بسم الله الرحمن الرحيم

Amenorrhoea

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HPO AXIS

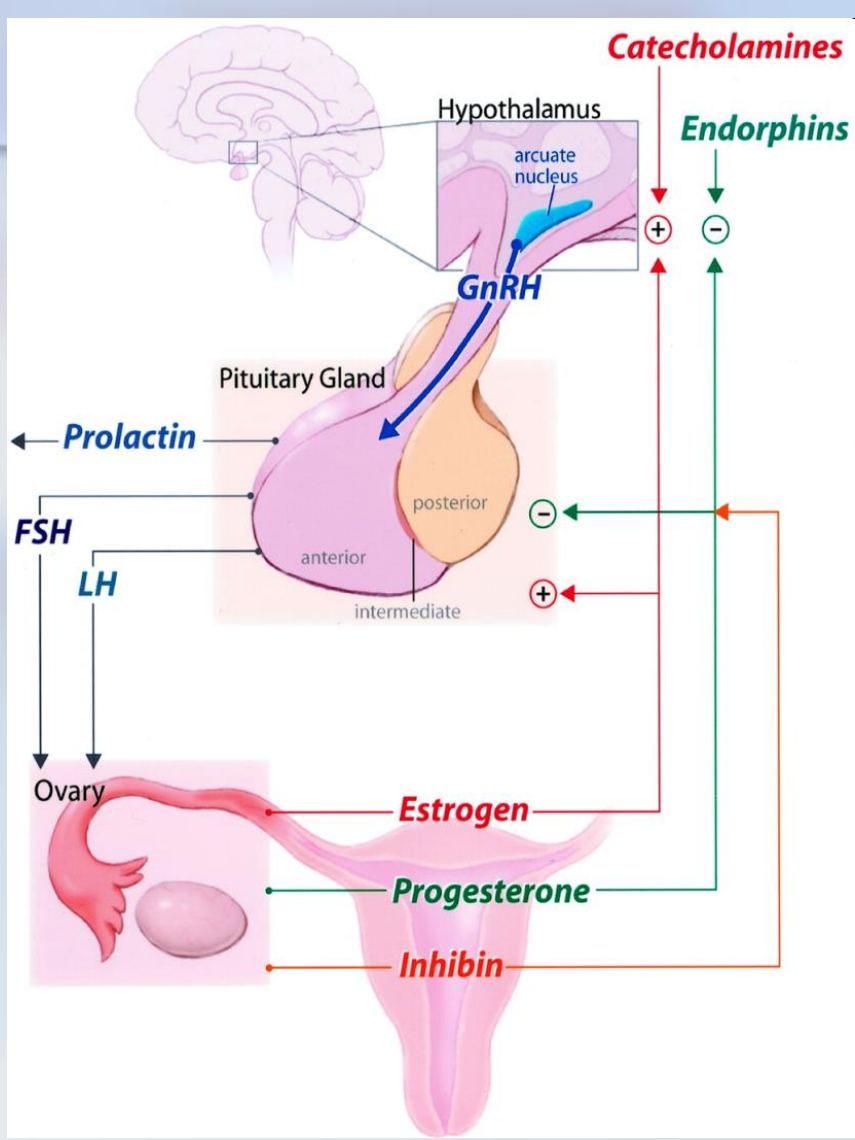
The menstrual cycle is actually 3 different inter-related cycles synchronously taking place at the same time.

These are:

(1) the ovarian cycle

(2) the hormonal cycle

(3) the endometrial cycle.



Amenorrhea

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Amenorrhea

- Amenorrhea can be physiologic, when it occurs during pregnancy and the postpartum period (particularly when nursing).
- or pathologic, when it is produced by a variety of endocrinologic and anatomic disorders.
- In the latter circumstance, the failure to menstruate is a symptom of these various pathologic conditions.
- Thus, amenorrhea itself is not a pathologic entity and should not be used as a final diagnosis.

Evaluate for potential underlying cause of amenorrhea

- Sexual history may indicate possible pregnancy
- Family history of delayed menarche suggests constitutional delay of puberty
- Vasomotor symptoms (eg, night sweats, hot flashes) may indicate primary ovarian insufficiency or natural menopause
- Previous chemotherapy or radiation therapy may suggest impairment of specific organ (eg, brain, pituitary gland, ovaries)
- Severe and/or persistent headaches, intractable vomiting, or changes in thirst, urination, or vision may indicate a central nervous system tumor or empty sella syndrome
- Galactorrhea may indicate a pituitary tumor

Evaluate for potential underlying cause of amenorrhea

- Cyclic abdominal pain may indicate imperforate hymen or transverse vaginal septum
- Prior or current use of illegal or prescription drugs (eg, opiates, antipsychotics, antidepressants, antihypertensives, antihistamines) may alter prolactin levels
- Acne, increased facial hair, and male pattern hair loss may indicate hyperandrogenism, polycystic ovary syndrome, ovarian or adrenal tumor, congenital adrenal hyperplasia, or Cushing syndrome
- Temperature intolerance, palpitations, diarrhea, constipation, or tremor may suggest thyroid disease
- History of dieting, weight loss, malnutrition, eating disorders, excessive exercise, or psychosocial stress may suggest functional hypothalamic amenorrhea

Physical examination

- Measure height, weight, and BMI
  - Turner syndrome
  - Elevated BMI may be associated with polycystic ovary syndrome [1]
  - Low BMI may be associated with functional hypothalamic amenorrhea [4]
- Evaluate for clinical signs associated with specific underlying causes
  - Goiter or thyroid nodule indicate thyroid disorder
  - Dysmorphic features such as webbed neck, low hairline, and short stature indicate Turner syndrome
  - Cushing syndrome
  - Hirsutism (particularly facial hair), acne, or male pattern baldness may indicate hyperandrogenism, caused by polycystic ovary syndrome (most commonly), ovarian or adrenal tumor, congenital adrenal hyperplasia, or Cushing syndrome

Inspect external genitalia and perform pelvic and speculum examination (if no vaginal obstruction)

- Clitoromegaly suggests an androgen-secreting tumor or congenital adrenal hyperplasia
- Bulging, bluish mass at entrance to vagina suggests imperforate hymen
- Short, blind vaginal pouch suggests a transverse vaginal septum, müllerian agenesis, or androgen insensitivity syndrome
- Thin or red vaginal mucosa may indicate low estrogen levels
- Absent or abnormal cervix or uterus suggests müllerian agenesis or androgen insensitivity syndrome
- Cervical scarring may suggest intrauterine synechiae caused by an operation on the uterus (Asherman syndrome)

Primary Amenorrhea

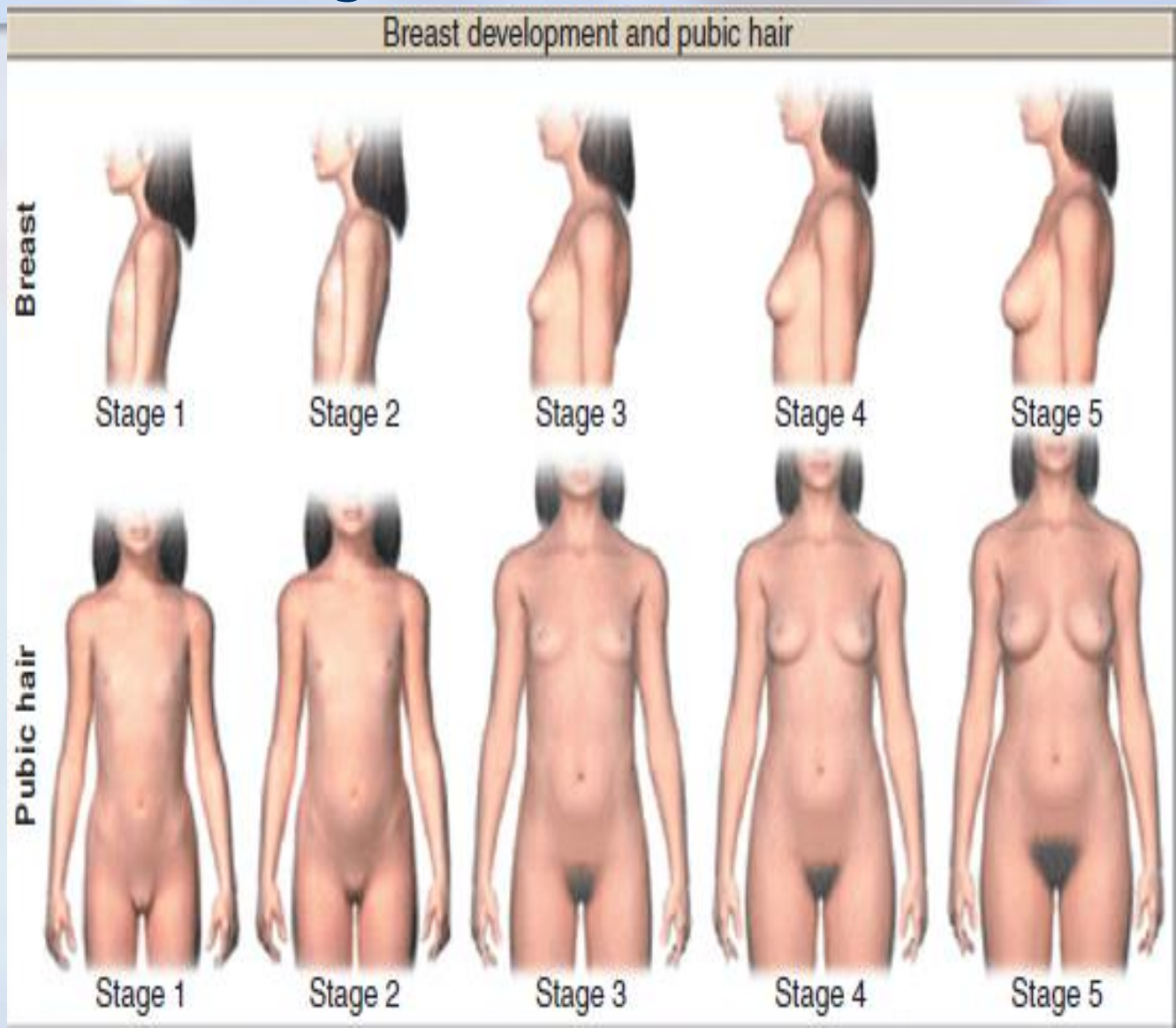
- The most common cause of primary amenorrhea is primary ovarian failure resulting from gonadal dysgenesis, most commonly as a result of Turner syndrome accounting for almost 50% of patients with this syndrome.
- The second most common cause of primary amenorrhea is congenital absence of the uterus and vagina, 15%.
- Third most common: idiopathic hypogonadotropic hypogonadism.
- In western world the most important and probably most common cause of amenorrhea (both types) in general in adolescent girls is anorexia nervosa.

Events of Puberty

- Thelarche (breast development)
  - Requires estrogen
- Pubarche/adrenarche (pubic hair development)
  - Requires androgens
- Menarche
  - Requires:
    - GnRH from the hypothalamus
    - FSH and LH from the pituitary
    - Oestrogen and progesterone from the ovaries
    - Normal outflow tract

Pubertal rating according to Tanner stage. Breast development in girls

- Is rated from 1 (prepubertal) to 5 (adult).
- Stage 2 breast development (appearance of the breast bud) marks the onset of gonadarche.
- For girls, pubic hair Stage 2 marks the onset of adrenarche.



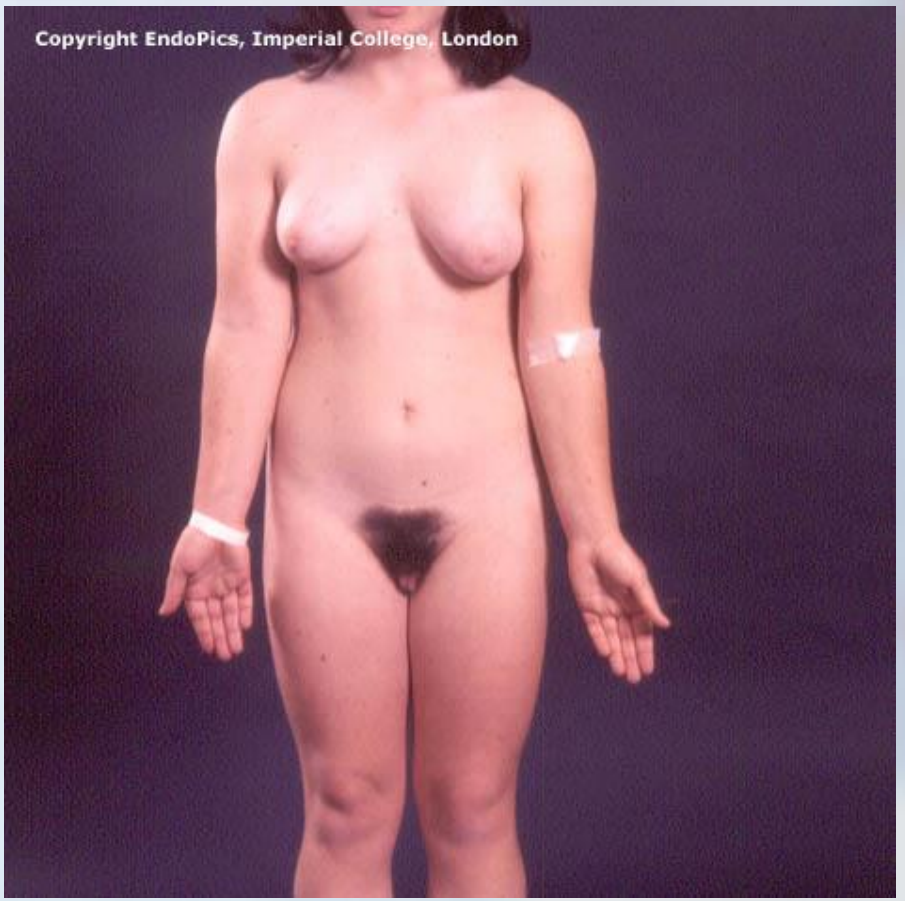
Tanner staging

Classification	Description
Breast Growth	
B1	Prepubertal: elevation of papilla only
B2	Breast budding
B3	Enlargement of breasts with glandular tissue, without separation of breast contours
B4	Secondary mound formed by areola
B5	Single contour of breast and areola
Pubic Hair Growth	
PH1	Prepubertal—no pubic hair
PH2	Labial hair present
PH3	Labial hair spreads over mons pubis
PH4	Slight lateral spread
PH5	Further lateral spread to form inverse triangle and reach medial thighs

Mean Ages of Girls at the Onset of Pubertal Events (United States)

Event	Mean Age ± SD (yr)
Initiation of breast development (B2)	10.8 ± 1.10
Appearance of pubic hair (PH2)	11.0 ± 1.21
Menarche	12.9 ± 1.20

Are there secondary sexual characteristics?



