Practical Approach to Amenorrhea

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Definition

Primary amenorrhea is diagnosed if;

(1) the absence of menstruation by the age of 14 years in the absence of growth or development of secondary sex characters, or

(2) No menstruation by the age of 16 with or without growth or development of secondary sex characters.

Definition

***Secondary amenorrhea*:** is the absence of menstruation for 6 months or more or for a period of time equivalent to that of previous 3 consecutive cycles in a woman who was previously menstruating.

PRIMARY AMENORRHEA

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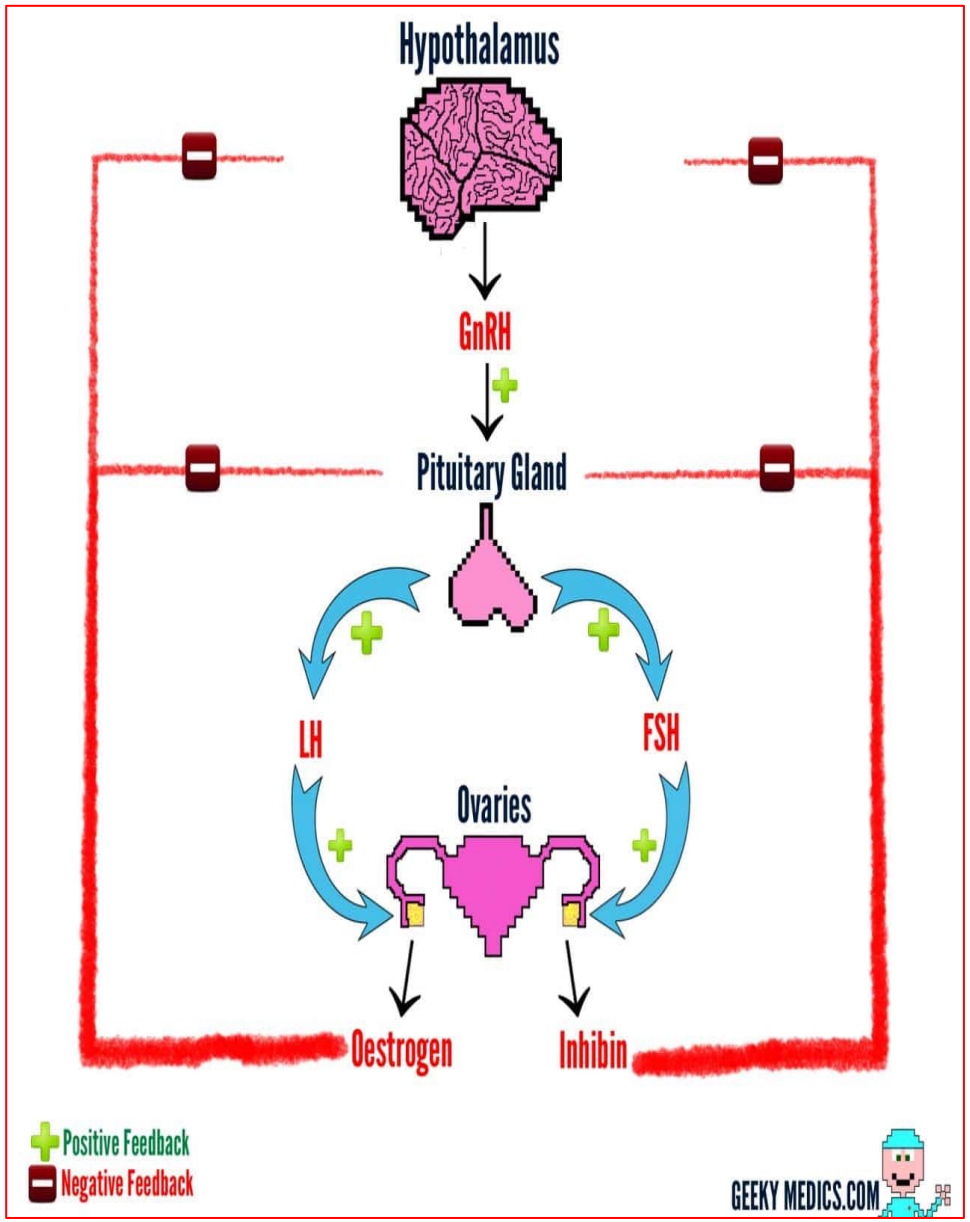
