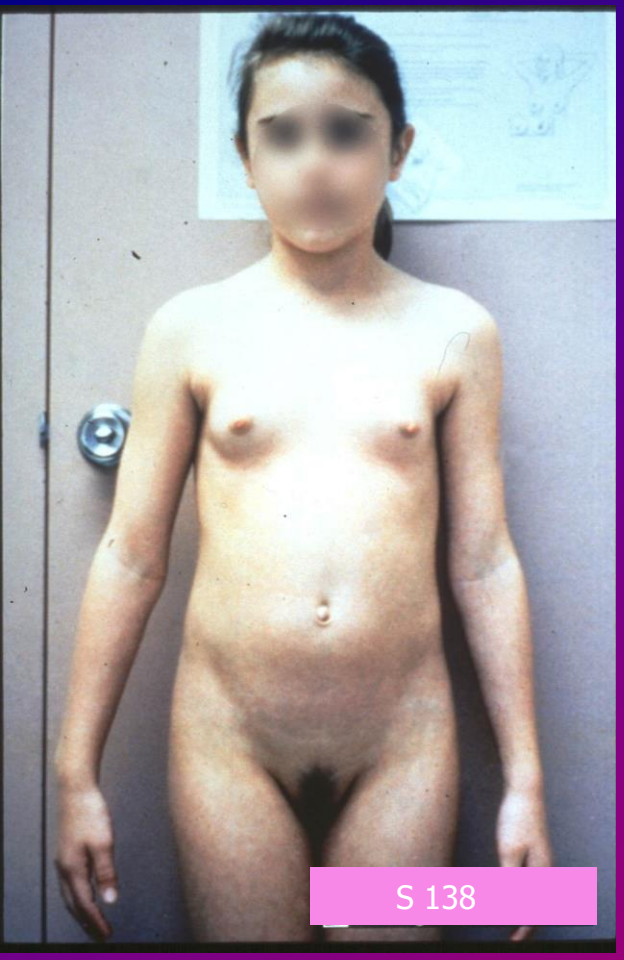

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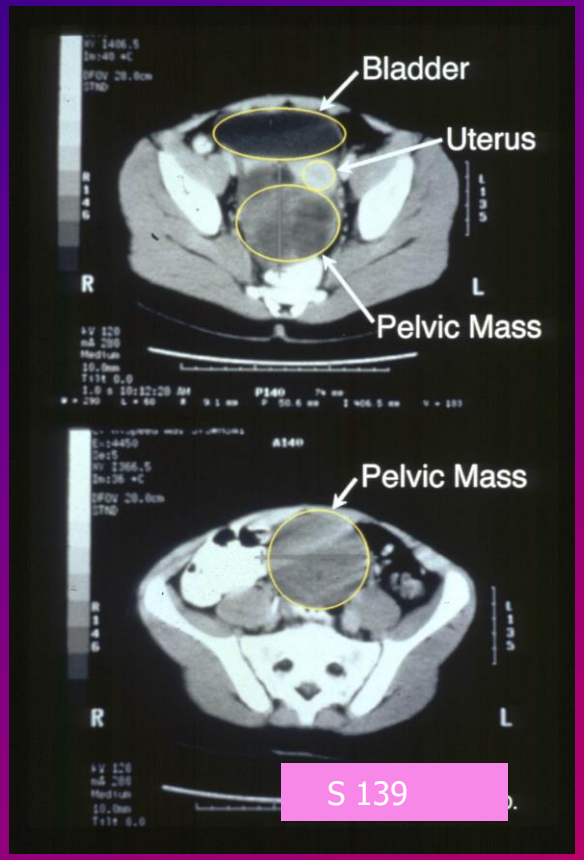

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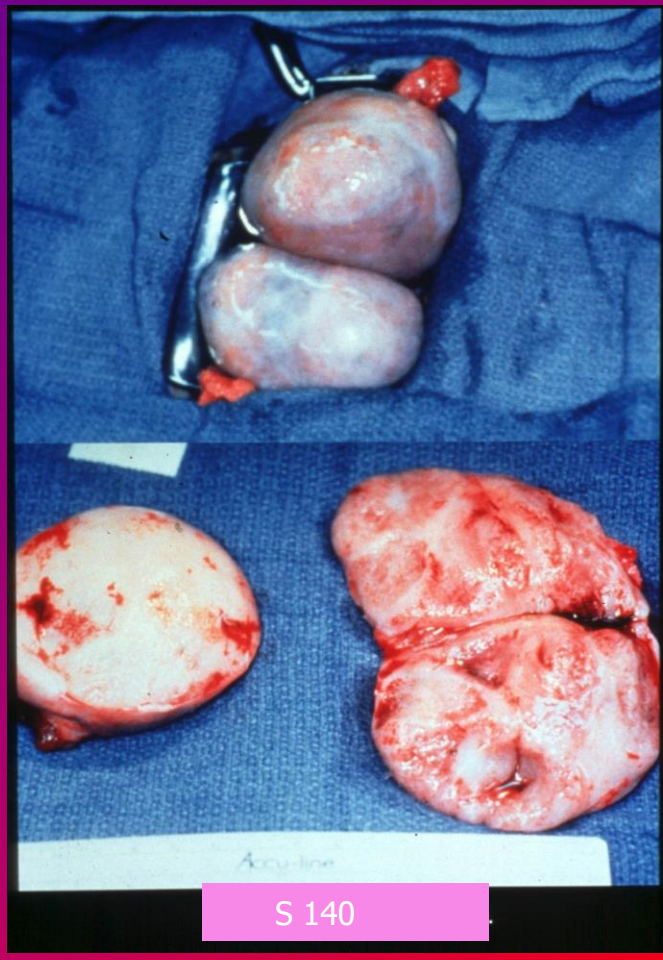