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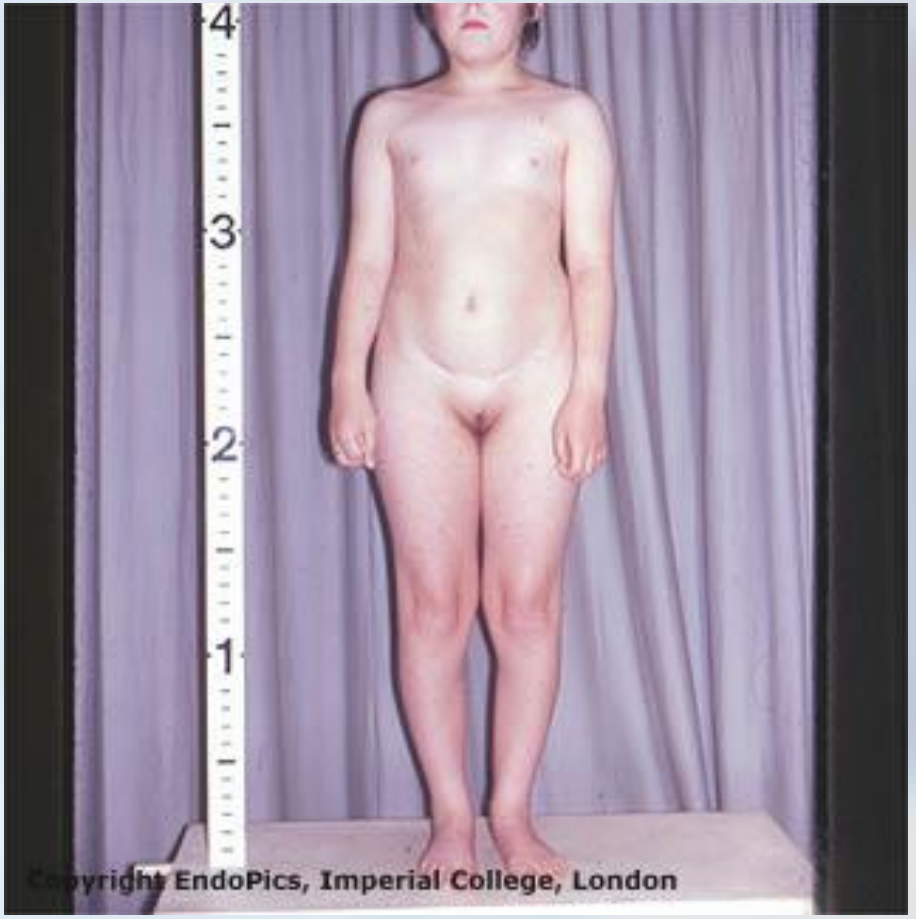


PRIMARY AMENORRHOEA

Quick Rules to Remember

No breast – no or low oestrogen

< FSH, LH – hypothalamic or pituitary

> FSH, LH – ovarian

No uterus – check T and karyotype

46XX –Mullerian agenesis

46XY – Pseudohermaphroditism

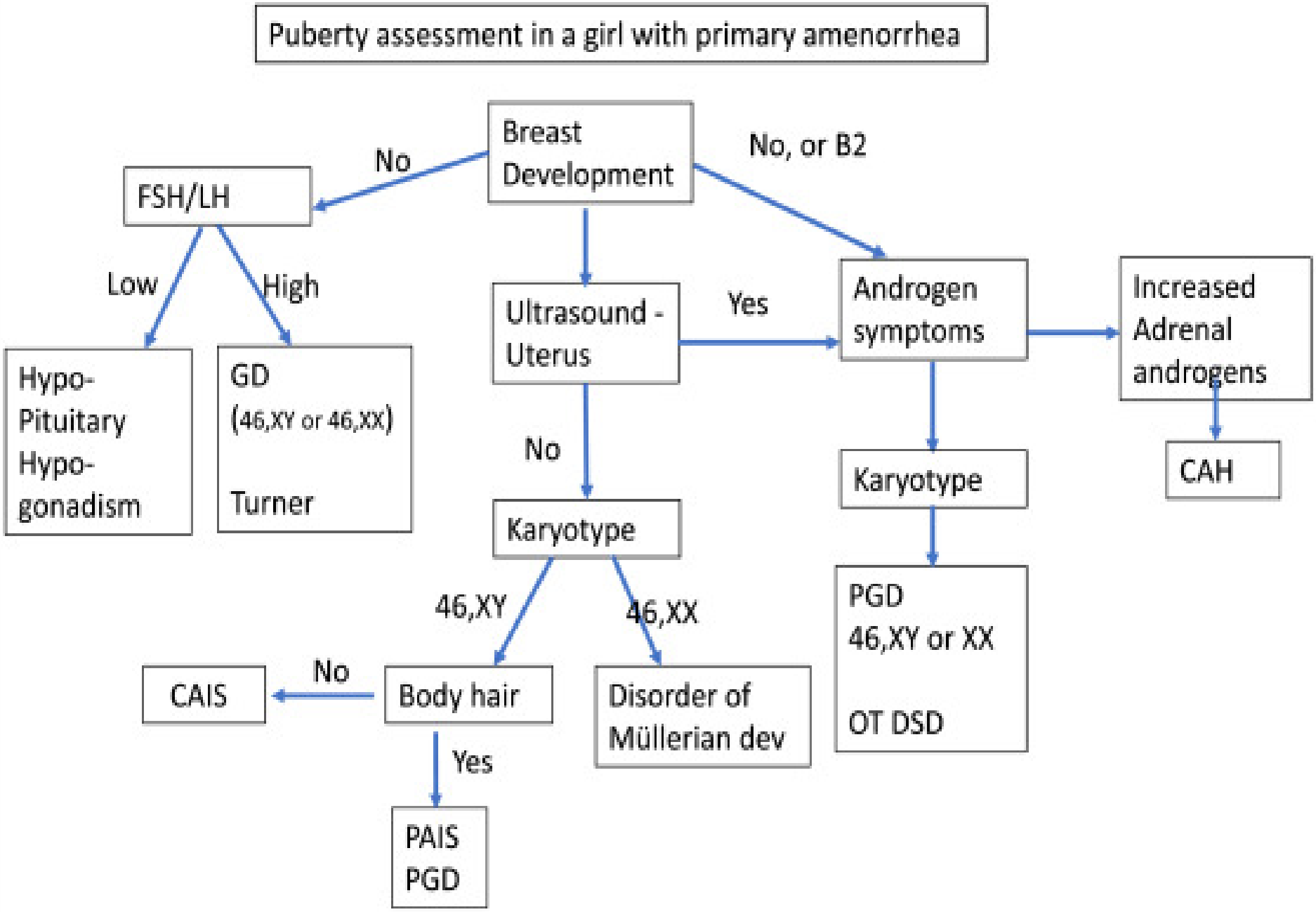
Diagnostic Evaluation by Compartments

I Outflow Tract (uterus – vagina)

II Ovary

III Anterior Pituitary

IV CNS – Hypothalamus (environment and psyche)


Puberty assessment in a girl with primary amenorrhea
Breast Development
No
No, or B2
FSH/LH
Low
High
Hypo-Pituitary Hypo-gonadism
GD (46,XY or 46,XX)
Turner
Ultrasound - Uterus
Yes
Androgen symptoms
Increased Adrenal androgens
CAH
No
Karyotype
Karyotype
46,XY
46,XX
PGD 46,XY or XX
OT DSD
CAIS
No
Body hair
Disorder of Müllerian dev
Yes
PAIS PGD

Evaluation Categories

- Breast Absent – Uterus Present -most common
- Breast Present – Uterus Present
- Breast Present – Uterus Absent
- Breast Absent – Uterus Absent

Amenorrhea classification by category

Primary Amenorrhoea	Without breast	With breast
Without uterus	Category 3	Category2
With uterus	Category 1	Category 4

PRIMARY AMENORRHEA

Category 1: Breasts Absent and Uterus Present

– Think low oestrogen, check FSH

A. Gonadal failure:

High FSH (hypergonadotropic)

1. 45X (Turner's Syndrome)
2. 46X; abnormal X (Deletion Disorders)
3. Mosaicism (X/XX, X/XX/XXX)
4. Pure XX (PGD, 46XX or Perrault syndrome)
5. 17 alpha-hydroxylase deficiency (46XX)

PRIMARY AMENORRHEA

Category 1: Breasts Absent and Uterus Present

B. Hypothalamic failure secondary to inadequate GnRH release

1. Insufficient GnRH secretion because of neurotransmitter defect
2. Inadequate GnRH synthesis (Kallman's syndrome)
3. Congenital anatomic defect in central nervous system
4. CNS neoplasm (craniopharyngioma)

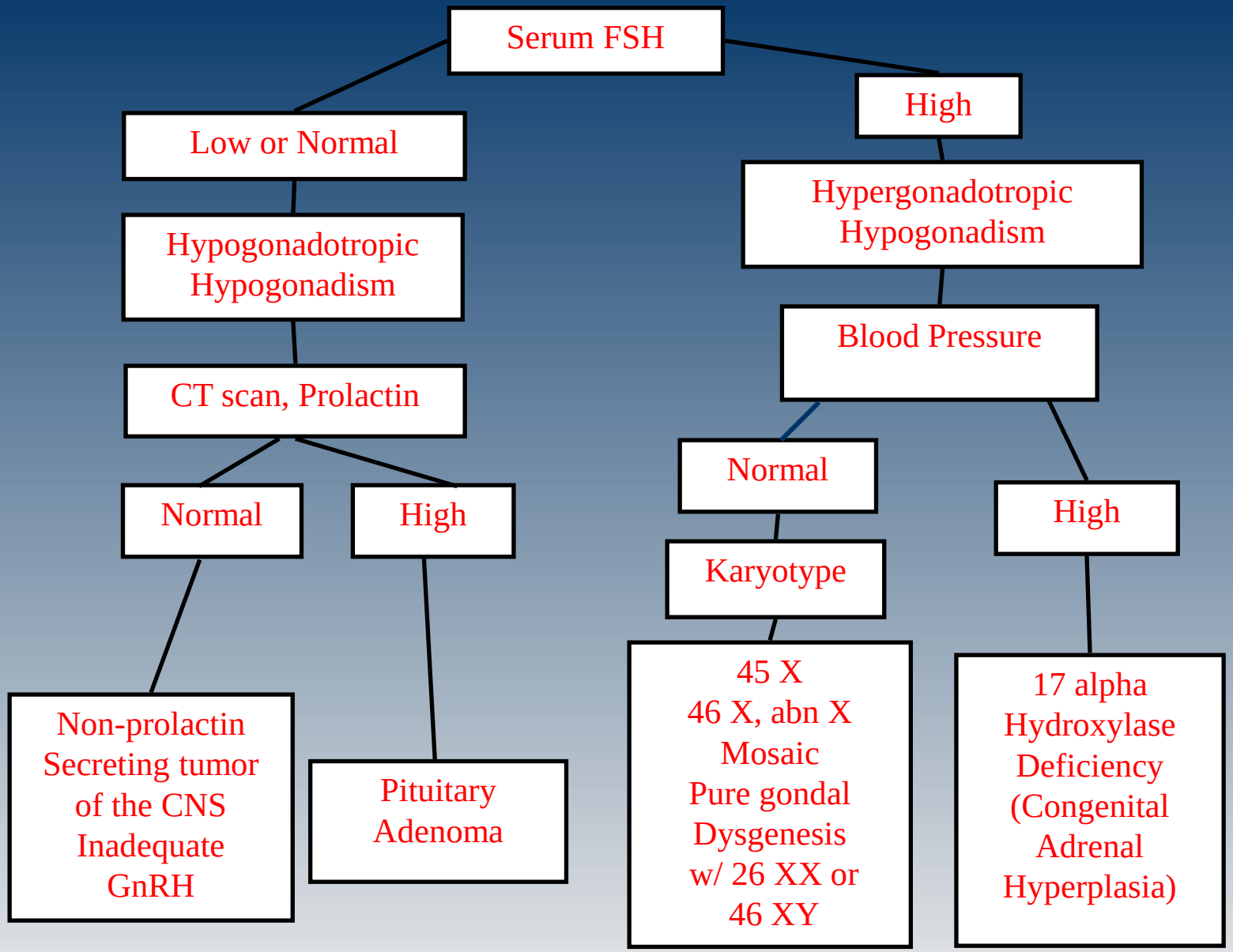
PRIMARY AMENORRHEA

Category 1: Breasts Absent and Uterus Present

C. Pituitary failure

1. Isolated gonadotrophin insufficiency (thalassemia major, retinitis pigmentosa)
2. Pituitary neoplasia (chromophobe adenoma)
3. Mumps, encephalitis
4. Newborn kernicterus
5. Prepubertal hypothyroidism