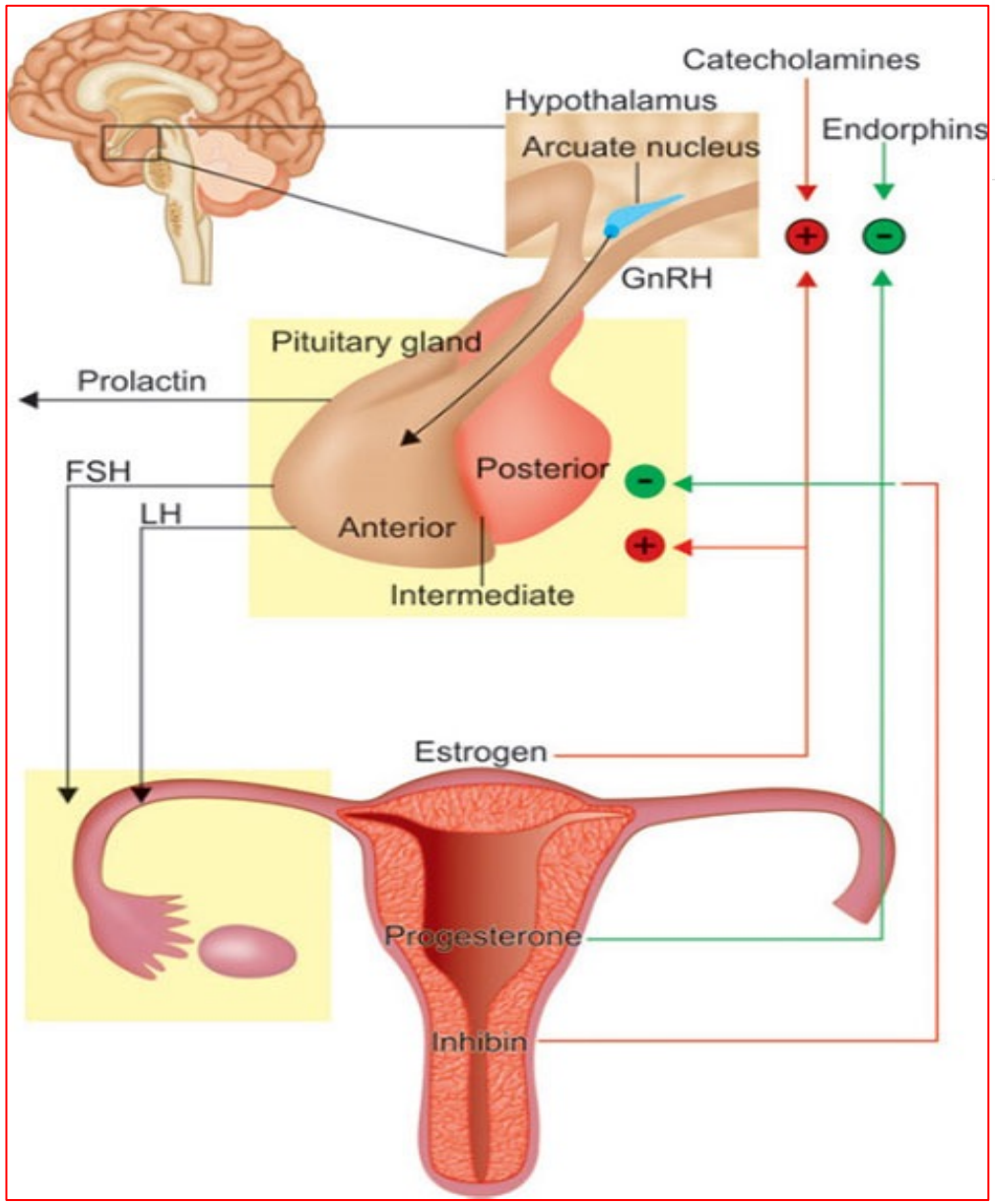
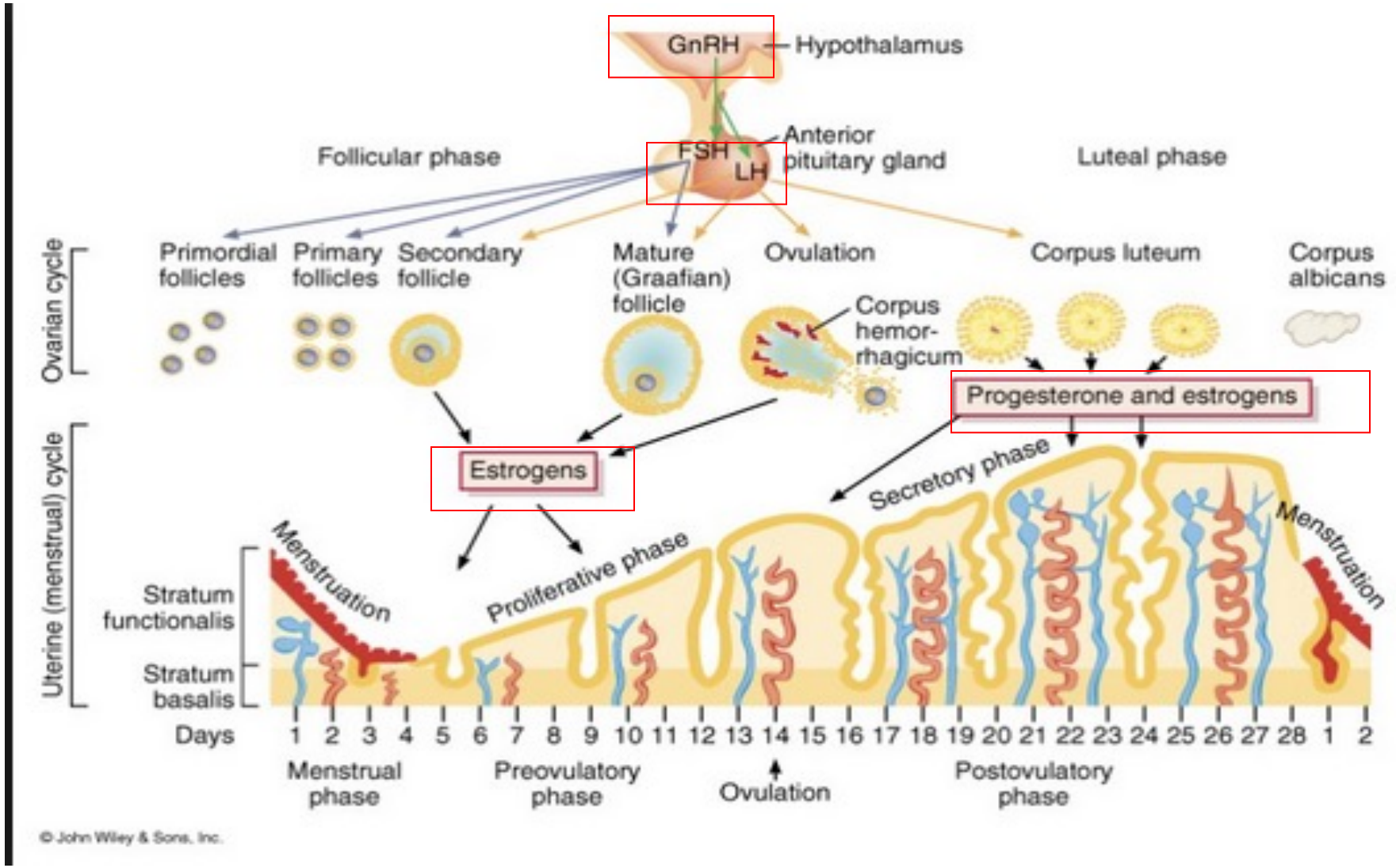
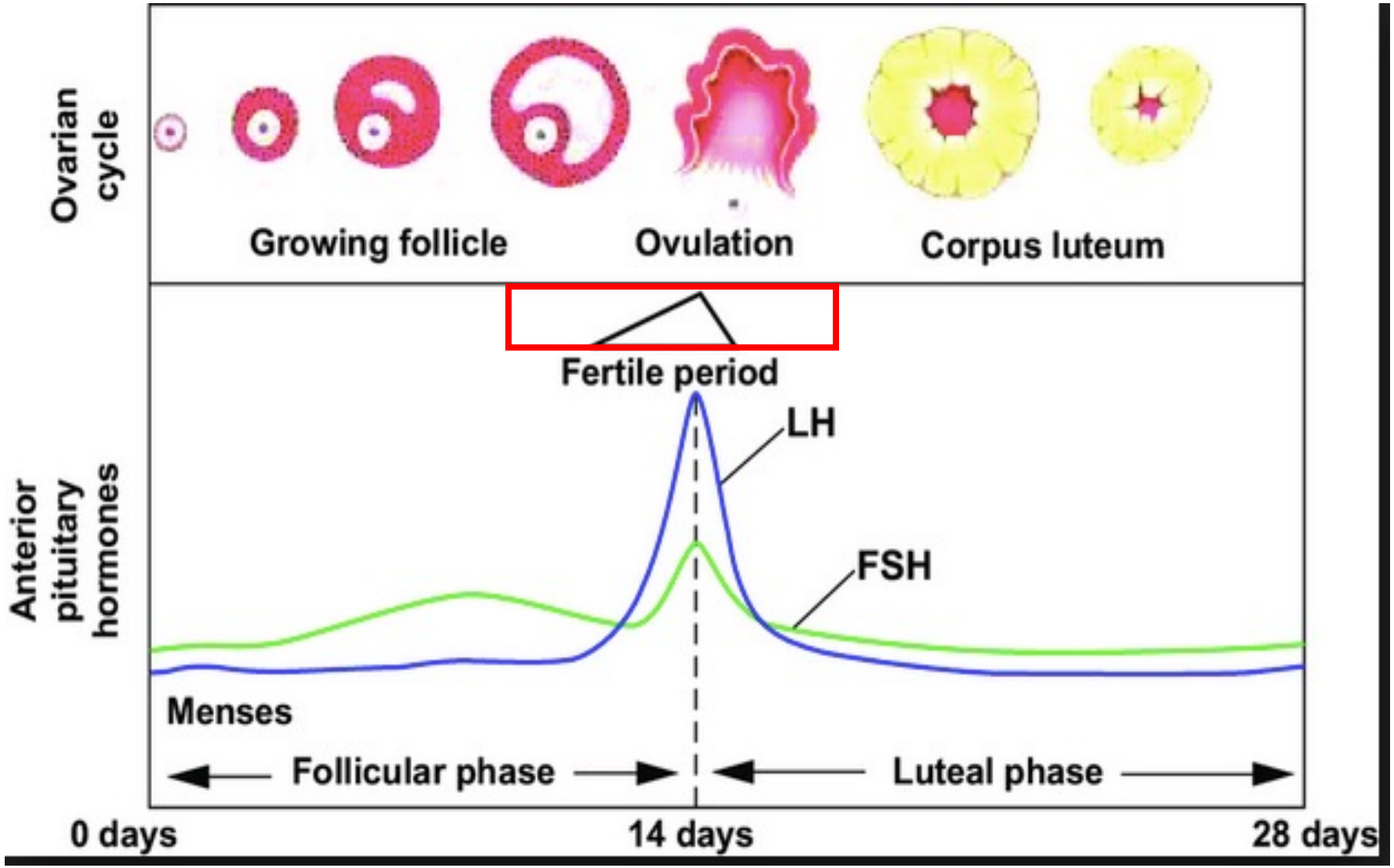
Background

- Development of the breast and feminine constitution depends on E_2 secreted by the granulosa cells of the developing ovarian follicles. E_2 exerts its action via estrogen receptors in the target organ.
- The uterus (and most genital tract) develops from the mullerian ducts in the female fetus with 46XX karyotype in the absence of AMH.
- The external male genitalia develps in 46xy embryo under the effect of dihydrotestosterone exerting its action on its specific androgen receptors in the target organs.