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8 Y old, 3 M Hx of vaginal bleeding , breast &pubic hair Tanner III ,Ht 70th % Wt 95th %, pelvic mass. FSH 4.1 LH 3.2 TSH 2.3 prolactin 21 LDH 192 HCG 103 AFP 5.

Laparotomy BSO ,appendectomy , omentectomy.

Dx Bilateral Dysgerminoma arising in aGonadoblastoma , Karyotype XY

RX 8 coarses of chemotherapy, no recurrence at 20 M

CAUSES OF PPP

CONT'D **C-Functioning ovarian tumors**

- Cystadenoma
- Gonadoblastoma
- Lipoid

} May produce estrogen or androgn or both / Rare

D-Functional ovarian cysts

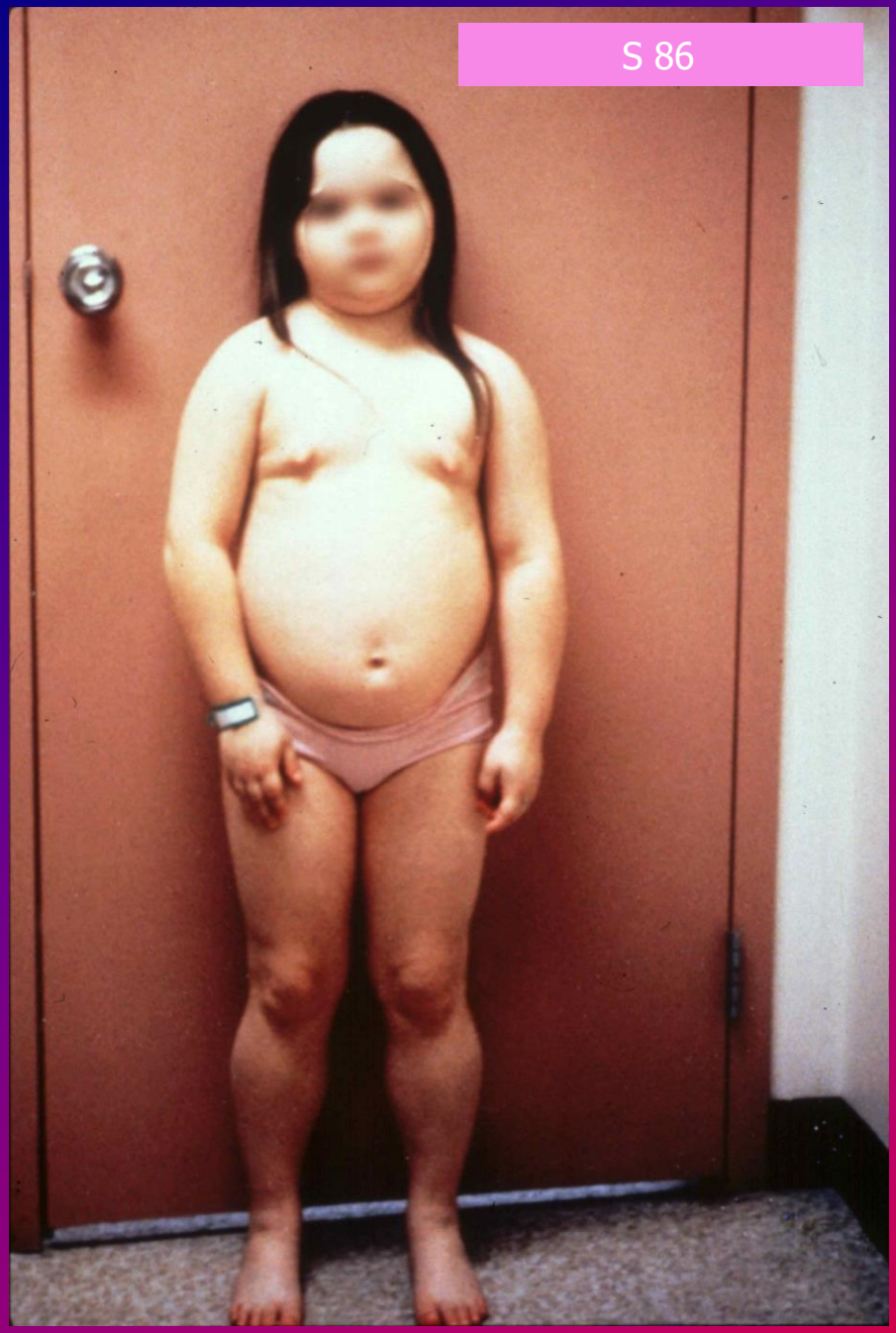
- Secrete estrogen ⇨ breast development
- Rupture or resolution ⇨↓ estrogen ⇨ vaginal bleed
- Surgery should be avoided