Category 1: Breasts Absent and Uterus Present



PRIMARY AMENORRHOEA

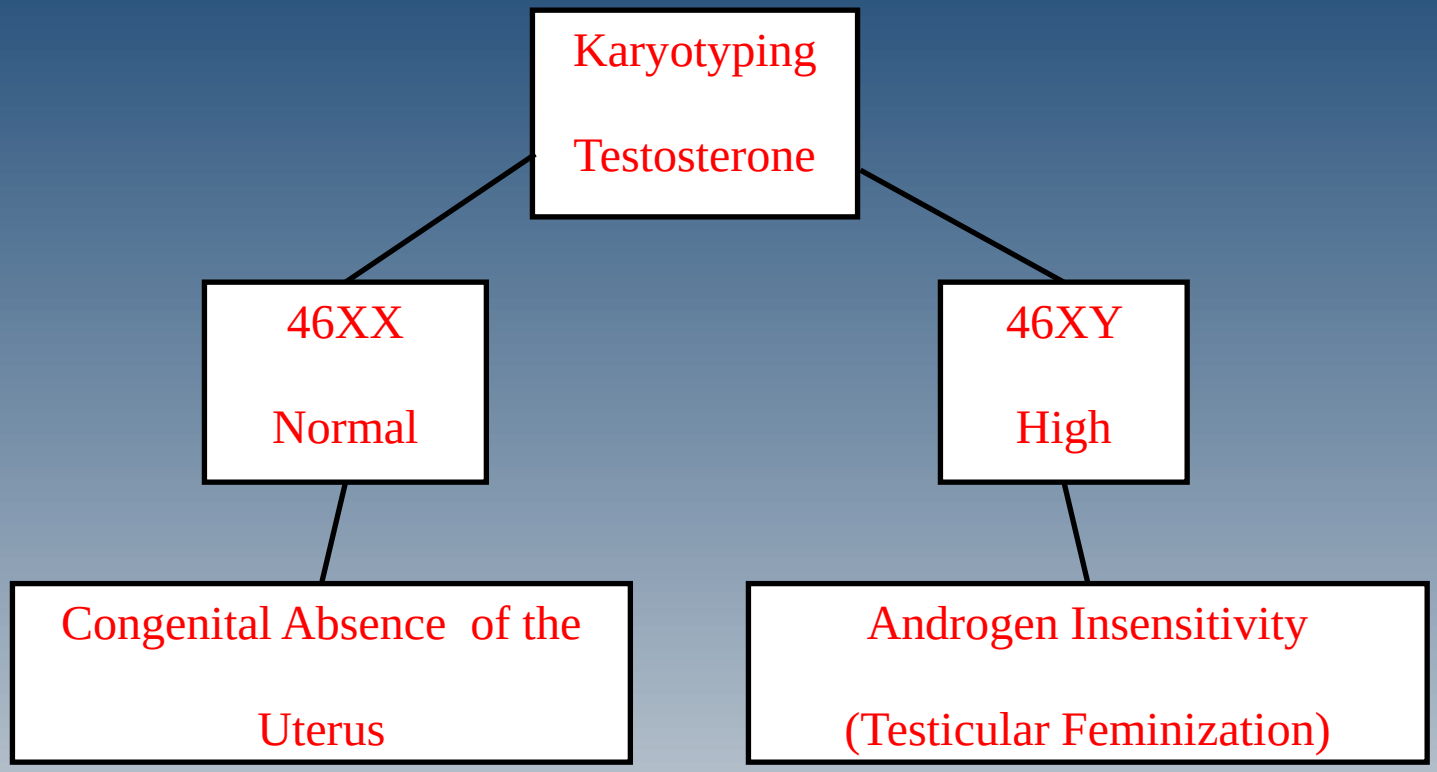
Category 2: Breasts Present and Uterus Absent

– Think (+) oestrogen, (?) MIF: check karyotype

A. Mayer Rokitansky Kuster Hauser Syndrome (46XX) vaginal agenesis and no uterus caused by random birth defect

B. Androgen Insensitivity Syndrome (46 XY)
cells are not receptive to testosterone thus patient has intra-abdominal testes and no uterus or vagina

Category 2: Breasts Present and Uterus Absent



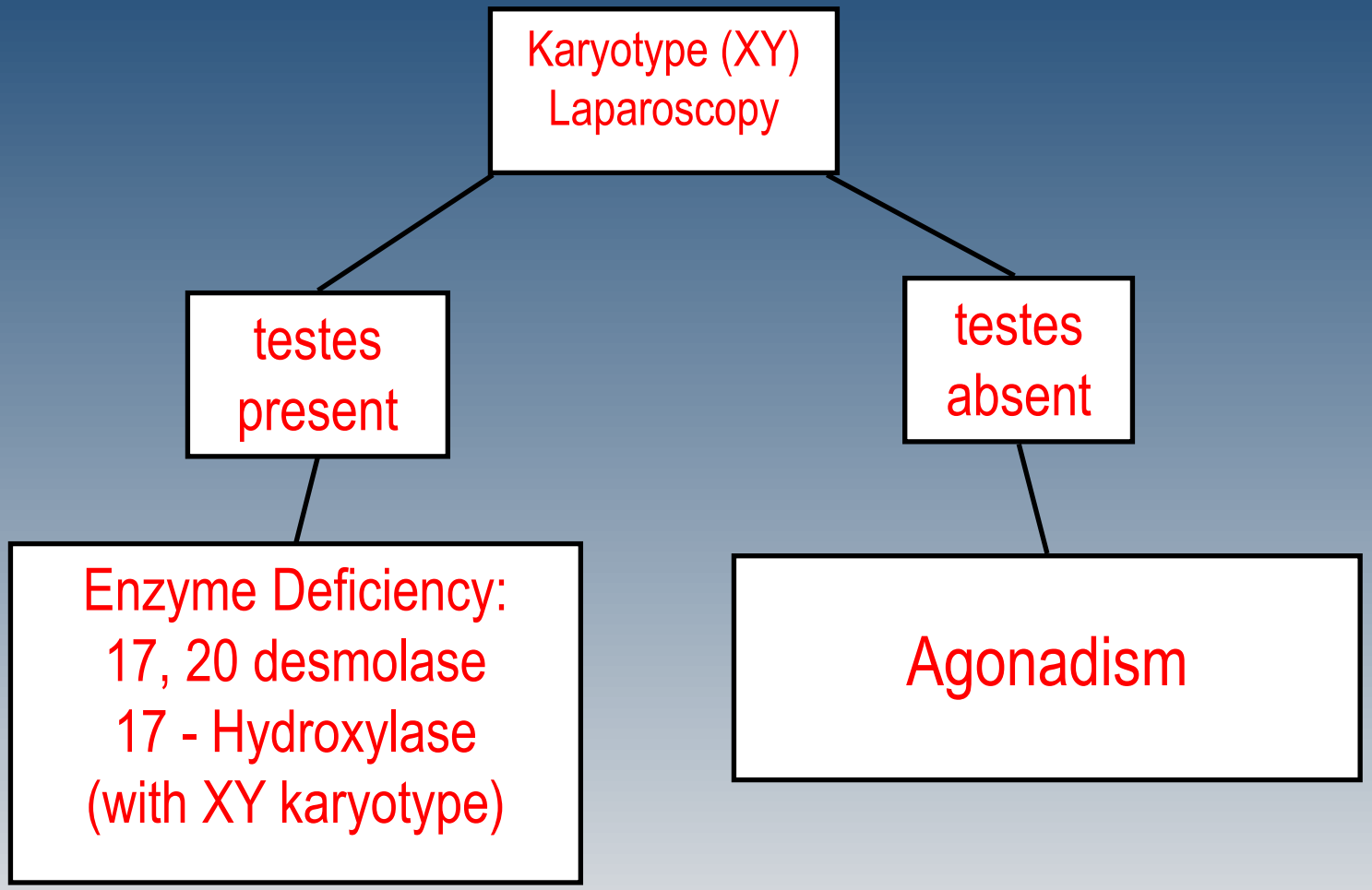
PRIMARY AMENORRHOEA

Category 3: Breasts Absent and Uterus Absent

– This is rare.
– Think low estrogen and (+) MIF: check a karyotype

A. 17, 20-Desmolase deficiency (46 XY)
B. 17 alpha hydroxylase deficiency (46 XY)
C. Pure XY (PGD, 46XY or Swyer's Syndrome)
D. Agonadism