PRIMARY AMENORRHEA

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Etiology

- First and foremost, it is imperative to rule out pregnancy. Additional diagnoses of primary amenorrhea usually result from a genetic or anatomic abnormality.
- The relative prevalence of primary amenorrhea includes *hypergonadotropic hypogonadism* (48.5% of cases), hypogonadotropic hypogonadism (27.8%), and eugonadism (pubertal delay with normal gonadotropins; 23.7%)

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ETIOLOGY

(A). The hypergonadotropic hypogonadism category includes:

1). patients with abnormal sex chromosomes (ie, Turner syndrome), who make up 29.7% of all primary amenorrhea cases, and

2). patients with normal sex chromosomes. The latter group includes both patients who are 46,XX (15.4%) and those who are 46,XY (3.4%).

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ETIOLOGY

(B)- Hypogonadotropic hypogonadism includes the following:

1. Congenital abnormalities
2. Endocrine disorders
3. Tumor
4. Systemic illness (2.6%)
5. Eating disorder (2.3%)

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ETIOLOGY

Congenital abnormalities that can cause hypogonadotropic hypogonadism include the following:

1. Isolated GnRH deficiency (8.3%)
2. Forms of hypopituitarism (2.3%)
3. Congenital central nervous system (CNS) defects (0.8%)
4. Constitutional delay (6%)

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ETIOLOGY

Endocrine disorders that can cause hypogonadotropic hypogonadism include the following:

1. Congenital adrenal hyperplasia (CAH) (0.8%)
2. Cushing syndrome (0.4%)
3. Pseudohypoparathyroidism (0.4%)
4. Hyperprolactinemia (1.9%)

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ETIOLOGY

Tumors that can cause hypogonadotropic hypogonadism include the following:

1. Unclassified pituitary adenoma (0.8%)
2. Craniopharyngioma (1.1%)
3. Unclassified malignant tumor (0.4%)

PRIMARY AMENORRHEA

ETIOLOGY

Eugonadism may result from anatomic abnormalities or intersex disorders.

1- Anatomic abnormalities include congenital absence of the uterus and vagina (CAUV; 16.2%) and cervical atresia (0.4%).

2- Intersex disorders include androgen insensitivity (1.5%), 17-ketoreductase deficiency (0.4%), and inappropriate feedback (5.3%).

World Health Organization classification of anovulation

Remember this classification for Anovulation

WHO class 1: Hypogonadotropic hypogonadal anovulation (hypothalamic amenorrhea)

These women have low or low-normal serum follicle-stimulating hormone (FSH) concentrations and low serum estradiol concentrations due to decreased hypothalamic secretion of gonadotropin-releasing hormone (GnRH) or pituitary unresponsiveness to GnRH.

WHO class 2: Normogonadotropic normoestrogenic anovulation

These women may secrete normal amounts of gonadotropins and estrogens. However, FSH secretion during the follicular phase of the cycle is subnormal. This group includes women with polycystic ovary syndrome (PCOS). Some ovulate occasionally, especially those with oligomenorrhea.

WHO class 3: Hypergonadotropic hypoestrogenic anovulation

The primary causes are premature ovarian failure (absence of ovarian follicles due to early menopause) and ovarian resistance (follicular form).

Hyperprolactinemic anovulation

These women are anovulatory because hyperprolactinemia inhibits gonadotropin and therefore estrogen secretion; they may have regular anovulatory cycles, but most have oligomenorrhea or amenorrhea. Their serum gonadotropin concentrations are usually normal.

CLINICAL APPROACH TO A CASE OF PRIMARY AMENORRHEA

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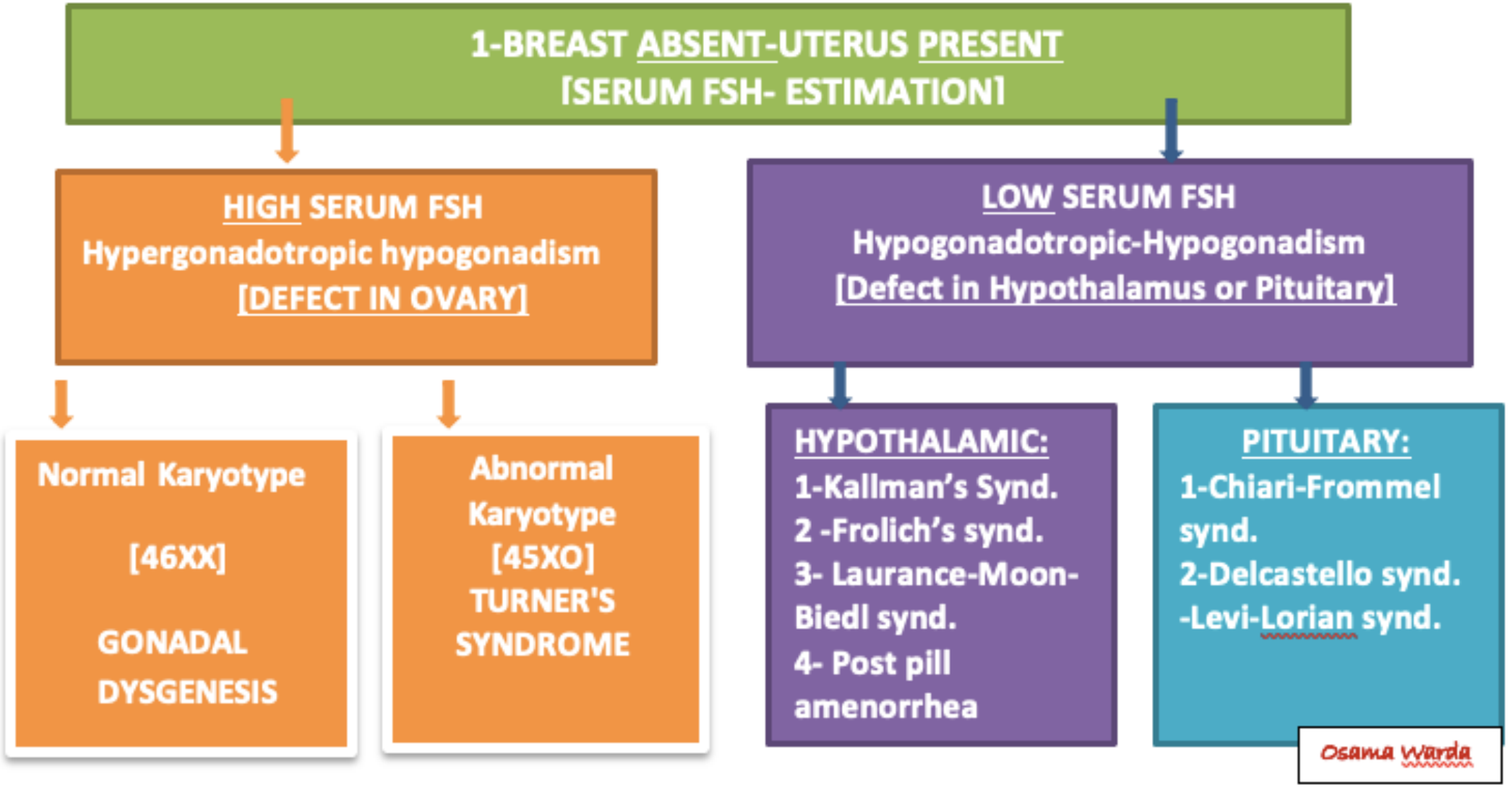
The patient is one of four:

1. **Breast absent- uterus present group [B-/U+]**
2. **Breast developed- uterus absent group [B+/U-].**
3. **Breast absent- uterus absent group [B-/U-].**
4. **Breast developed- uterus present group [B+/U+].**