E-Adrenal tumors RARE

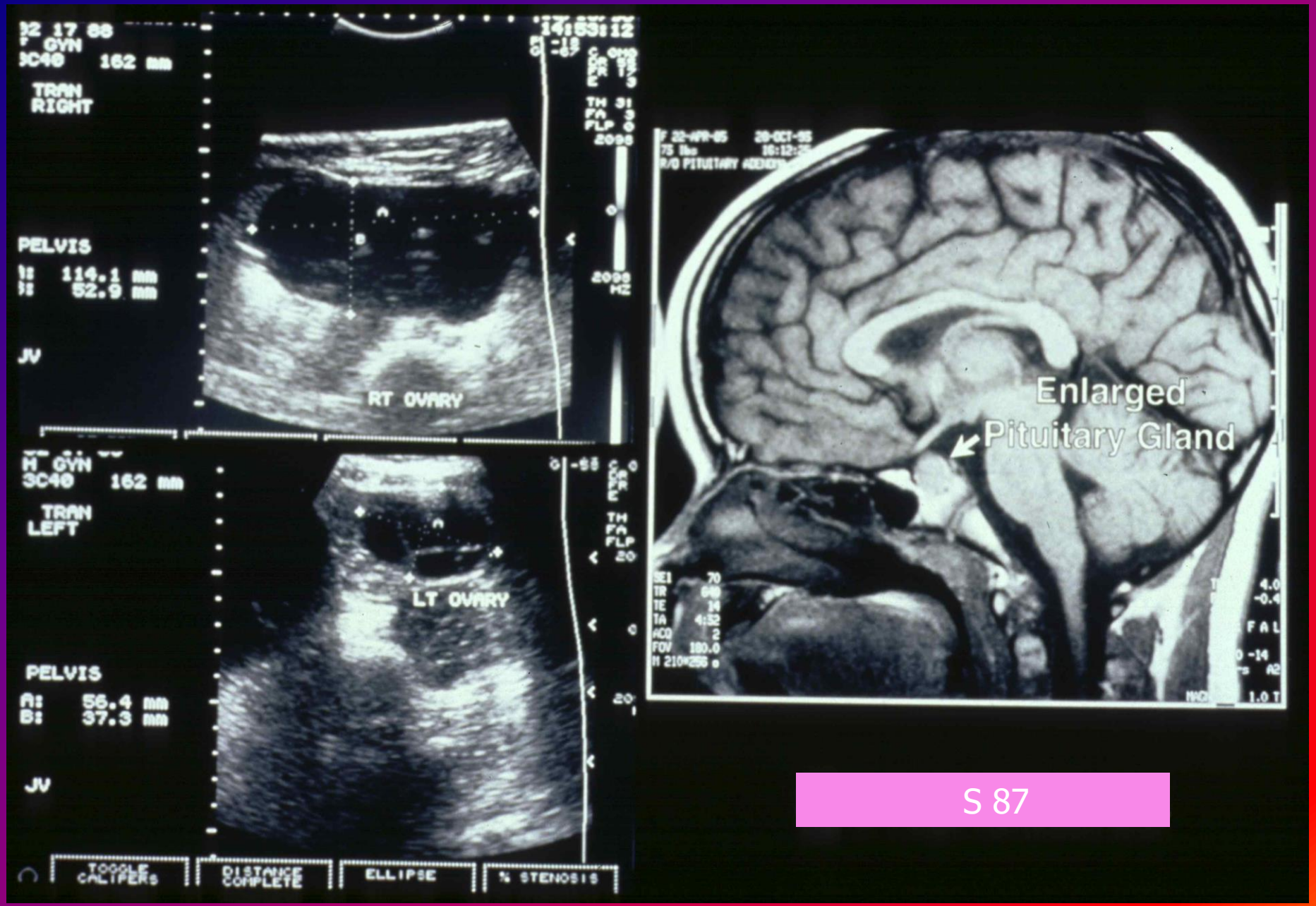
F-Congenital adrenal hyperplasia

G-CHRONIC 1RY HYPOTHYROIDISM

- TSH ⇨ acts on FSH receptors ⇨ PPP
- RX ⇨ thyroxin ⇨ resolution of the PPP



- Ht 20^{tho}%
- Wt 95^{tho}%
- Thyroid slightly prominent
- Breasts Tanner lll
- Pubic hair Tanner ll
- Hymen Well estrogenized
- P/R Pelvic mass 5cm
- FSH 5.4 IU/L
- LH 0.3
- Estradiol 94 pg/ml
- TSH 50 mIU/ml


TRAN
RIGHT
PELVIS
JV
RT OVARY
TRAN
LEFT
PELVIS
JV
LT OVARY
TOGGLE CALIPERS
DISTANCE COMPLETE
ELLIPSE
% STENOSIS
Enlarged
Pituitary Gland