Category 3: Breasts Absent and Uterus Absent



PRIMARY AMENORRHOEA

Category 4: Breasts Present and Uterus Present

–Think (+) oestrogen, (-) MIF

– Evaluate like secondary amenorrhea

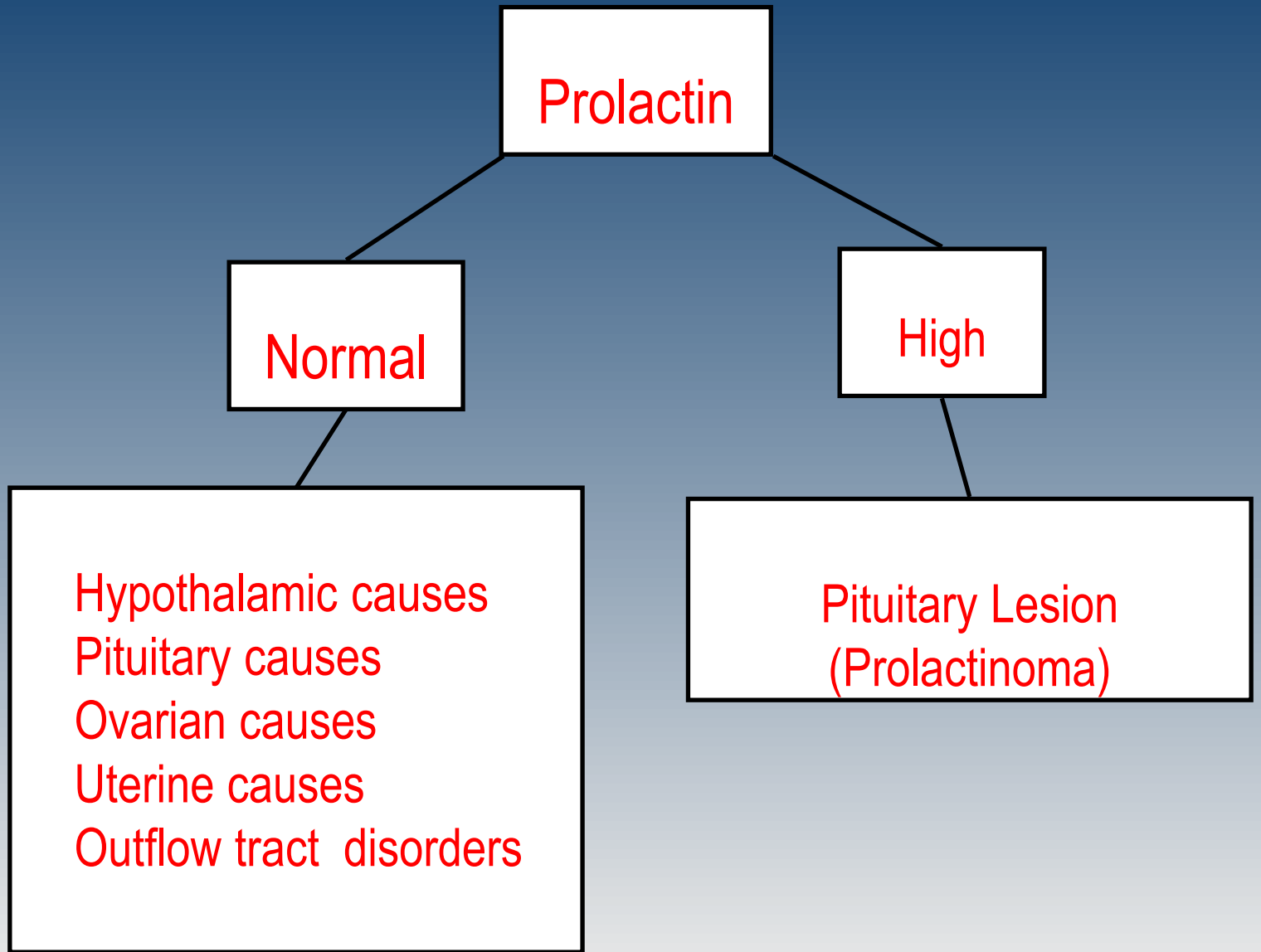
A. Hypothalamic causes

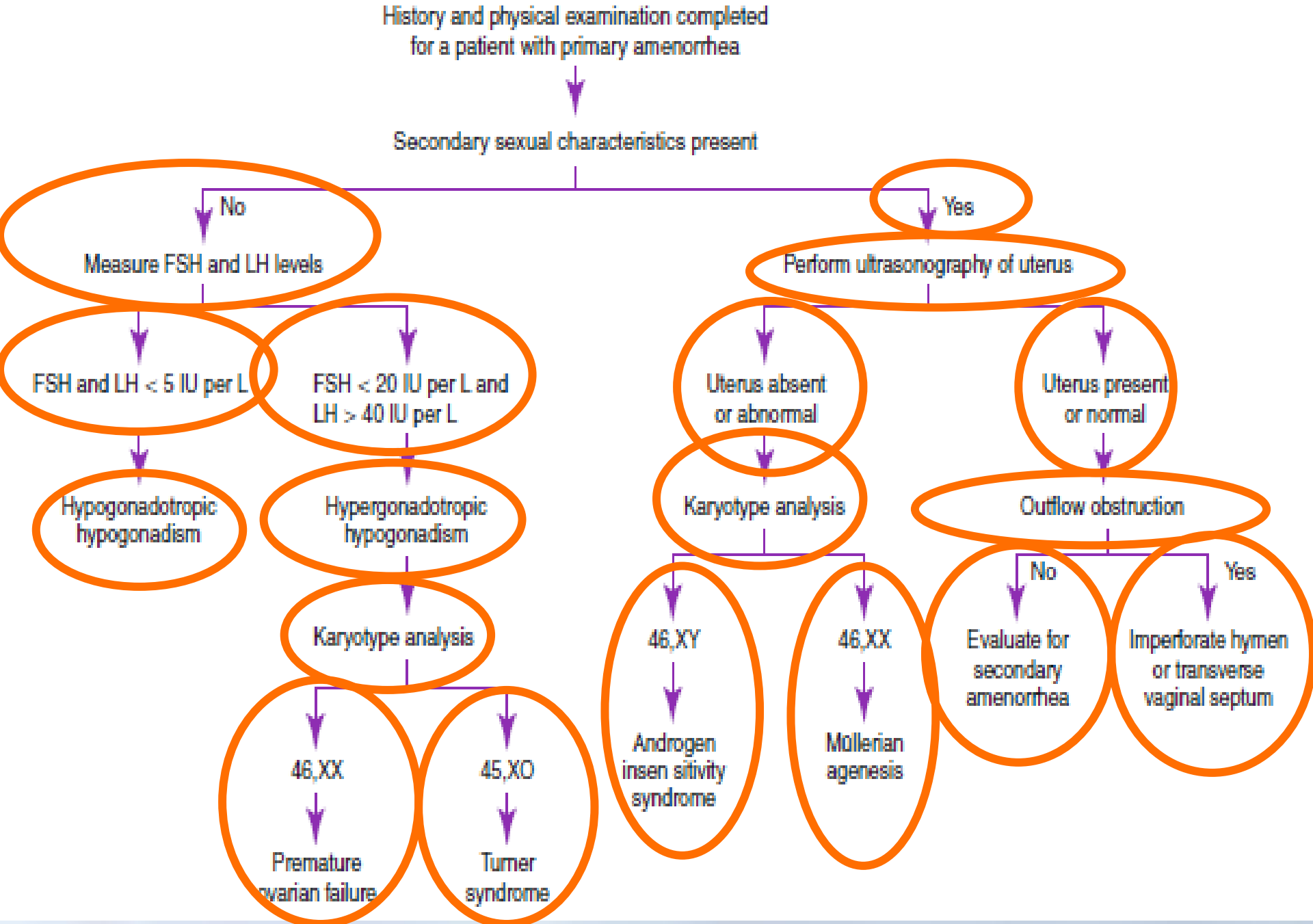
B. Pituitary causes

C. Ovarian causes

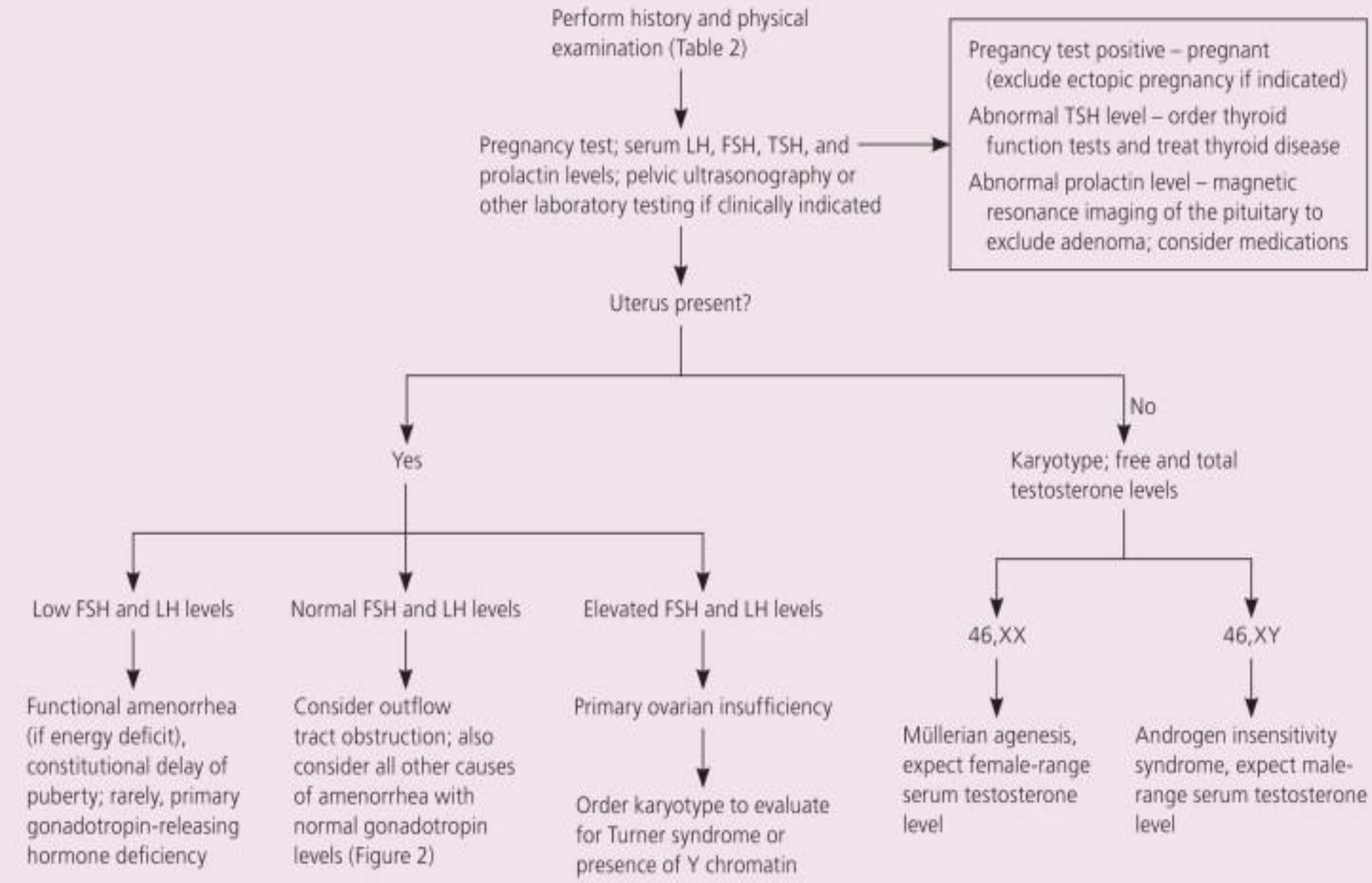
D. Uterine causes and outflow tract causes (?)

Category 4: Breasts Present and Uterus Present




History and physical examination completed for a patient with primary amenorrhea
Secondary sexual characteristics present
No
Measure FSH and LH levels
FSH and LH < 5 IU per L
Hypogonadotropic hypogonadism
FSH < 20 IU per L and LH > 40 IU per L
Hypergonadotropic hypogonadism
Karyotype analysis
46,XX
Premature ovarian failure
45,XO
Turner syndrome
Yes
Perform ultrasonography of uterus
Uterus absent or abnormal
Karyotype analysis
46,XY
Androgen insensitivity syndrome
46,XX
Müllerian agenesis
Uterus present or normal
Outflow obstruction
No
Evaluate for secondary amenorrhea
Yes
Imperforate hymen or transverse vaginal septum

Diagnosis of Primary Amenorrhea



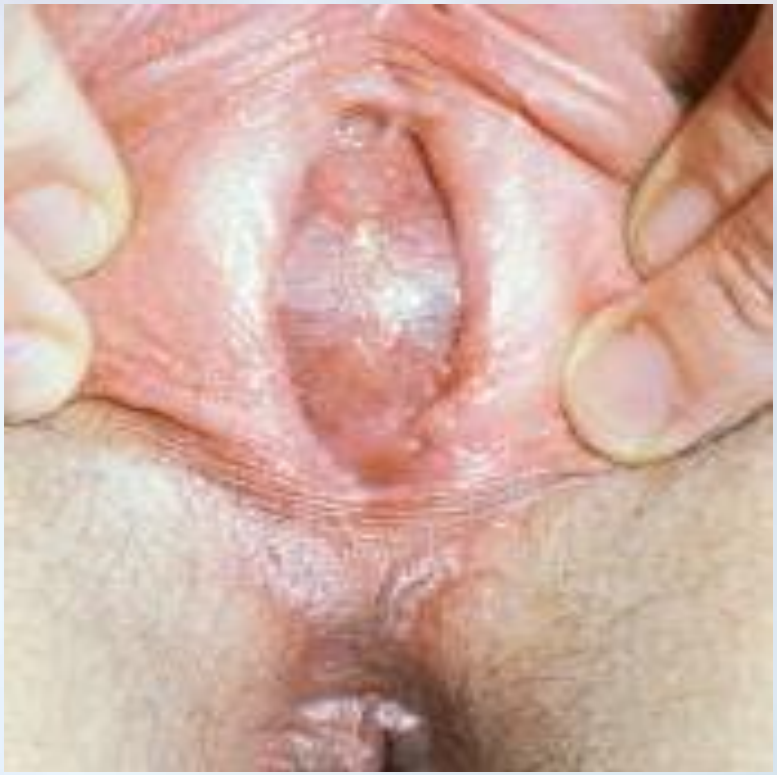
Cryptomenorrhea

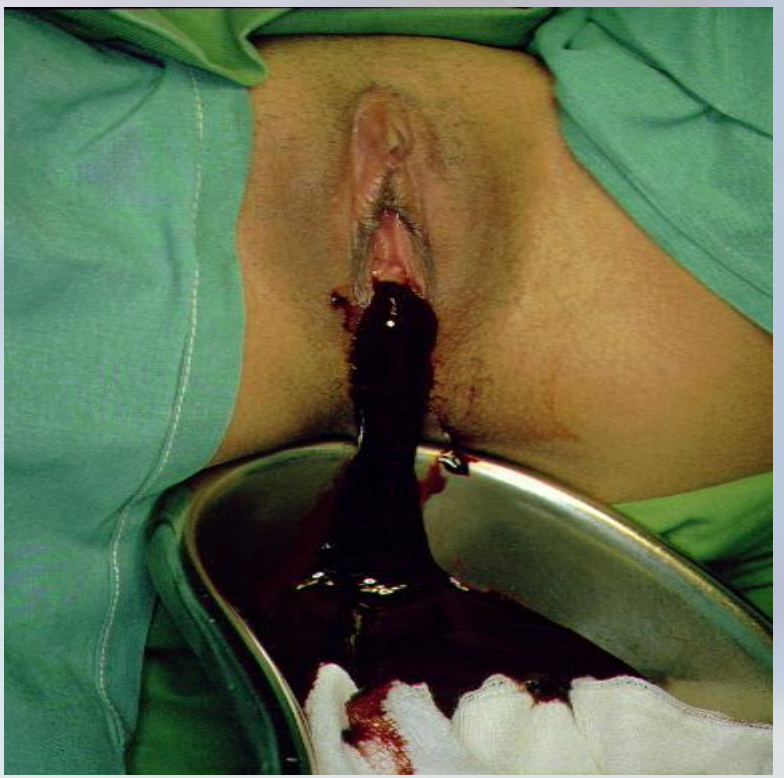
Despite the absence of menstrual flow, withdrawal bleeding does take place – albeit concealed.

intermittent abdominal pain
possible difficulty with micturition
possible lower abdominal swelling

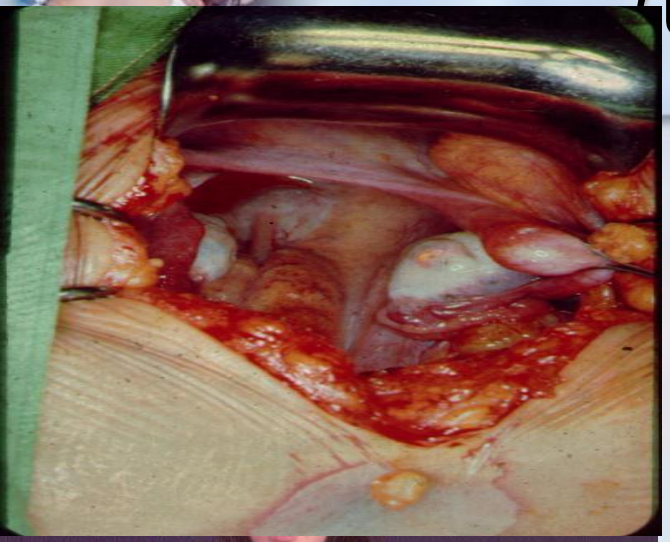
- imperforate hymen
- transverse vaginal septum with functioning uterus
- isolated vaginal agenesis with functioning uterus
- isolated cervical agenesis with functioning uterus

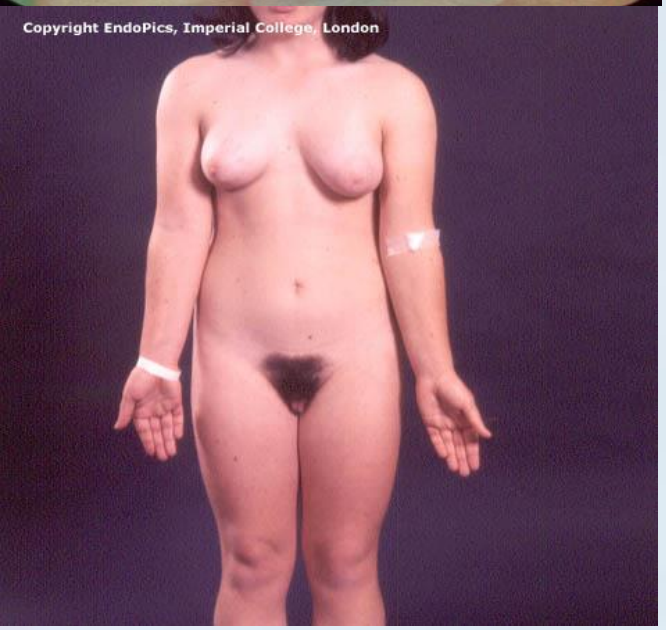
Cryptomenorrhea





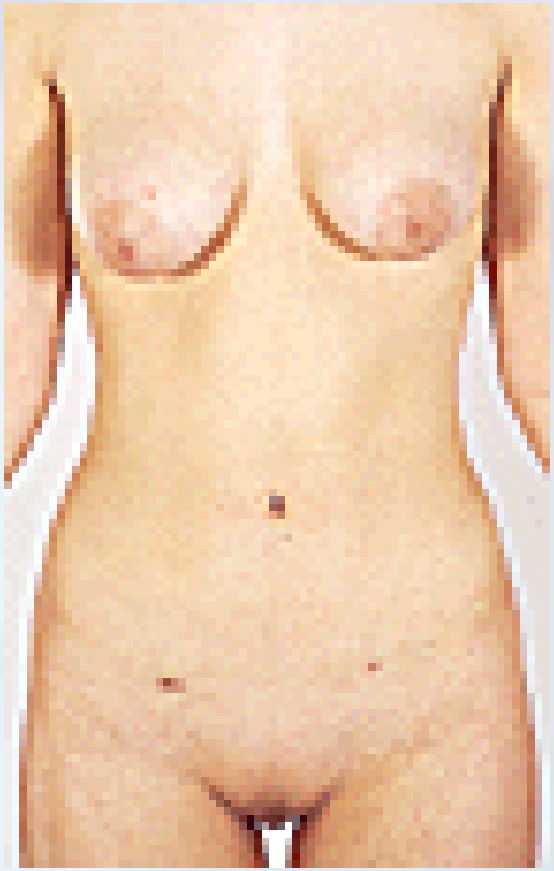
Mayer-Rokitansky-Kuster-Hauser Syndrome (utero-vaginal agenesis)