1-BREAST ABSENT-UTERUS PRESENT
[SERUM FSH- ESTIMATION]
HIGH SERUM FSH
Hypergonadotropic hypogonadism
[DEFECT IN OVARY]
LOW SERUM FSH
Hypogonadotropic-Hypogonadism
[Defect in Hypothalamus or Pituitary]
Normal Karyotype
[46XX]
GONADAL DYSGENESIS
Abnormal Karyotype
[45XO]
TURNER'S SYNDROME
HYPOTHALAMIC:
1-Kallman's Synd.
2 -Frolich's synd.
3- Laurance-Moon-Biedl synd.
4- Post pill amenorrhea
PITUITARY:
1-Chiari-Frommel synd.
2-Delcastello synd.
-Levi-Lorian synd.
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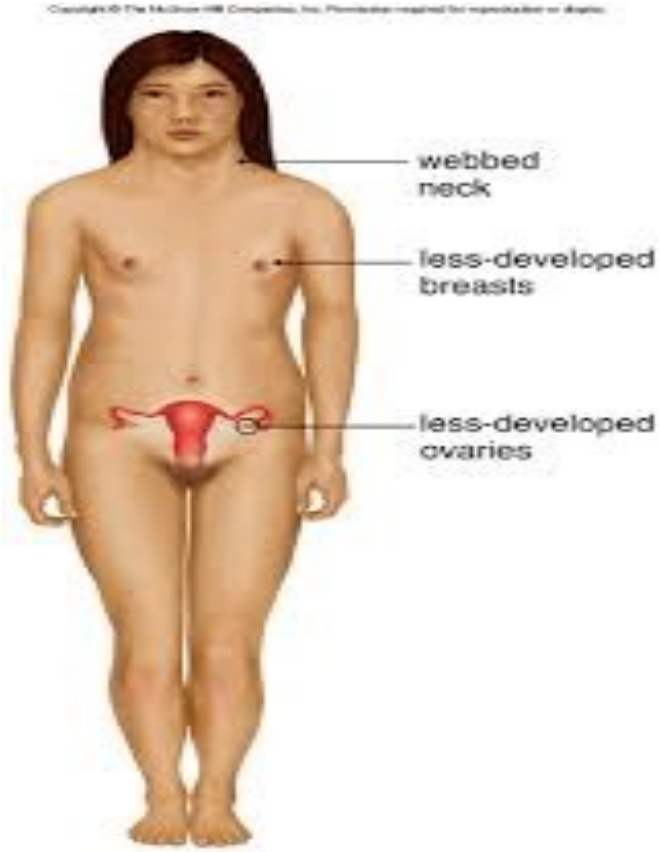
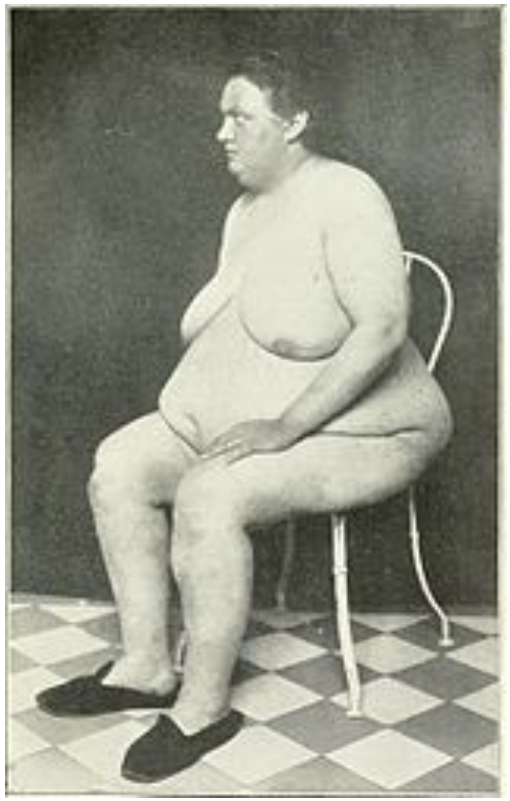
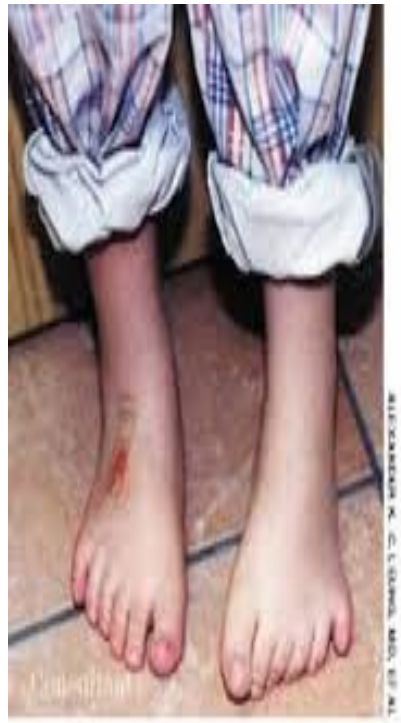
PRIMARY AMENORRHEA