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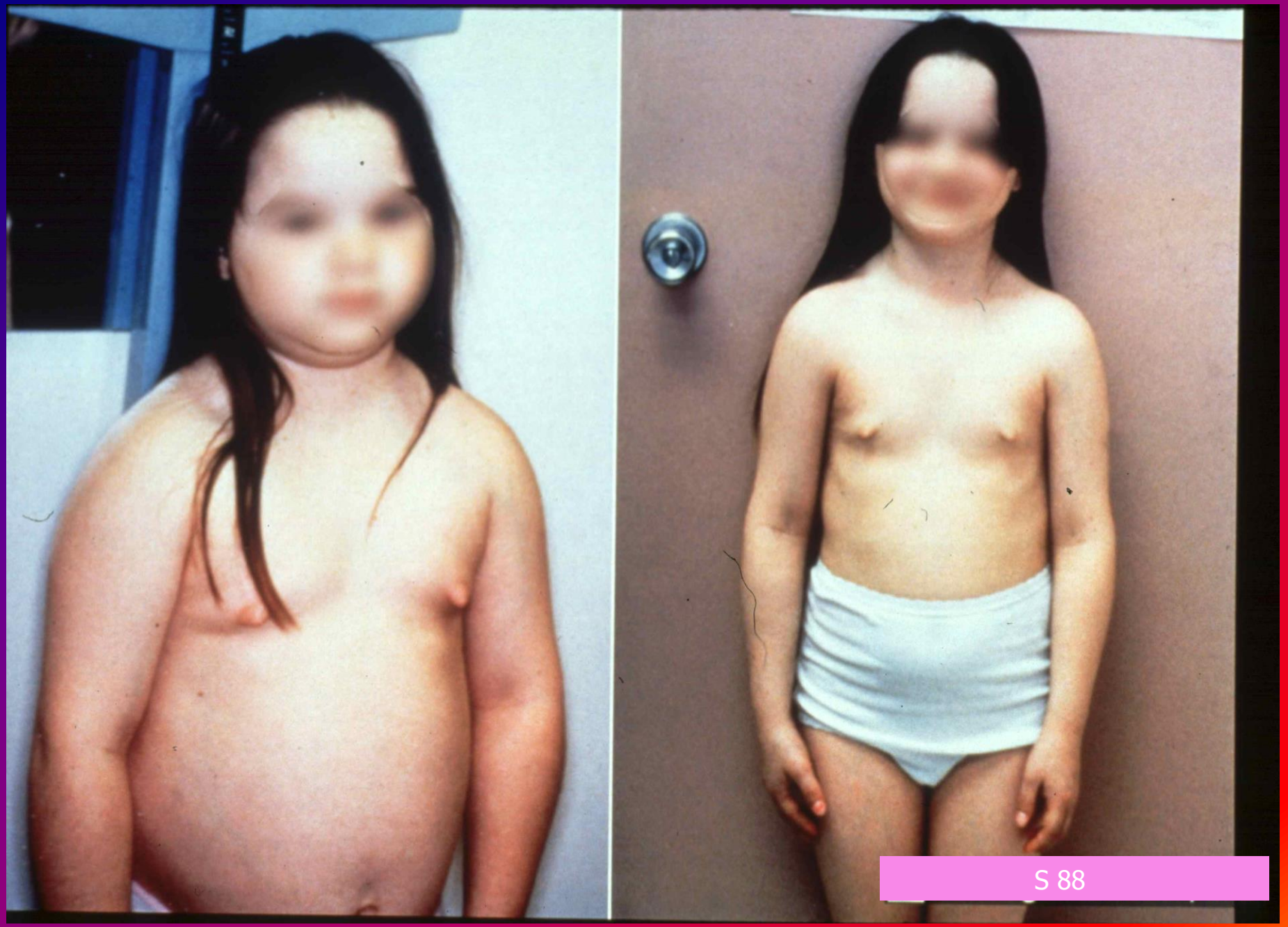
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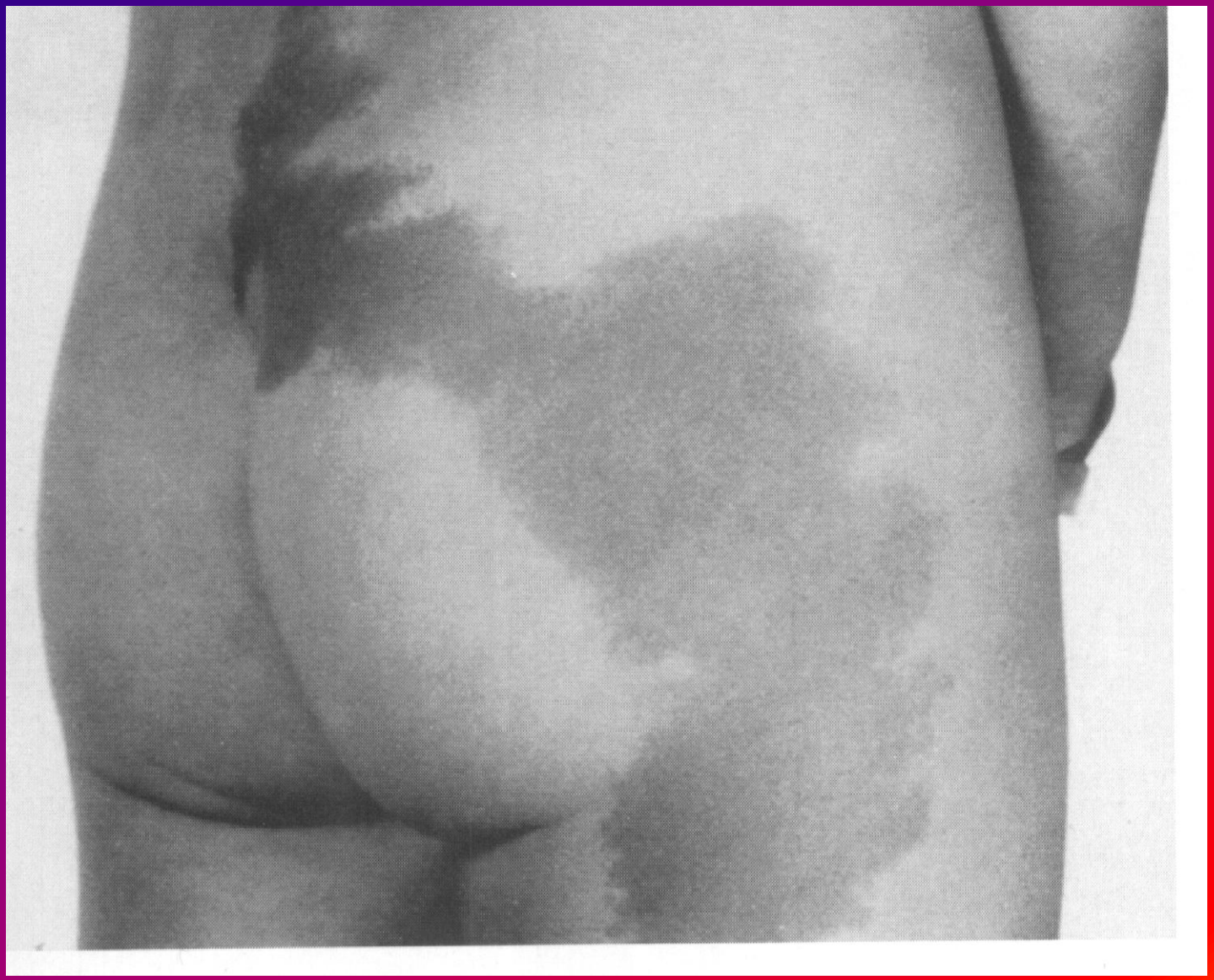
CAUSES OF PPP