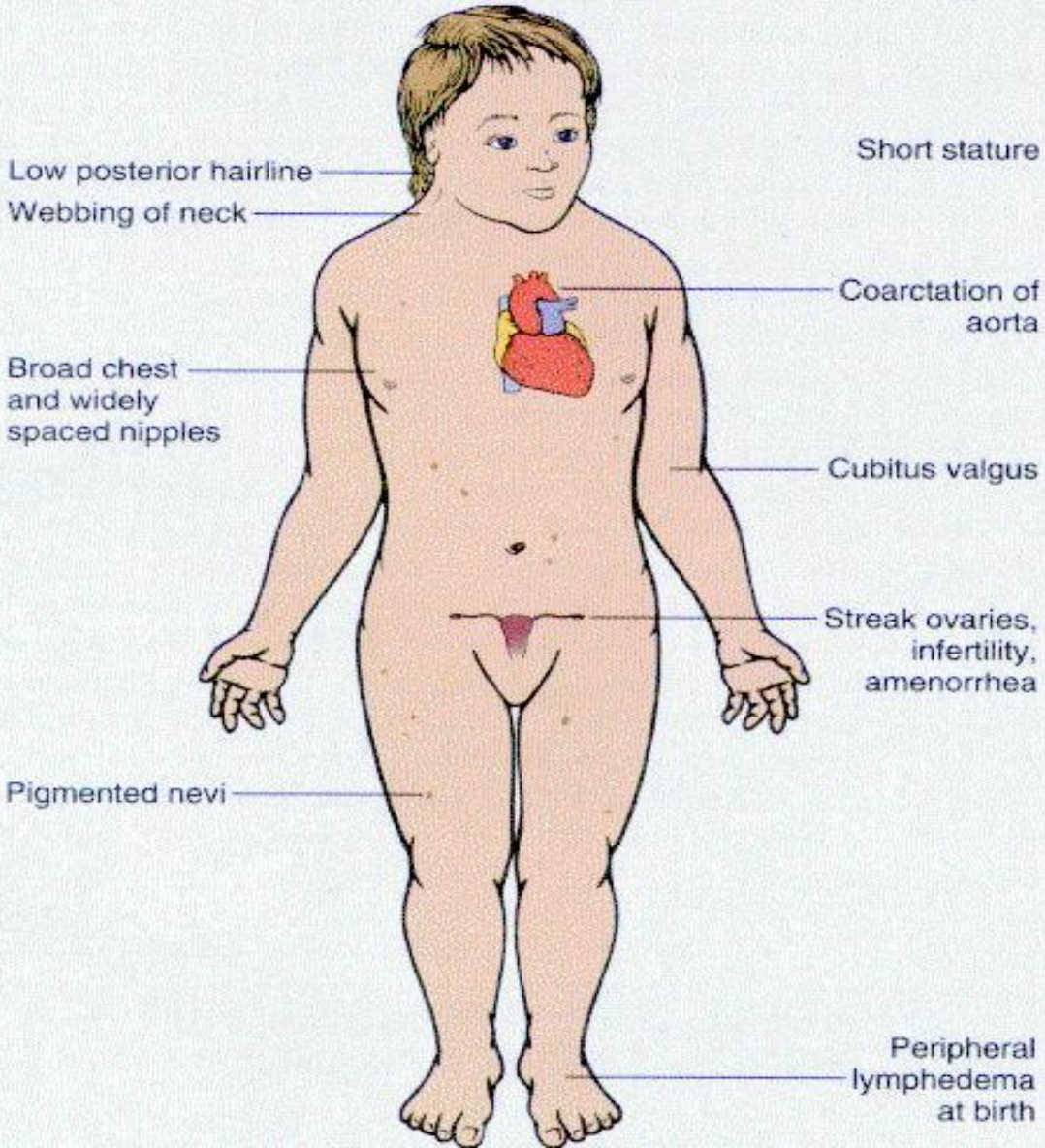
- 15% of primary amenorrhoea
- Normal secondary development & external female genitalia
- Normal female range testosterone level
- Absent uterus and upper vagina & normal ovaries.
- Congenital renal abnormalities occur in approximately one third of women with congenital absence of the uterus.
- Karyotype 46-XX
- 15-30% renal, skeletal and middle ear anomalies

Androgen Insensitivity



- Normal breasts but no sexual hair
- Normal looking female external genitalia
- Absent uterus and upper vagina
- Karyotype 46, XY
- Male range testosterone level.
- The testes of individuals with androgen resistance have approximately a 20% chance of becoming malignant after the age of 20 years.
- Treatment : gonadectomy after puberty + HRT

Typical features of Turner Syndrome



TURNER SYNDROME

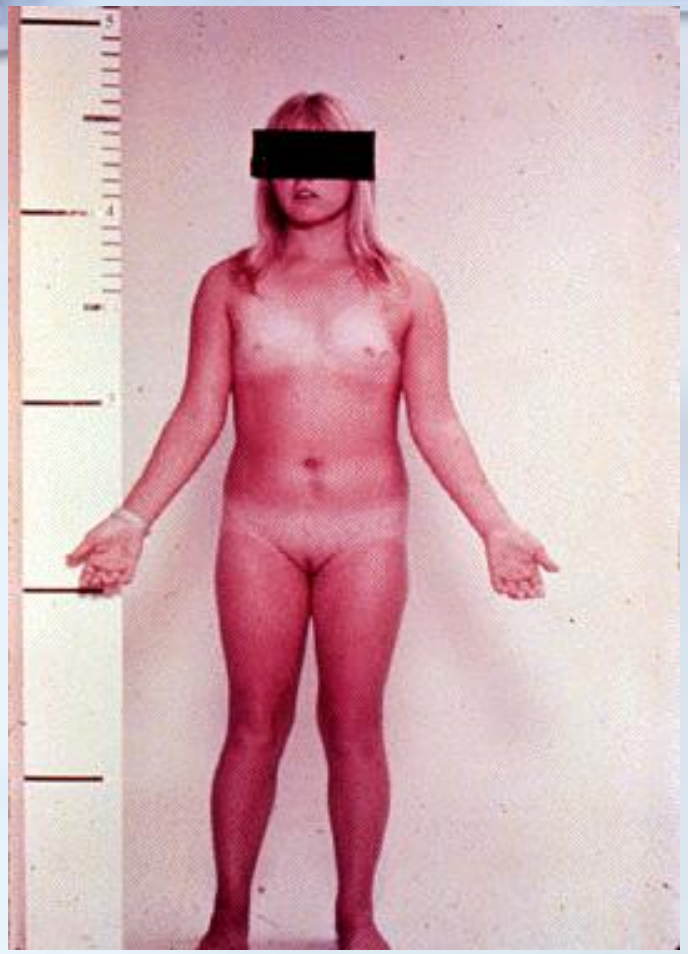
Incidence: 1 in 3000 female births

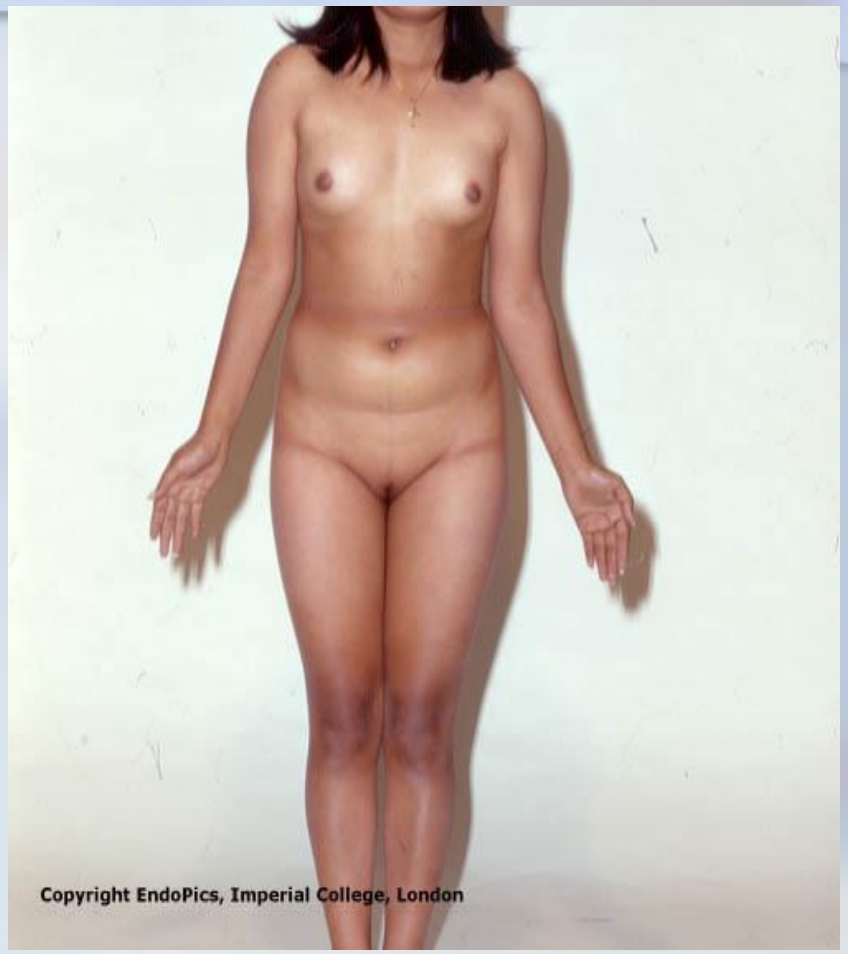
Karyotypes:	
Classic:	45,X
Defective second X chromosome:	46,X,i(Xq) 46,XXq– 46,XXp– 46,X, r(X)
Mosaic type:	45,X/46,XX

Turner's syndrome

- Sexual infantilism and short stature.
- Associated abnormalities, webbed neck,coarctation of the aorta,high-arched pallate, cubitus valgus, broad shield-like chest with wildely spaced nipples, low hairline on the neck, short metacarpal bones and renal anomalies.
- High FSH and LH levels.
- Bilateral streaked gonads.
- Karyotype - 80 % 45, X0
  - 20% mosaic forms (46XX/45X0)
- Treatment: HRT

Turner’s syndrome





(Classic 45-XO) **Mosaic (46-XX / 45-XO)**

Primary Amenorrhoea

- Treatment
  - Cyclic oestrogen/progestin
  - Remove gonadal streaks if XY or mosaic
    - Increased (52%) risk of gonadoblastomas, dysgerminomas, and yolk sac tumors
  - Pulsatile GnRH for ovulation induction in select patients
  - Surgical resection of intrauterine, cervical, and vaginal adhesions/septa

Hormonal treatment
Primary Amenorrhoea with absent secondary sexual characteristics

To achieve pubertal development

Premarin 5mg D1-D25 + provera 10mg D15-D25 X 3 months; ↓ 2.5mg premarin X 3 months and

↓ 1.25mg premarin X 3 months

Maintenance therapy

0.625mg premarin + provera OR ready HRT preparation OR 30µg oral contraceptive pill

TREATMENT
1-BREAST ABSENT UTERUS PRESENT

Hypothyroidism → Thyroxin

↓Wt ↑Exercise Stress

Gonadal Dysgenesis

17αOH-Dif Cortisol

XX

XY

XO

CNS Tmr

Treat accordingly

Psychiatric Help Treat thecause

Kallman's Syndrome

Gonadectomy

Estrogen Progestrone Replacement

Estrogen Progestrone Replacement

Breast development / Menses Improve Bone Min Density

2-BREAST PRESENT UTERUS PRESENT

↑ TSH
Hypothyroid

↑Prolactin
TSH→N

MRI/CT
Pituitary

Karyotyping

Prolactin → N
TSH → N

↑FSH

Ovarian
Failure

-Progestrone
chalange

+Progestrone
chalange

Out flow
Tract
Obstruction

MRI/CT
R/O
CNS TMR

↓FSH

Hypoth/ pituit
Failure

Anovulatory
cycle

TREATMENT
2-BREAST PRESENT UTERUS PRESENT

- ↑ TSH Hypothyroid → Thyroxin
- Out flow Tract Obstruction → Surgery
- ↑Prolactin TSH→N → Bromocriptin
- Anovulatory cycle → Progestin D16-25
- Ovarian Failure → HRT
- Hypoth/ pituit Failure → HRT

Secondary Amenorrhoea

- Differential
  - similar to that of primary amenorrhoea with uterus and secondary sex changes present
- Work up
  - r/o pregnancy
  - r/o hyperprolactinemia
  - if prolactin level elevated, evaluate thyroid function
  - measure FSH and LH
  - measure 17a-hydroxylase progesterone and progesterone
  - do a progesterone challenge test

Secondary Amenorrhoea

- Pregnancy!
- CNS disorders
- Pituitary gland
- Premature ovarian failure
- Thyroid
- Ovary
- Uterus
- Systemic disorders
  - Renal failure, liver disorders, DM
- Medications: anti-psychotics, reserpine

Secondary Amenorrhoea

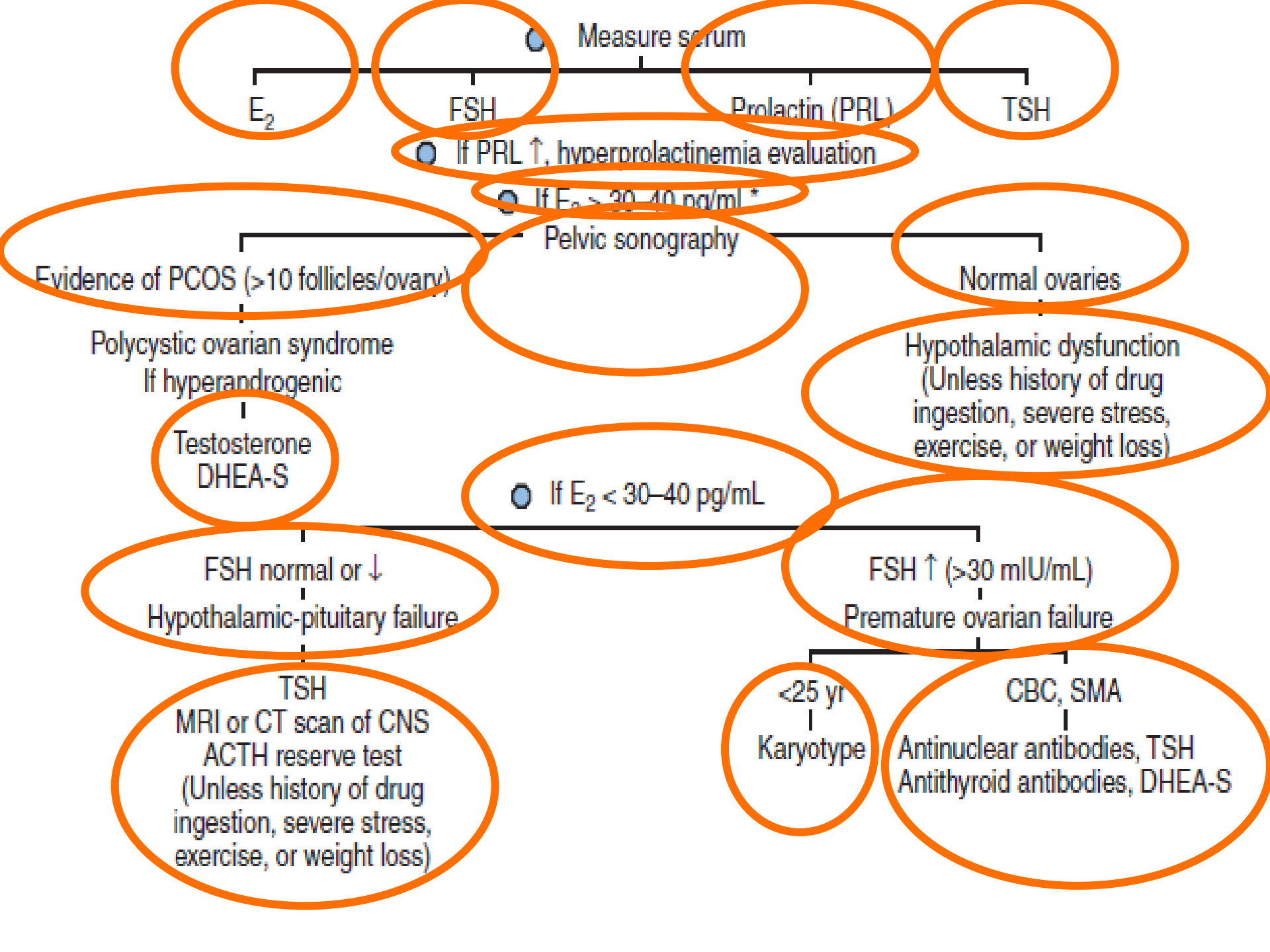
- CNS disorders
  - Chronic hypothalamic anovulation
    - Stress
    - Increased exercise levels
    - Anorexia nervosa
  - Head trauma
  - Space-occupying lesions