a. A female with Turner (XO) syndrome

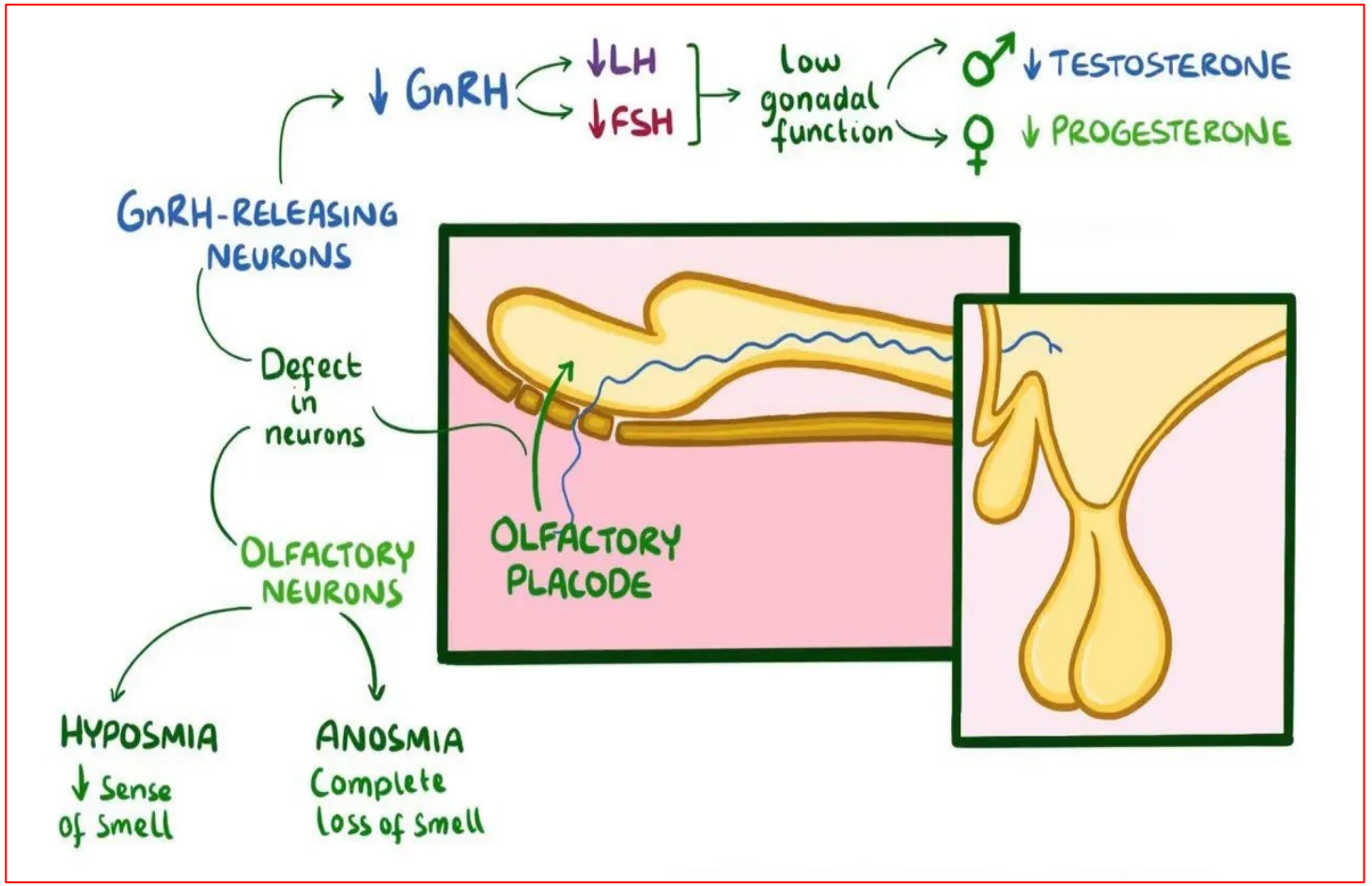


Frohlich syndrome= adepogenital syndrome

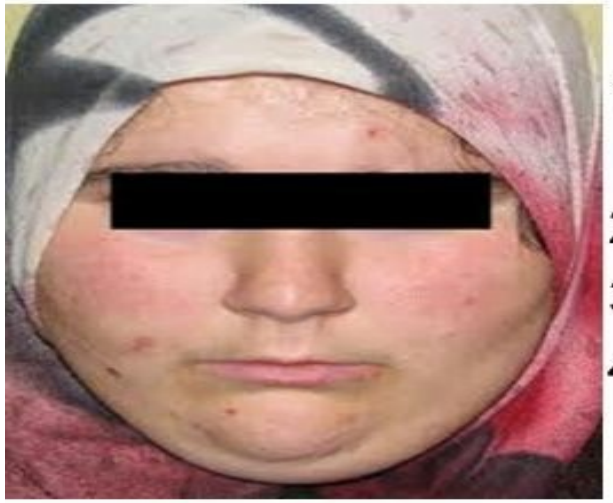


L-M-B-syndrome

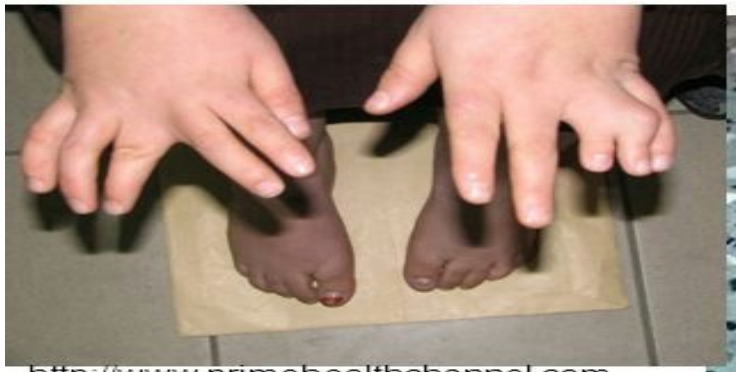
Kallmann's syndrome

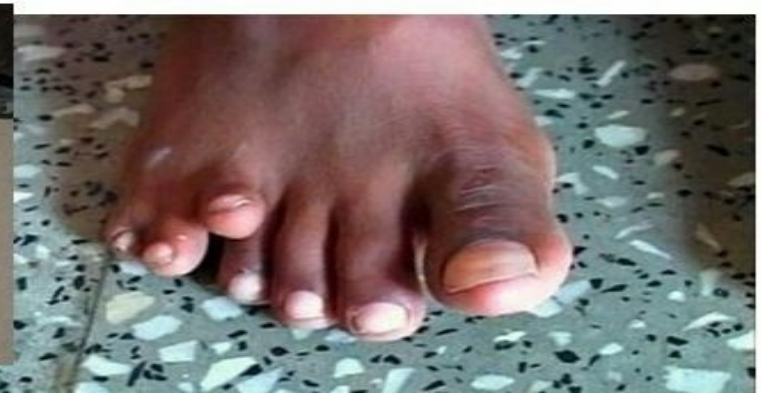


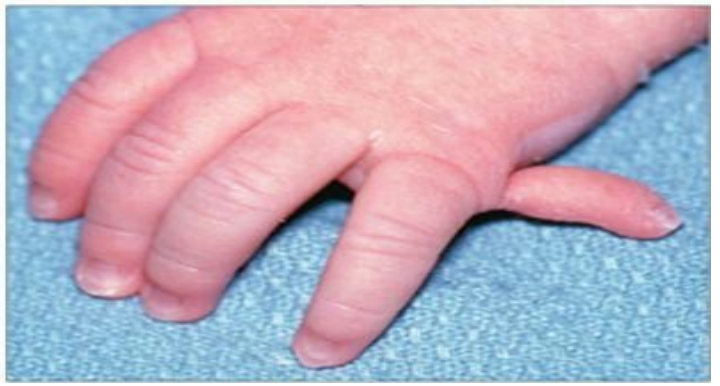
Laurence-Moon-Biedl syndrome or *Laurence-Moon-Biedl-Bardet*



1. Obesity, hypogenitalism like in patients with Babinsky-Frelych's disease.
2. Decreased mental activity or debility.
3. Pigmental retinitis.
4. Bones or inner organs abnormalities (polydactylia, syndactylia and others)







Frohlich syndrome

Cause: Damage of both hypothalamus & pituitary by a tumor.

Clinical picture:

- Diabetes insipidus (due to ⇩ ADH).
- Disturbance of temperature & sleep .
- Increased appetite & Obesity.
- Infantilism (due to ⇩ Gonadotropins)
- Stunted growth & Short stature (due to ⇩ GH).
- Stupid person. (due to ⇩ TSH ⇨ ⇩ Thyroxin).

(Adiposo-Genital Dystrophy)

Chiari –Frommel syndrome

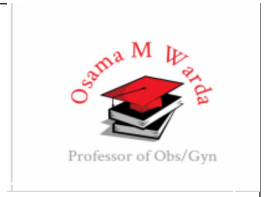
- Persistence of lactation(galactorrhea) & amenorrhea in women who donot nurse after delivery.
- Associated with some genital atrophy
- Due to persistent prolactin secretion without secretion of FSH & LH necessary to produce maturation of new follicles & ovulation.
- Non pregnant ♀ - pituitary tumour -CFS

Ahumada-Del Castillo Syndrome

- Ahumada-Del Castillo syndrome is caused by compression of the pituitary stalk. When this occurs, the pituitary gland is unable to function properly .
- Common signs and symptoms of Ahumada-Del Castillo syndrome include:

1. -Estrogen deficiency
2. -Low urine excretion
3. -Galactorrhea
4. -Amenorrhea
5. Anovulation

2- BREAST DEVELOPED- UTERUS ABSENT



Only in 2 cases; androgen insensitivity syndrome (testicular feminization), and Müllerian agenesis:

Item	Androgen insensitivity	Mullerian agenesis
1- Axillary & pubic hair	Absent	Present
2- Serum testosterone	Male level	Female level
3- Karyotyping *	46XY (most important)	46XX
4- Gonads	Testes (mostly inguinal)	Normal ovaries
5- Fertility	Impossible	Possible via surrogate uterus (she will be the genetic mother)
6- Gonadectomy	Indicated before 25 years age (protect against malignancy)	Contraindicated
7- Inheritance	X-linked	Not hereditary

3-BREAST ABSENT- UTERUS ABSENT

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- This is a very rare condition.

- Karyotype is 46XY (i.e. genitically males)in all.