H-McCune-Albright syndrome

- Café-au-lait spots
- Polyostotic fibrous dysplasia
- GnRH independent PP
- Endocrine disorder
  (hyper thyroidism, hyperparath, Cushing S)
- Autonomous functioning ovaries with 1 or 2 ovarian cysts ⇨↑ estrdiol

- Rx ⇨ Testalactone ⇨inhibit aromatase activity
  ⇨↓ estrogen synthesis

McCUNE-ALBRIGHT SYNDROME



Rx of PPP

1-TREAT THE CAUSE (IF POSSIBLE)

2-Drugs

- Testolactone ⇨ aromatase inhibitor , inhibit conversion of testosterone to estrogen 35mg/kg/D 3 divided doses

- Ketoconazole ⇨ inhibit steroid biosynthesis 200mg tds

- Cyproterone acetate ⇨ Potent progestin & antiandrogen, inhibit androgens at the receptor level / supress gonadal & adrenal steroidogenesis : antigonadotrophic
  100 mg/m2 2 divided doses

Rx of PPP

- Spironolactone ⇨ inhibit androgens at the receptor level, ↓ ovarian androgen production, antimineralocorticoid 50-100mg bd

- Medroxyprogestrone acetate

Girls with prolonged PPP ⇨ prolonged exposure of the CNS to estrogen ⇨ central precocious puberty CPP