Secondary Amenorrhoea

- Pituitary disorders
  - Hyperprolactinemia
    - Prolactinoma
    - Medications
    - PCOS
    - Renal failure
  - Hypoprolactinemia
    - Pituitary resection
    - Sheehan's syndrome
- Thyroid disorders
  - Hyper- or hypothyroidism

Secondary Amenorrhoea

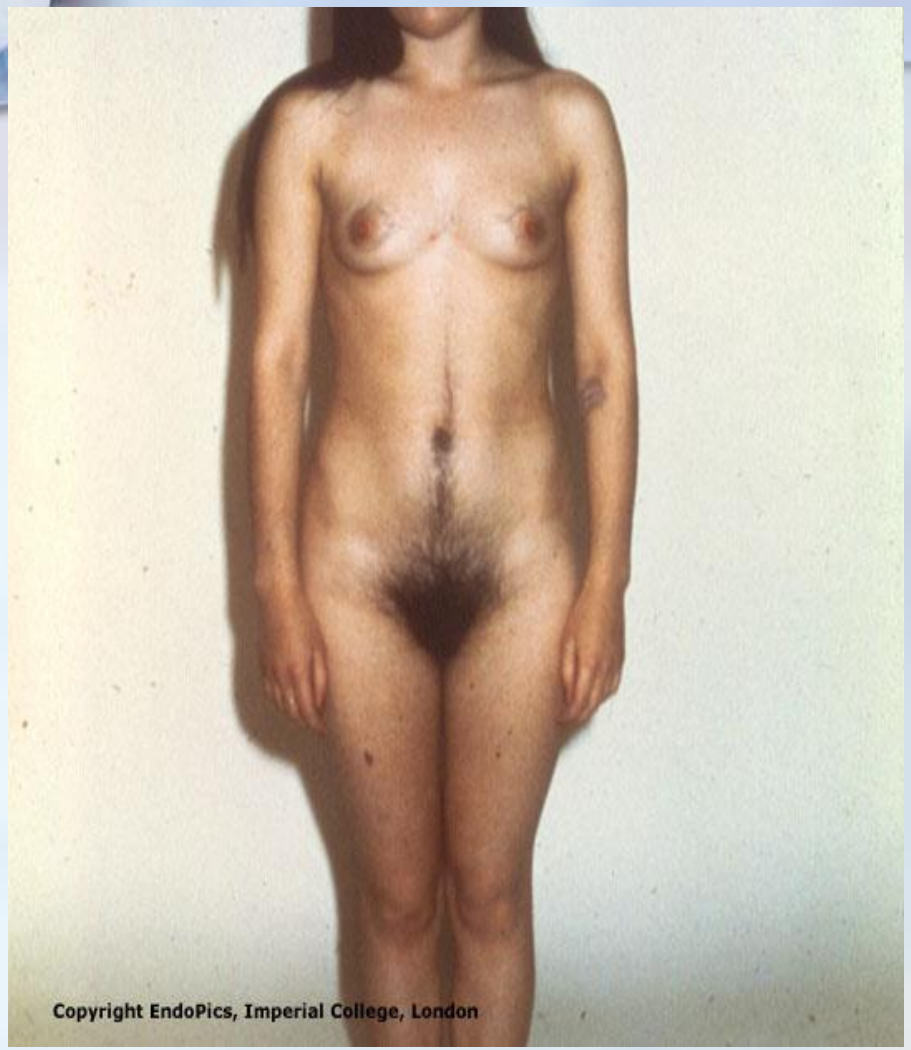
- Ovulation disorders
  - Polycystic ovarian syndrome
  - Premature ovarian failure
- Uterine abnormalities
  - Asherman’s syndrome
  - Cervical stenosis
- Drug-induced amenorrhea
  - Hormonal contraceptives
  - GnRH analogues


Measure serum
E_2
FSH
Prolactin (PRL)
TSH
If PRL ↑, hyperprolactinemia evaluation
If E_2 > 30–40 pg/mL *
Pelvic sonography
Evidence of PCOS (>10 follicles/ovary)
Normal ovaries
Polycystic ovarian syndrome
If hyperandrogenic
Testosterone
DHEA-S
Hypothalamic dysfunction
(Unless history of drug ingestion, severe stress, exercise, or weight loss)
If E_2 < 30–40 pg/mL
FSH normal or ↓
Hypothalamic-pituitary failure
FSH ↑ (>30 mIU/mL)
Premature ovarian failure
TSH
MRI or CT scan of CNS
ACTH reserve test
(Unless history of drug ingestion, severe stress, exercise, or weight loss)
<25 yr
Karyotype
CBC, SMA
Antinuclear antibodies, TSH
Antithyroid antibodies, DHEA-S

Polycystic ovary syndrome

- The most common cause of chronic anovulation
- Hyperandrogenism ; ↑ LH/FSH ratio (not always)
- Insulin resitance is a major biochemical feature (↑ blood insulin level→ hyperandrogenism)
- Long term risks: Obesity, hirsutism, infertility, type 2 diabetes, dyslipidemia, cardiovasular risks, endometrial hyperplassia and cancer

• Treatment depends on the needs of the patient and preventing long term health problems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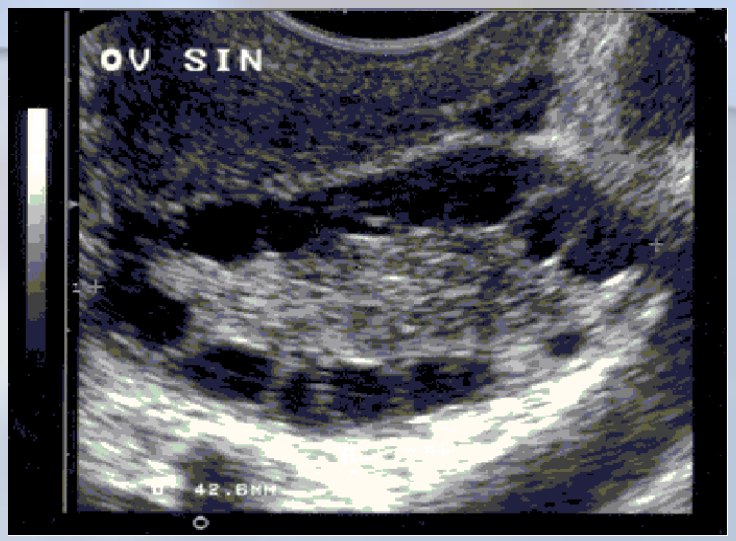
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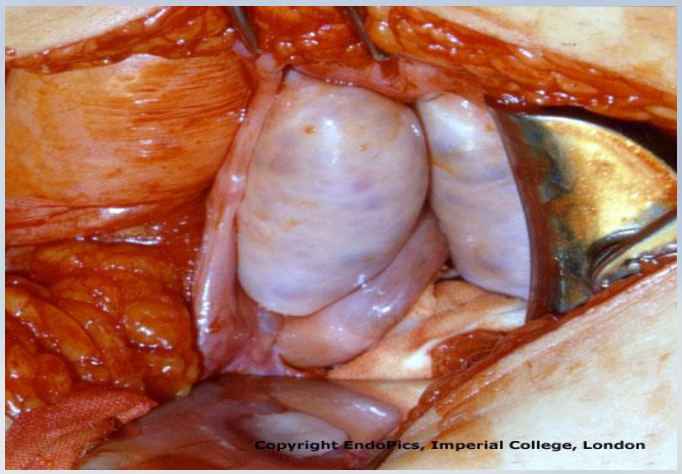
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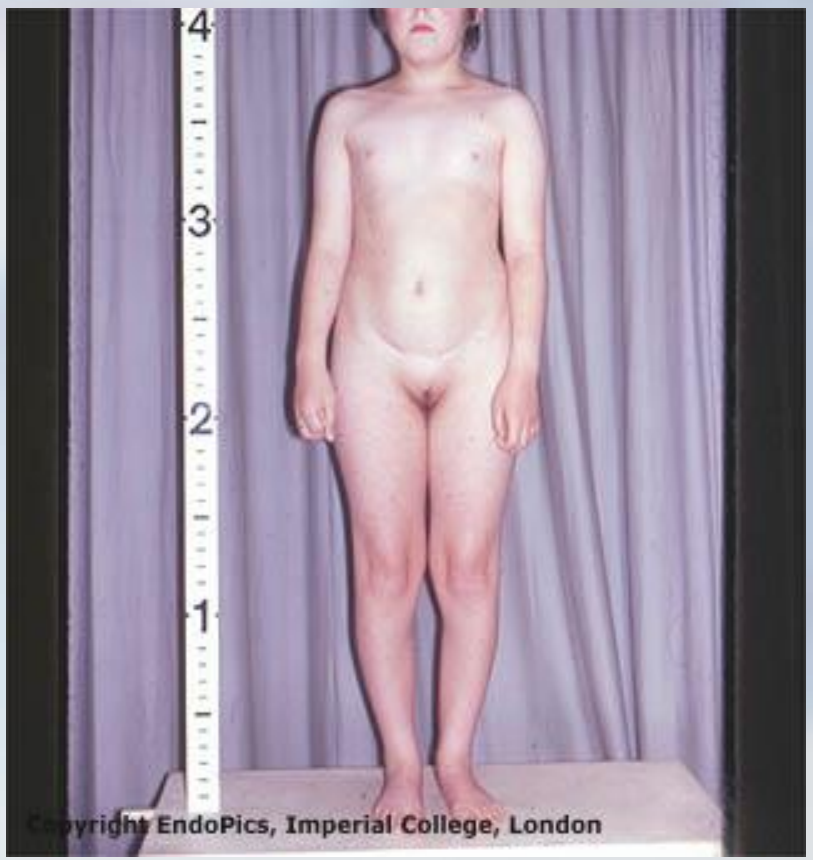
Hypogonadotropic Hypogonadism

- Normal hight
- Normal external and internal genital organs (infantile)
- Low FSH and LH
- MRI to R/O intra-cranial pathology.
- 30-40% anosmia (Kallmann's syndrome)
- Sometimes ⇨ constitutional delay
- Treat according to the cause (HRT), potentially fertile.

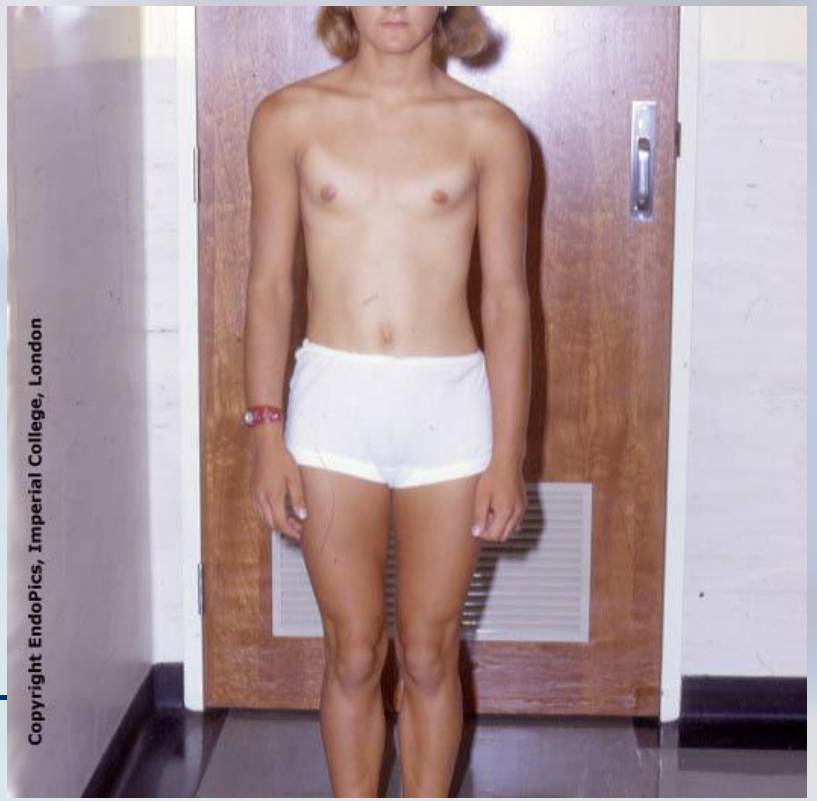


Constitutional pubertal delay

- Common cause (20%)
- Under stature and delayed bone age

  (X-ray Wrist joint)
- Positive family history
- Diagnosis by exclusion and follow up
- Prognosis is good

  (late developer)
- No drug therapy is required – Reassurance (? HRT)