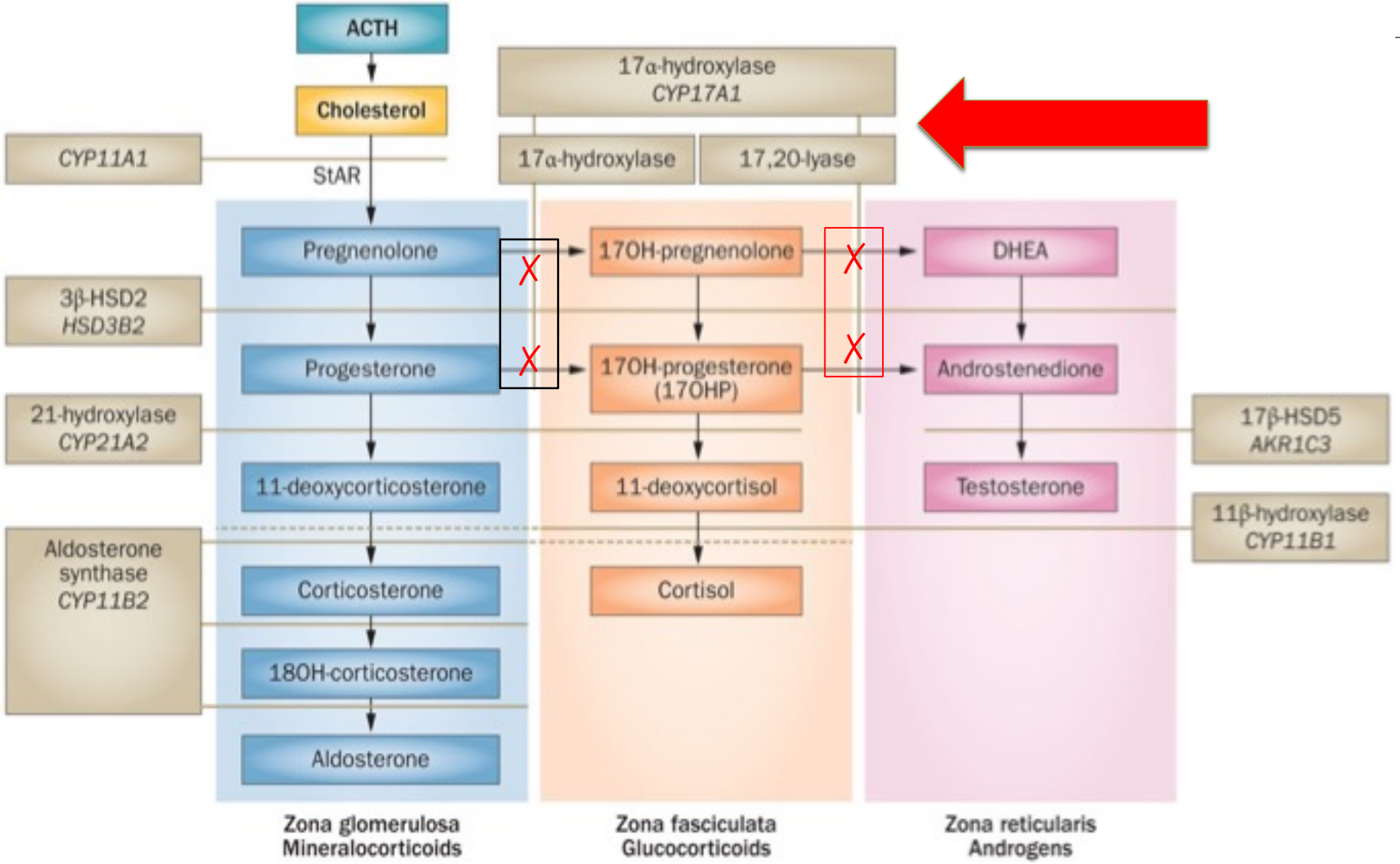
- It is due to enzymatic deficiency such as:

[a]. 17, 20 desmolase deficiency,

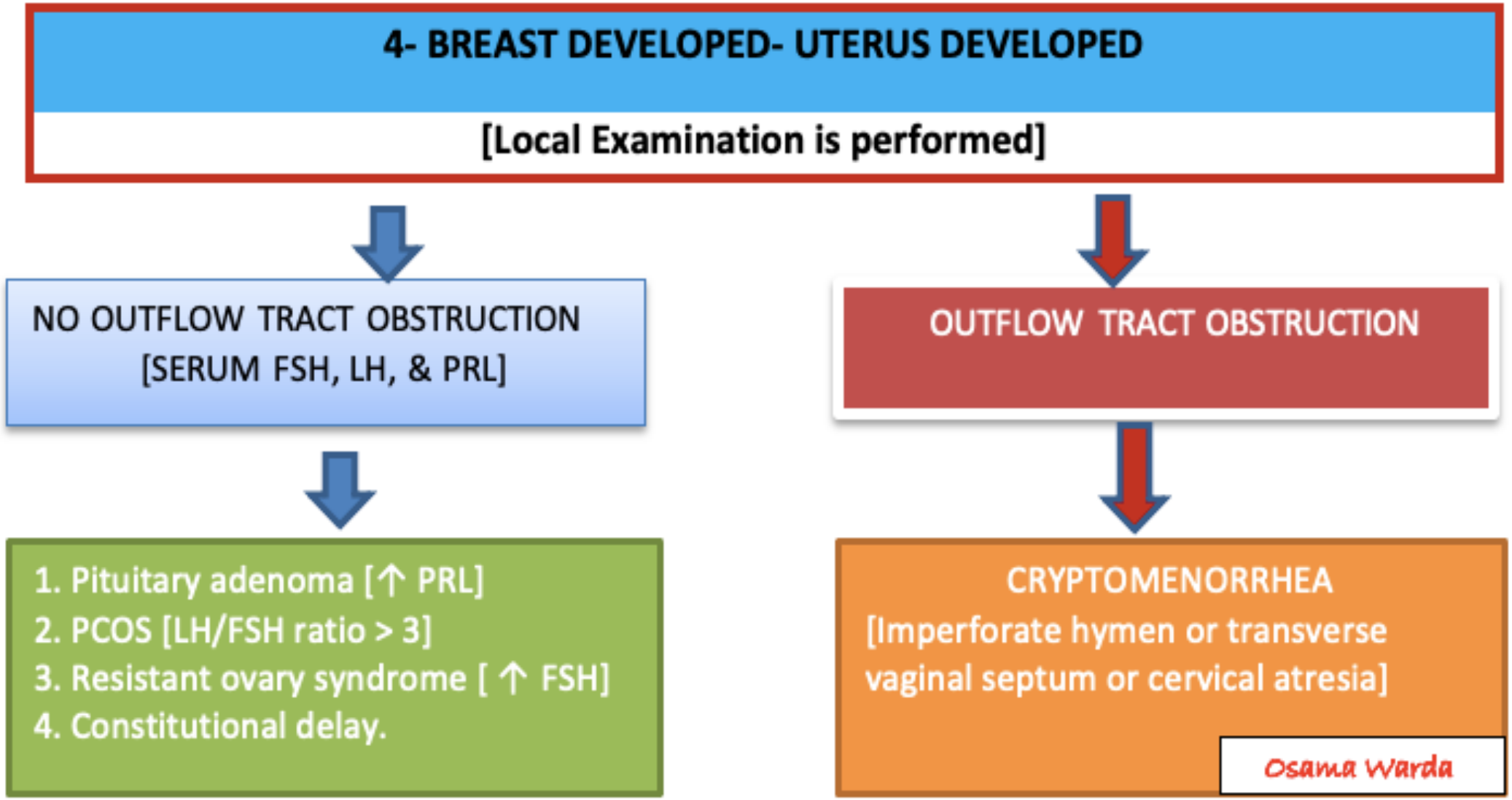
[b]. 17 alpha- hydroxylase deficiency in 46XY individuals, and

[c]. Agonadism.

- Those patients do not respond to exogenous estrogen replacement to help development of secondary sex characters such as breast development, hence the feminine constitution.