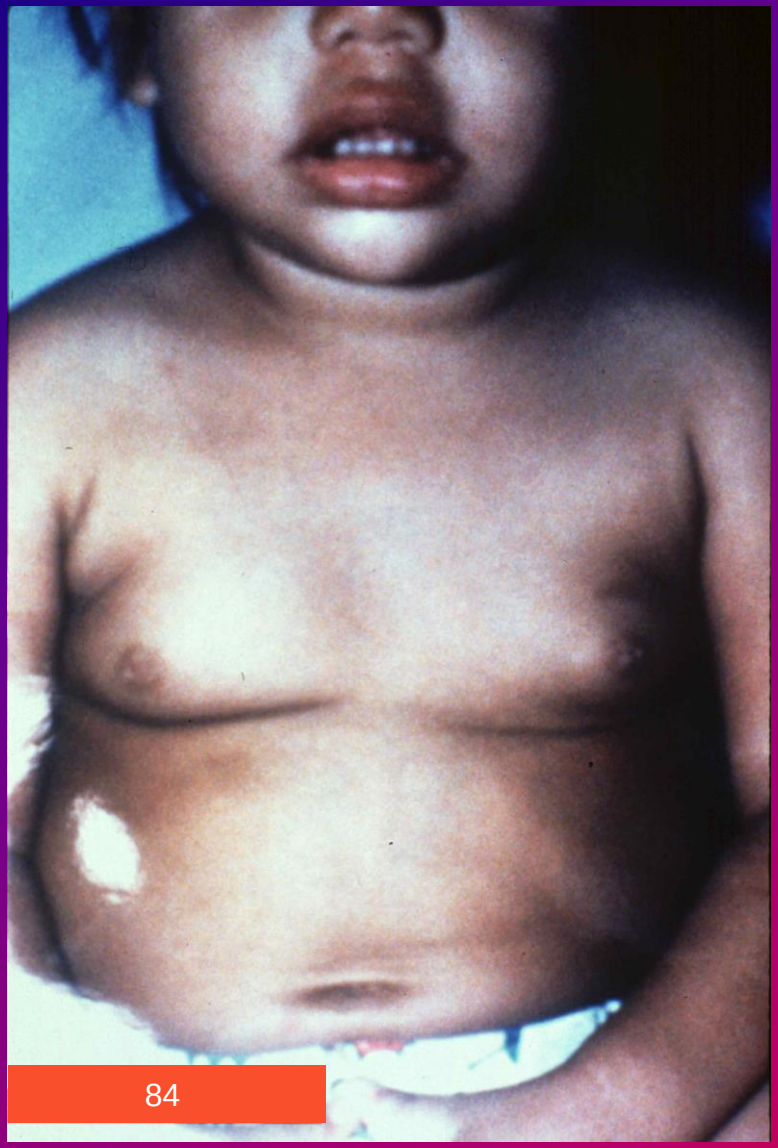
INCOMPLETE PRECOCITY

- Partial (often transient) pubertal development in the absence of other stigmata of puberty
- Slow progression , no change or waning of the physical finding may occur

1-PREMATURE THELARCHE

Premature beast development in the absence of other signs of sexual maturation

- Estradiol level ↑↑
- Unilateral or bilateral , without areolar development
- < 2 Y of age & non progressive
- Follow up should distinguish cases of slow progressing CPP
- No Rx is indicated & subsequent normal puberty occur



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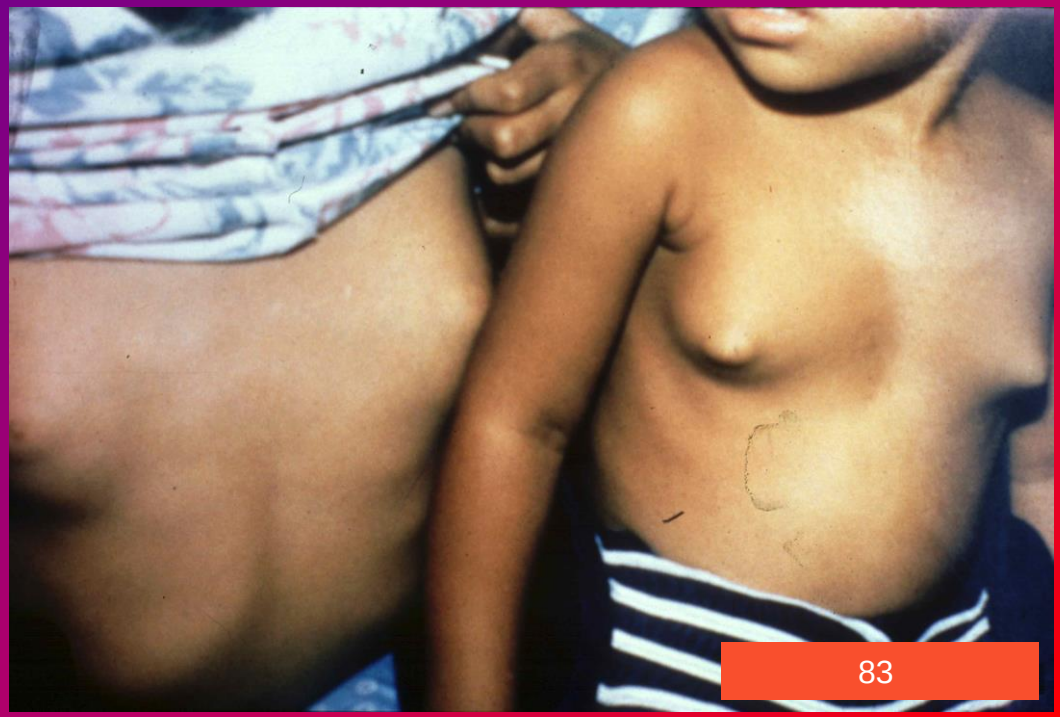

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2-PREMATURE PUBARCHE

- THE APPEARANCE OF PUBIC HAIR BEFORE 8 Y OF AGE IN GIRLS
- Early maturation of the normal pubertal adrenal androgen production "Adrenarche"
- It is evidence of premature adrenarche without activation of the HPO axis
- Beast development is absent
- Slightly accelerated growth velocity & advanced skeletal maturation
- Puberty occur normally at the appropriate age
- Dx by exclusion of CAH, androgen secreting tumors & CPP