Sheehan's syndrome

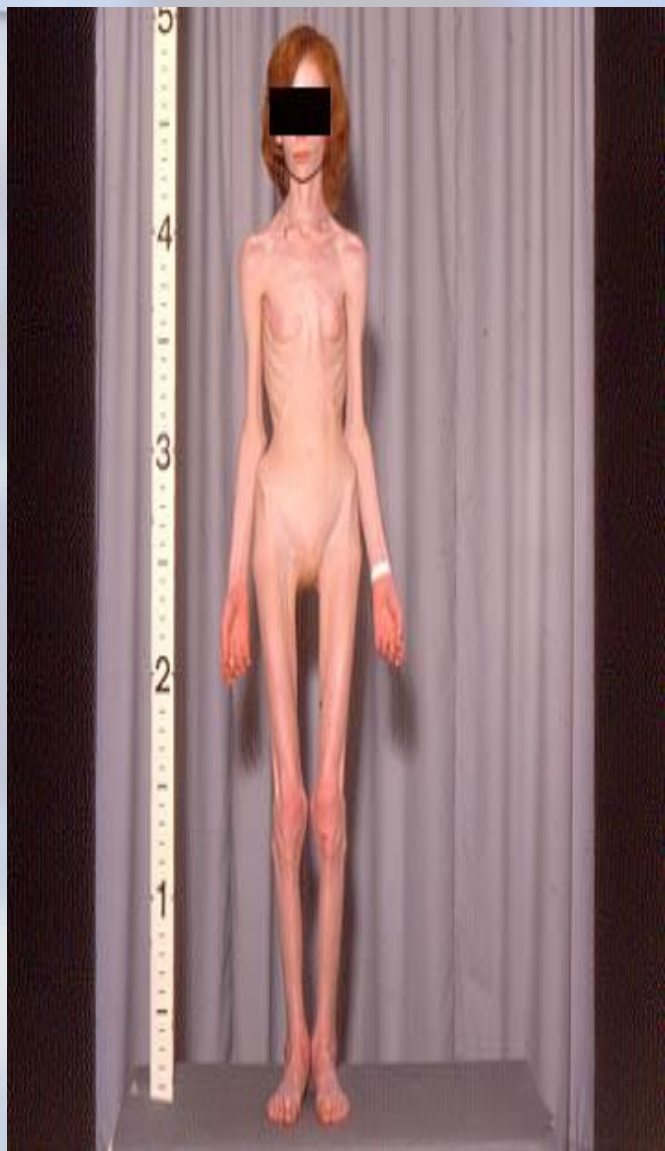
- Pituitary inability to secrete gonadotropins
- Pituitary necrosis following massive obstetric hemorrhage is most common cause in women
- Diagnosis : History and ↓ E2,FSH,LH

  + other pituitary deficiencies (MPS test)
- Treatment :

  Replacement of deficient hormones

Weight-related amenorrhoea
Anorexia Nervosa

- 1º or 2º Amenorrhea is often first sign
- A body mass index (BMI) <17 kg/m²→ menstrual irregularity and amenorrhea
- Hypothalamic suppression
- Abnormal body image, intense fear of weight gain, often strenuous exercise
- Mean age onset 13-14 yrs (range 10-21 yrs)
- Low oestradiol → risk of osteoporosis
- Bulemics less commonly have amenorrhea due to fluctuations in body wt, but any disordered eating pattern (crash diets) can cause menstrual irregularity.
- Treatment : ↑ body wt. (Psychiatrist referral)



Exercise-associated amenorrhoea

- Common in women who participate in sports (e.g. competitive athletes, ballet dancers)
- Eating disorders have a higher prevalence in female athletes than non-athletes
- Hypothalamic disorder caused by abnormal gonadotrophin-releasing hormone pulsatility, resulting in impaired gonadotrophin levels, particularly LH, and subsequently low oestrogen levels

Contraception related amenorrhoea

- Post-pill amenorrhea is not an entity
- Depot medroxyprogesterone acetate

  Up to 80 % of women will have amenorrhea after 1 year of use. It is reversible (oestrogen deficiency)
- A minority of women taking the progestogen-only pill may have reversible long term amenorrhoea due to complete suppression of ovulation.
- The incidence of amenorrhea lasting more than 6 months after discontinuation of oral contraceptives is 0.8%.

Late onset congenital adrenal hyperplasia

- Autosomal recessive trait
- Most common form is due to 21-hydroxylase deficiency
- Mild forms Closely resemble PCO
- Severe forms show Signs of severe androgen excess
- High 17-OH-progesterone blood level
- Treatment : cortisol replacement and ? Corrective surgery

Cushing's syndrome

- Clinical suspicion : Hirsutism, truncal obesity, purple striae,↑ BP
- If Suspicion is high :

dexamethasone suppression test (1 mg PO 11 pm) and obtain serum cortisol level at 8 am :

< 5 µg/ dl excludes Cushing's

- 24 hours total urine free cortisol level to confirm diagnosis
- 2 forms ; adrenal tumour or ACTH hypersecretion (pituitary or ectopic site)

PROGESTERONE CHALLENGE TEST (PCT)

10mg of progesterone orally for 5- 10 days

A withdrawal bleed occurring within ten days of a progesterone challenge is a positive result and a diagnosis of anovulation may be established.

PROGESTERONE CHALLENGE TEST (PCT)

POSITIVE

- HP Dysfunction
- Hyperthyroidism
- PCOS

NEGATIVE

- Hyperprolactenemia
- Hypothyroidism
- Hypopituitarism
- POF
- Asherman's

NEGATIVE PCT

Premature Ovarian Failure

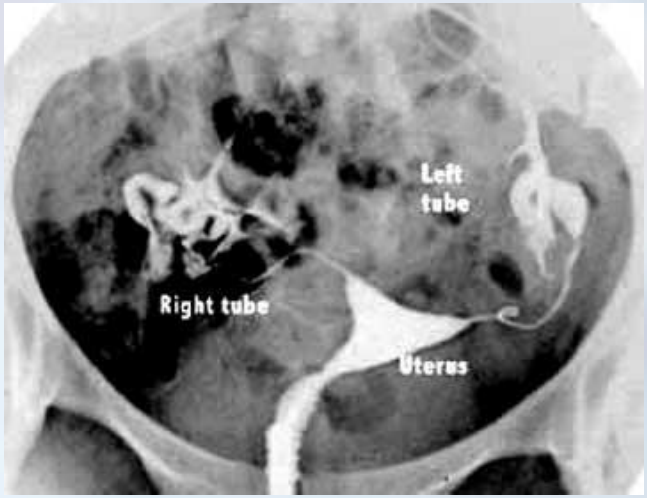
- is an end organ phenomenon
- occurring before the age of 40
- characterized by;
  - (1) lack of ovarian response to tropic stimulation;
  - (2) lack of gonadal negative feed-back;
  - (3) elevated circulating levels of FSH and LH
- pathogenesis of this disorder has not been determined
- it is possible that there is an autoimmune basis for this

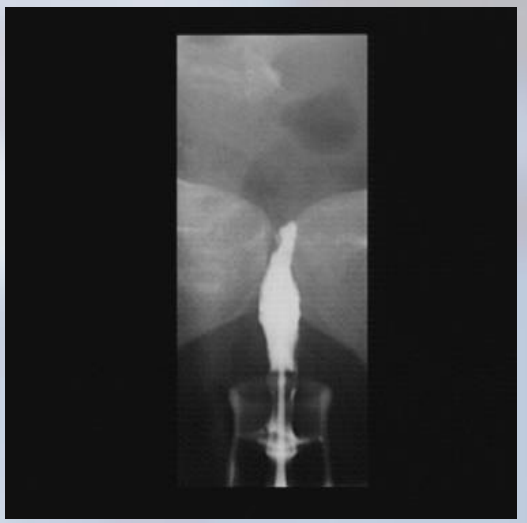
NEGATIVE PCT

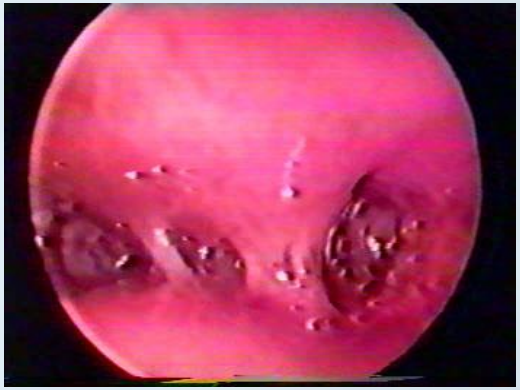
Asherman's Syndrome

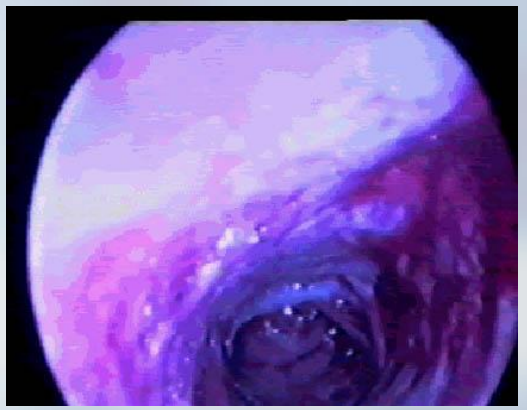
- is characterized by the formation of scar tissues obliterating the endometrial cavity that prevents the occurrence of normal menstrual periods
- occurs most frequently after a vigorous scraping during completion curettage
- can also result from other pelvic surgeries like cesarean sections, myomectomies, pelvic irradiation, schistosomiasis and genital tuberculosis
- cervical stenosis after a cone biopsy or LEEP