Adrenal steroidogenesis


4- BREAST DEVELOPED- UTERUS DEVELOPED
[Local Examination is performed]
NO OUTFLOW TRACT OBSTRUCTION
[SERUM FSH, LH, & PRL]
1. Pituitary adenoma [↑ PRL]
2. PCOS [LH/FSH ratio > 3]
3. Resistant ovary syndrome [↑ FSH]
4. Constitutional delay.
OUTFLOW TRACT OBSTRUCTION
CRYPTOMENORRHEA
[Imperforate hymen or transverse vaginal septum or cervical atresia]
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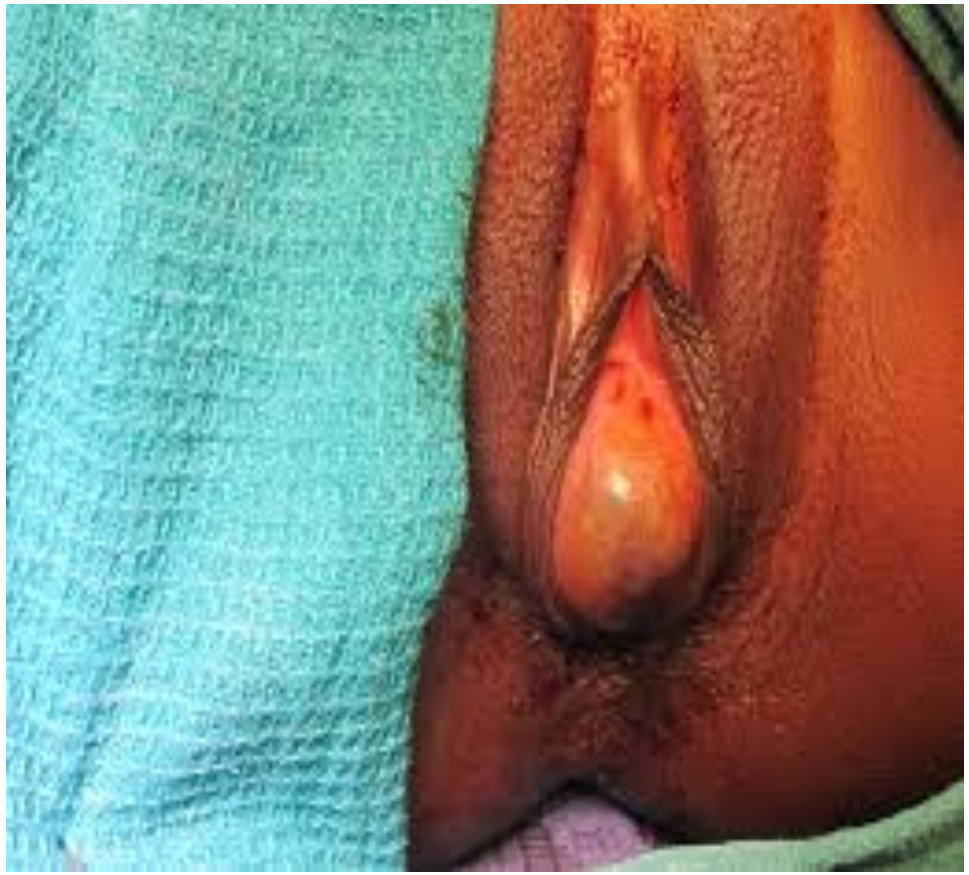
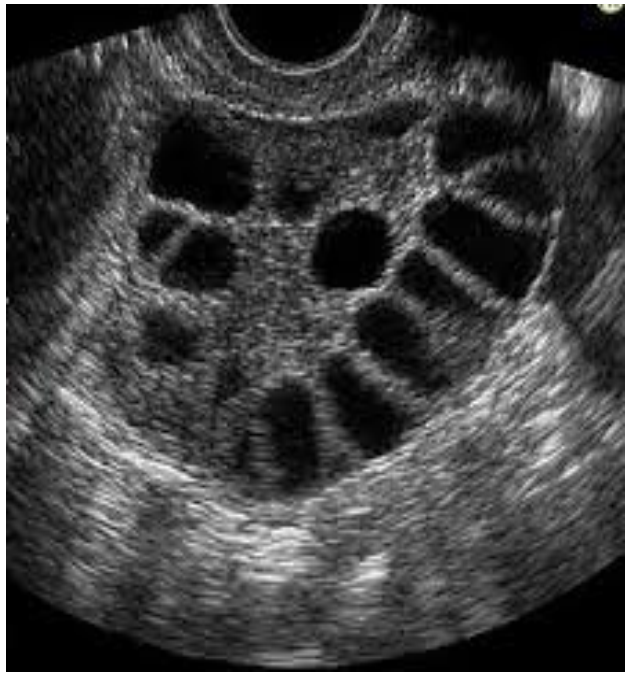
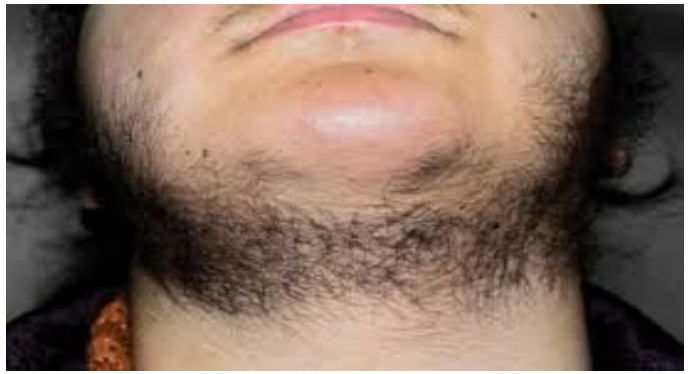