2-PREMATURE PUBARCHE

- 50% of pt. with premature pubarche progress to PCO

- Hyperandrogenism & insulin resistance are chct of PCO

- Late onset CAH may have a similar presentation

Dx ---ACTH stimulation test ⇨

Marked ↑ of 17-OH progestrone

--- ↑ plasma level of 17-OH progestrone, AND, DHEA

Rx ---- glucocorticoids

- CPP can occur 2ry to late Dx or inadequate Rx of CAH

3-ANDROGEN SECRETING TUMORS

ADRENAL TUMORS

- RARE
- Function autonomously
- ↑ DHEA , DHEAS, testosterone
- ↑ Cortisol
- Could benign or malignant with poor prognosis

OVARIAN TUMORS

- Arrhenoblastoma, lipoid cell tumors
- ↑ Testosterone , AND
- DHEA, DHEAS → NORMAL

4-PREMATURE MENARCHE

- Uncommon
- We should role out serious cause of bleeding

1-Neonatal period

- Due to withdrawal of estrogen produced by the fetoplacental unit

2-Spontaneous regression of ovarian cysts

3-Hypothyroidism

4-McCune Albright Syndrome

D. Dx

- Vulvovaginitis
- Foreign body in the vagina
- Trauma
- Sexual abuse
- Vaginal tumors

EVALUATION OF PATIENTS WITH SEXUAL PRECOCITY

WE HAVE TO DIFFERENTIATE BETWEEN CPP & PPP

1-HISTORY

- Onset & progression of symptom
  (N tempo ⇨CPP, Abrupt & rapid ⇨estrogen sec Tr)
- Hx of CNS trauma or infection
- Symptoms associated with neurological dysfunction
- Symptoms associated with endocrine dysfunction
- Exposure to exogenous steroids
- Hx of abdominal pain or swelling
- Family Hx ⇨ early puberty, short stature

2-PHYSICAL EXAMINATION

- Tall stature for age / changes in HT velocity
- 2ry sexual chct (Tanner staging) ⇨ synchronous ⇨ CPP
- Neurological examination
- Fundoscopy & gross visual field evaluation
- Virilization
- Evidence of hypothyroidism or hyperadrenalism
- Examin the skin for acne, odor, café-au-lait spots, hirsutism
- Abdomen ⇨ masses
- PR

INVESTIGATIONS

1-LAB STUDIES

- ↑DHEA, DHEAS ⇨ adrenarche
  ⇨ adrenal origion of PPP
- TSH, T4, hCG
- LH, FSH, Estradiol