Asherman's Syndrome

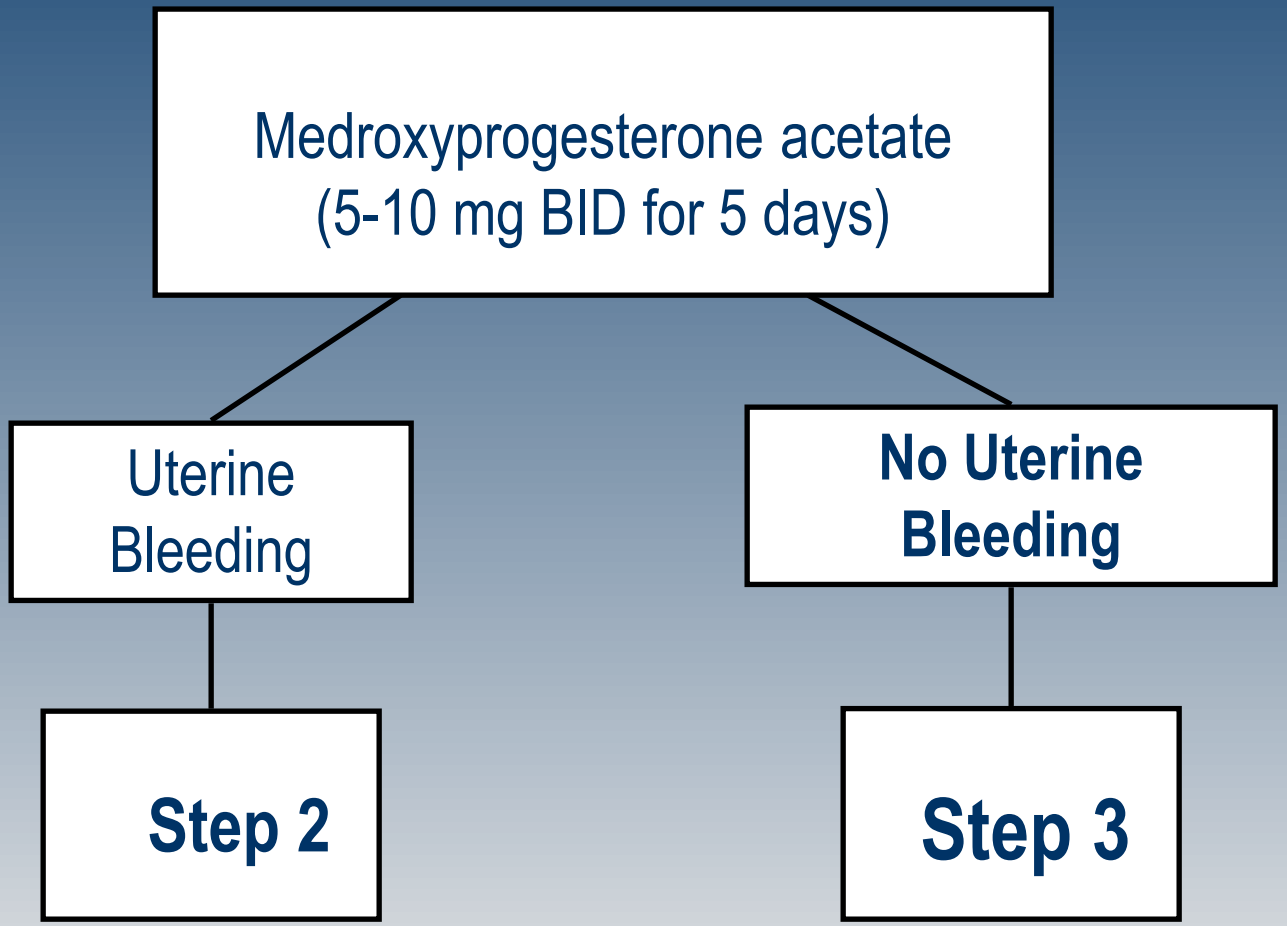




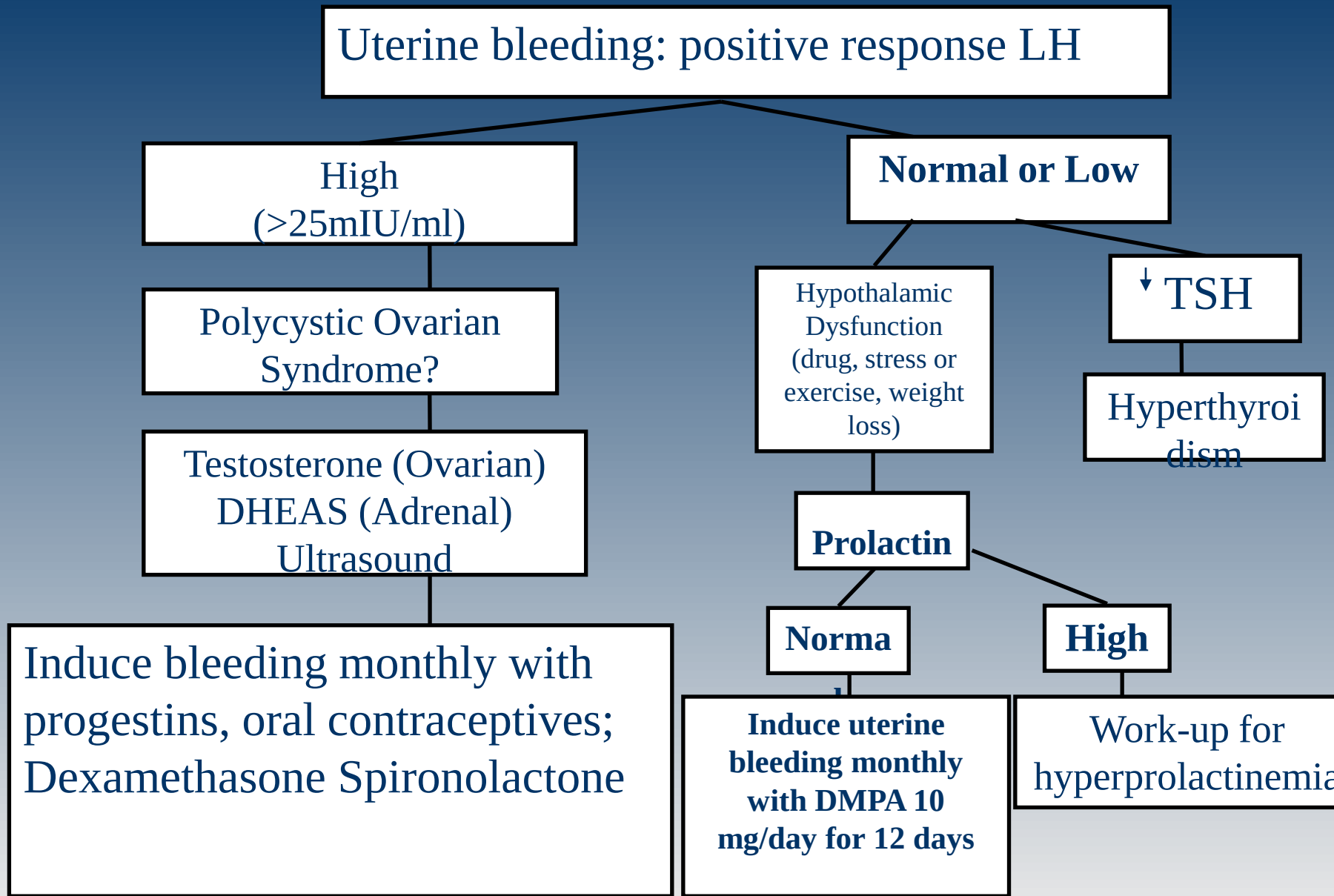




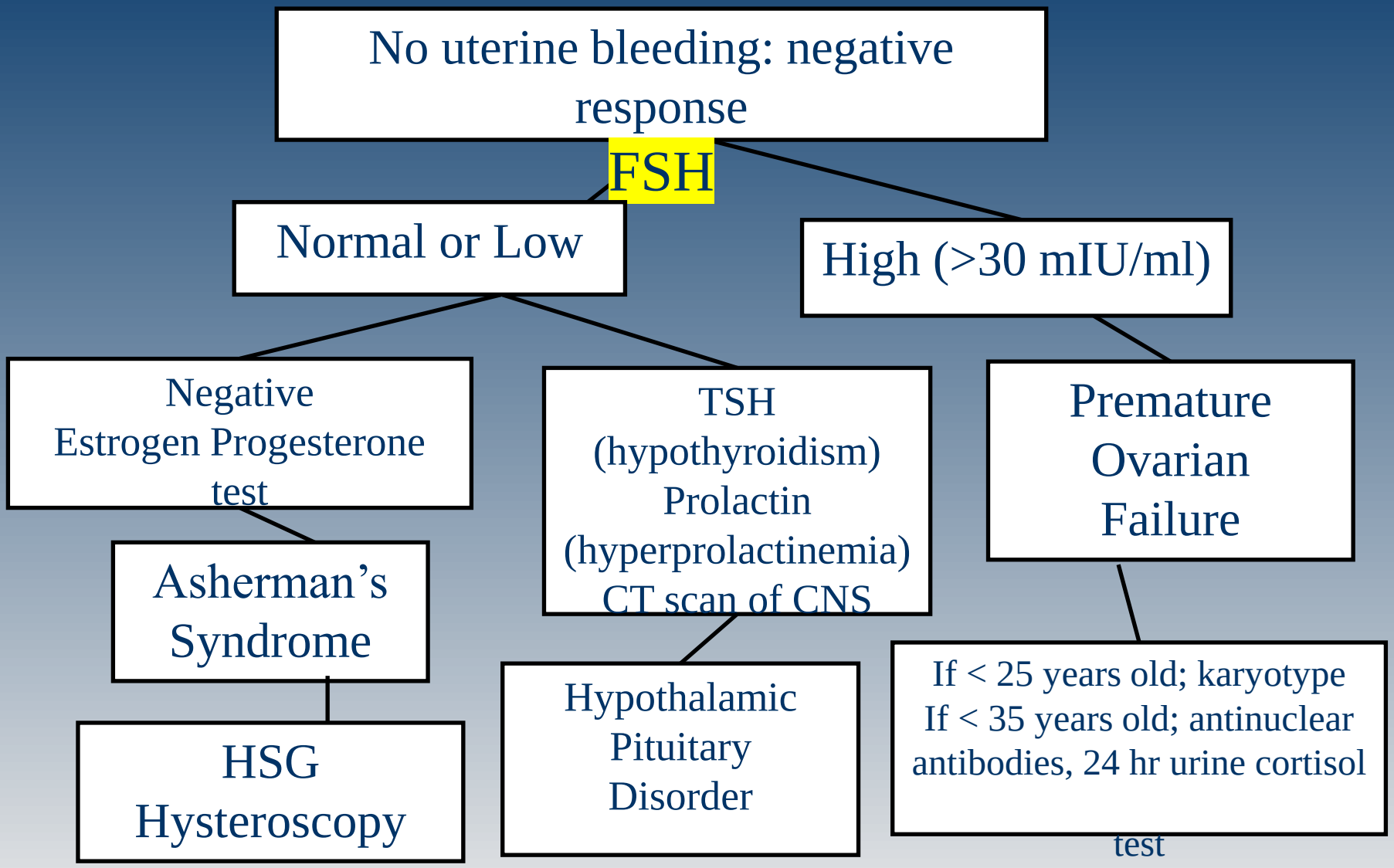
STEP 1: Evaluation of Secondary Amenorrhea



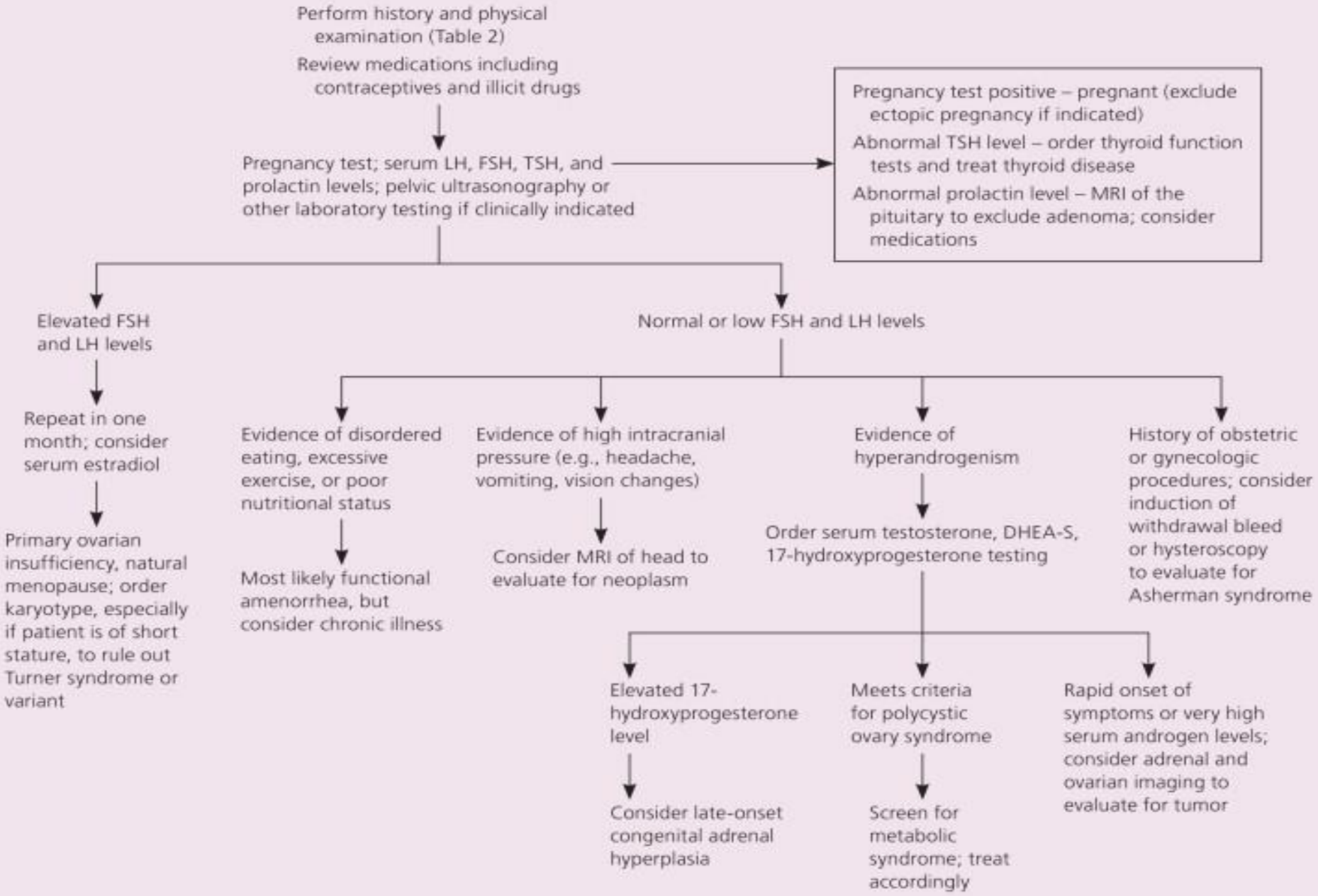
STEP 2: Evaluation of Secondary Amenorrhea



STEP 3: Evaluation of Secondary Amenorrhea



Diagnosis of Secondary Amenorrhea

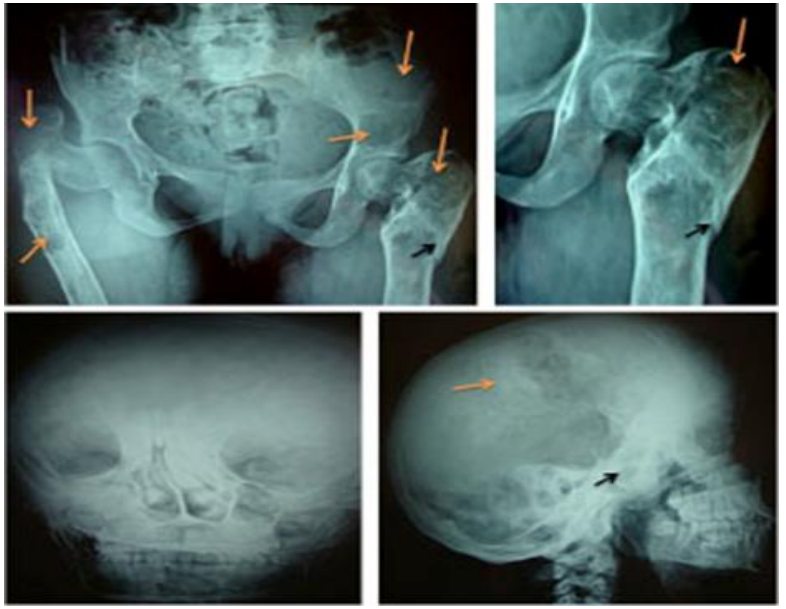


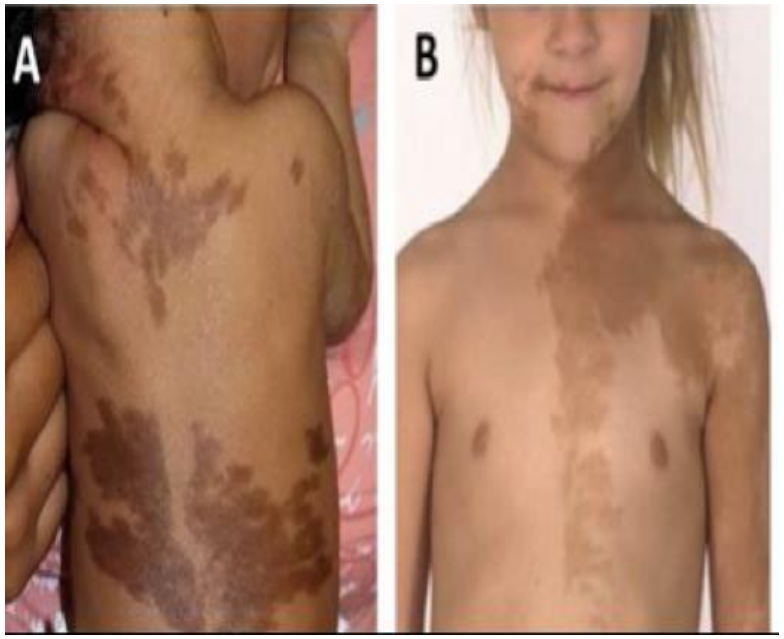
Case #I

- A 27-year-old multiparous female, presents complaining of having no periods for the last 6 months. She denies any pelvic pains, weight loss or excessive exercise. On examination, she is 168 cm in tall and weighs 64 kg. Her blood pressure is 110/60 mm Hg. Her thyroid gland is normal. She underwent a D&C few months ago due to septic miscarriage after which her periods become less and less and eventually stopped. She also mentioned that her last vaginal delivery was complicated by severe postpartum hemorrhage and uterine curettage. However, she breast fed her son for three months.
- 1) How can you label this case?
- 2) What is the most likely diagnosis and what are your differential diagnoses?
- 3) What is your next diagnostic step?
- 4) What is your therapeutic plan for this patient?

Case # II

An 8-year-old female presents to gyn clinic complaining of having early occurring periods. On examination, she is 130 cm in tall and weighs 31 kg. Her blood pressure is 110/60 mm Hg. Physical examination revealed pathology shown in figure 1: A &B. Her mother mentioned multiple visits to Emergency rooms due to bone pains & fractures after ordinary activities and showed recent report she had figure 2.





Case #II

- A 17-year-old nulliparous adolescent female, who may have only one kidney, presents with primary amenorrhea. She denies weight loss or excessive exercise. On examination, she is 165 cm in tall and weighs 55 kg. Her blood pressure is 140/88 mm Hg. mFG>12, Ludwig I, Acanthosis Nigricans +. Her thyroid gland is normal. She has appropriate Tanner stage IV breast development, axillary and pubic hair, and female external genitalia for the exception of mild enlargement of the clitoris.

1) Most likely diagnosis and your DD?
2) Next step in diagnosis:
3) Please build a diagram for your DD based on clinical findings
4) If your primary diagnosis is right what is your plan of management?


Thank You!