↓LH ⇨ LH/FSH ratio < 1 ⇨ Prepubertal gonadotropin secretion

↑ LH ⇨ LH/FSH ratio > 1 ⇨ Pubertal gonadotropin response CPP

INVESTIGATIONS

GnRH stimulation test

- 100 ugm of GnRH IV
- Check FSH & LH baseline, 20,40,60 min
- Prepubertal

⇨ FSH > LH

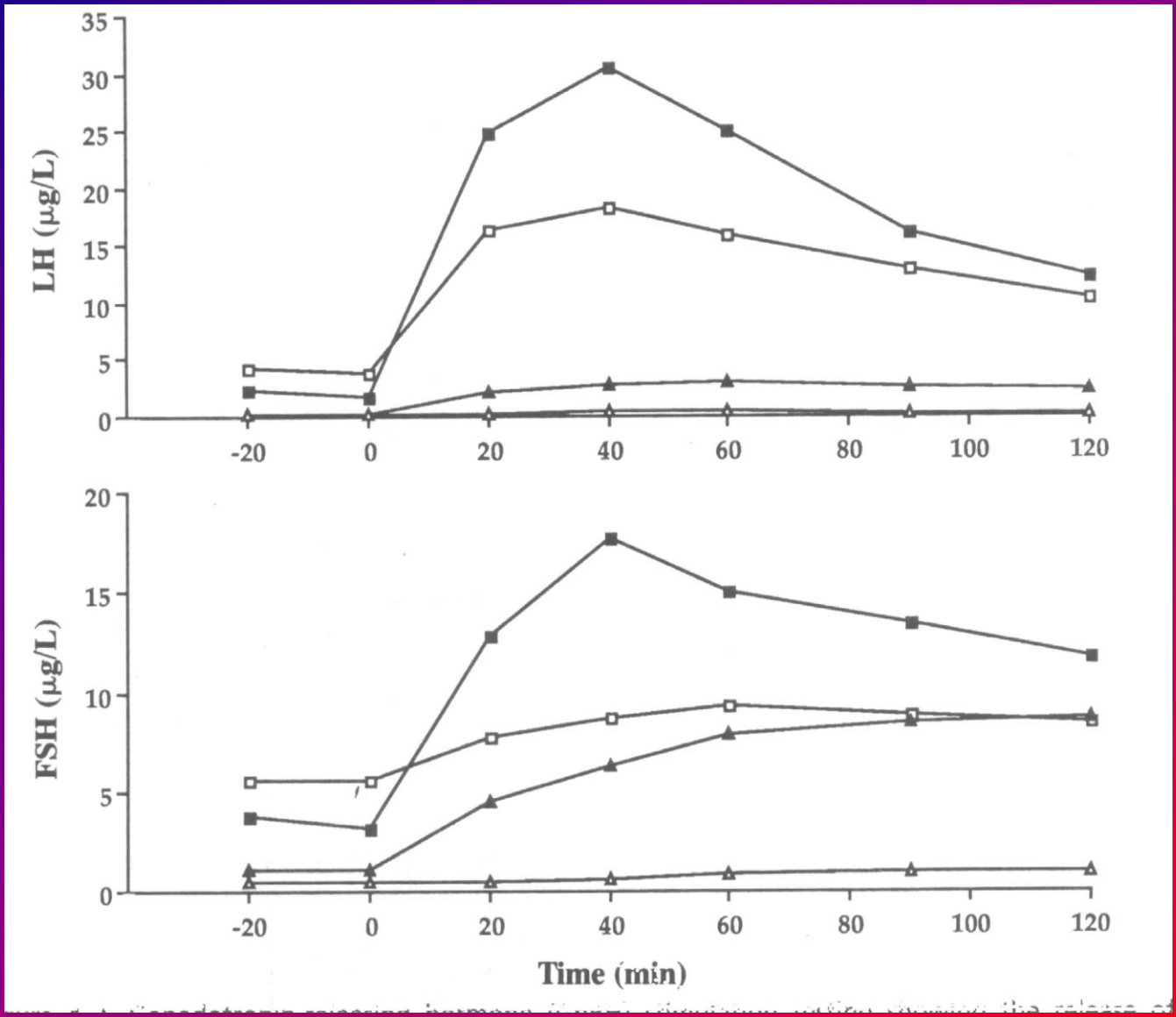
⇨LH rise is minimal < 10 IU/ml

Pubertal

⇨ ↑ LH > FSH

⇨LH peak above upper limit for prepubertal

GnRH STIMULATION TEST



- ■ 6 Y old with CPP
- □14Y old with normal puberty
- ▲ 16Y old with H-P destruction 2ry to cranio-pharyngioma
- △5Y old prepubertal

INVESTIGATIONS

2-Bone age radiography

- Advanced in both CPP & PPP
- Premature adrenarche ⇨ slightly ↑
- Premature thelarche ⇨ Normal

3- CT / MRI OF THE HYPOTHALAMIC PITUITARY REGION

- Important in all Pt. with suspected CPP or Pt. with neurological symptoms & signs

INVESTIGATIONS

4-U/S

- Adrenal
- Ovaries ⇨ role out ovarian cysts or tumors & to assess size
- Uterus ⇨ to assess size

5-Vaginal smear for pyknotic index

- A simple method of assessing the level of estrogen stimulation
- Result is expressed in the form of % of basal , parabasal & superficial cells
- The greater the % of superficial cells the greater the estrogen effect

TREATMENT OF CPP

Purpose of treatment

- To gain normal adult height

(Pt with CPP will have an ultimately shortened adult height)

- Amelioration of the psychosocial consequences of ↑ size ⇨ unrealistic adult expectations

Who should be treated?

- Pt. with early puberty (<6Y) , accelrated growth & advanced skeletal age should be treated, (bone age >2Y>chronologic age. Menarche <8Y
- Pt. with early onset but without indication that puberty is advancing should be followed up

TREATMENT OF CPP

1-THE TREATMENT OF CHOICE IS A GnRH ANALOGUE

- GnRH agonists (zoladex) ⇨ bind to GnRH receptors (competitive inhibition) ⇨ down regulation of receptor function ⇨ ↓ gonadotropin secretion ⇨ inhibition of the HPO axis ⇨ ↓ estrogen secretion ⇨ regression of the manifestation of puberty
- The goal of therapy is complete suppression of gonadotropin secretion ⇨ prepubertal GnRH stimulation test result
- Adult Ht of Rx pt. > utreated
- Adult Ht is related to skeletal age at the onset of Rx
- Adult Ht of Rx pt. is still < target Ht / predicted Ht

TREATMENT OF CPP

- Rx is continued until the progress of puberty is age appropriate
- Best statural outcome ⇨ pt. treated until bone age 12 -12.5 years
- Growth hormone may be added to Rx
- After discontinuation of Rx resumption of puberty occurs & precedes at a normal pace
- Side effects: local injection reaction & sterile abscess

2-Medroxyprogestrone acetate

- Used in the past
- Supress the progression of puberty & menses
- NO effect on skeletal maturation & adult height

PSYCHOSOCIAL CONSEQUENCES OF PRECOCITY

1-Children with PP are taller & appear older than their peers ⇨ unrealistic expectation from parents , teachers & others ⇨ child will be under stress

2-They perceive them selves as different ⇨ however this does not have any long term effect & they do well psychologically

3-Sexual maturity at an immature age make them vulnerable to be victims of sexual abuse