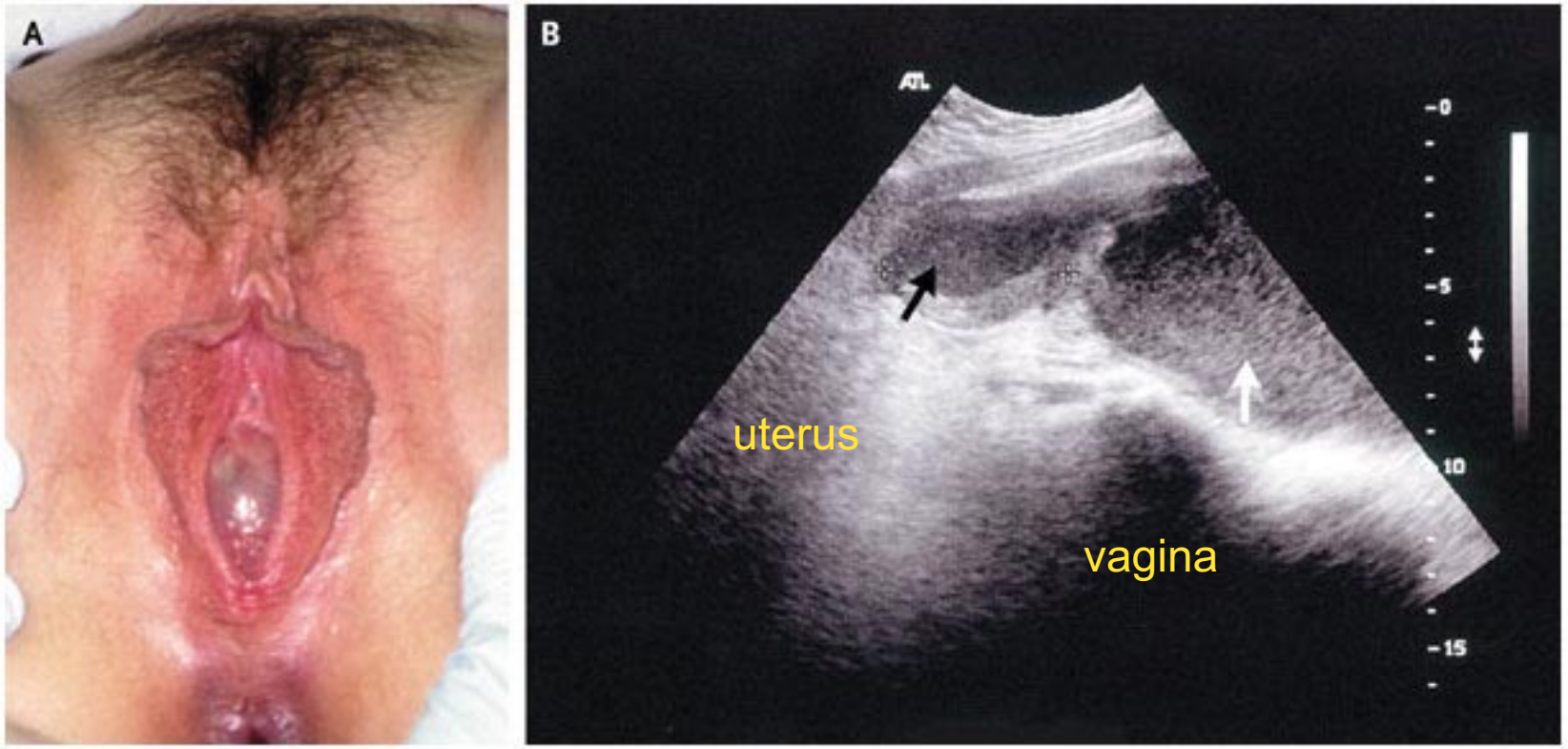
Imprforate hymen



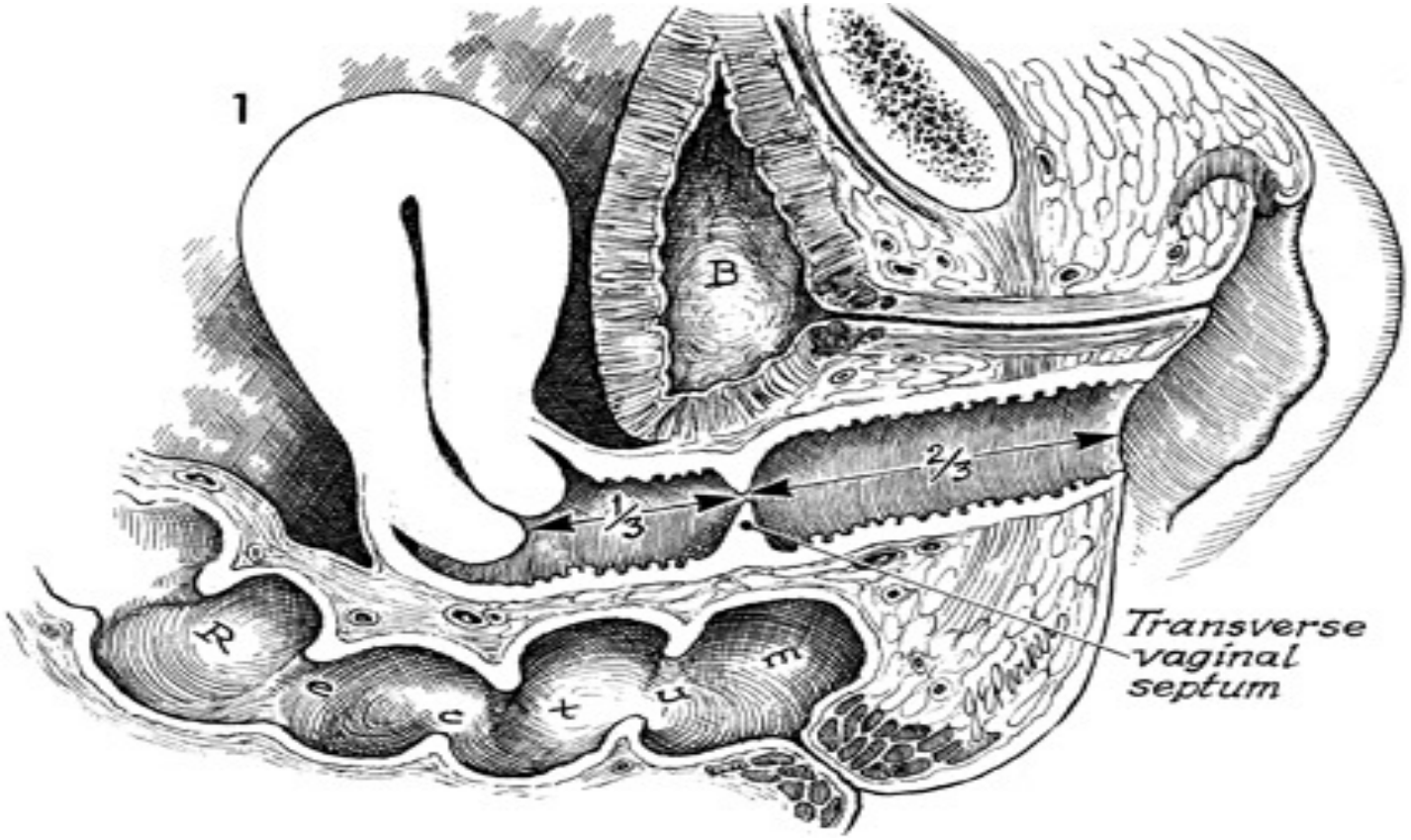


PCOS

Imperforate Hymen



Transverse Vaginal Septum



Summary

Breast	Uterus absent	Uterus present
Absent	17,20 desmolase deficiency	• Turner synd. (45XO)
	17 α hydroxylase deficiency (46XY)	• Gonadal dysgenesis
	Agonadism	• 17 α hydroxylase deficiency (46XX)
		• Hypothalamic failure
		• Pituitary failure
Present	AIS [androgen insensitivity synd.]	• cryptomenorrhea
	Mullerian agenesis	• Hyperprolactinemia, PCOS

SECONDARY AMENORRHEA

Etiology

(A)-Disorders associated with a **low** or **normal** FSH, which account for 66% of cases of secondary amenorrhea, include the following:

1. Weight loss/anorexia
2. Nonspecific hypothalamic
3. Chronic anovulation including PCOS
4. Hypothyroidism
5. Cushing syndrome
6. Pituitary tumor, empty sella, Sheehan syndrome

Etiology

(B). Disorders in which the FSH is **high** (12%) include the following:

1. 46,XX spontaneous POI
2. Premature ovarian failure due to abnormal karyotype (45,X mosaic/ring chromosome)
3. Pure gonadal dysgenesis

Etiology

(C)-Hyperandrogenic states as a cause of secondary amenorrhea (2%) include the following:

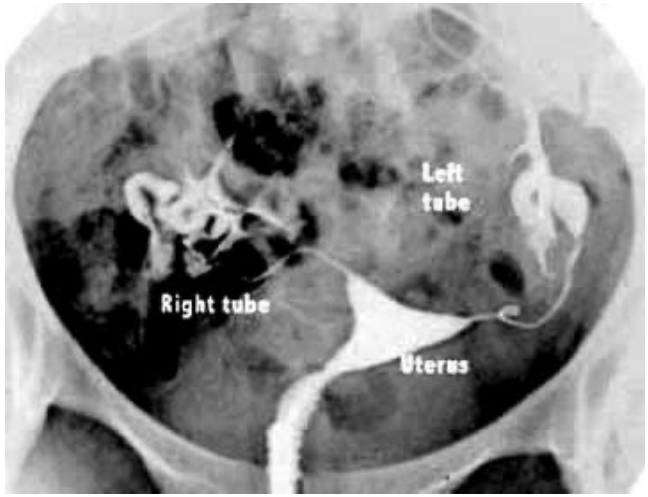
1. Polycystic ovarian syndrome (PCOS)
2. Ovarian tumor
3. Non-classic CAH
4. Undiagnosed

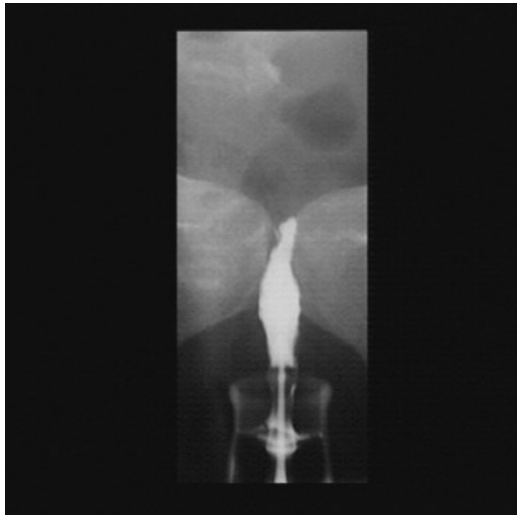
Etiology

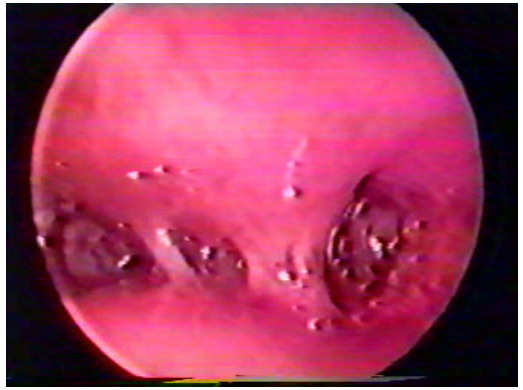
(D)- OTHERS:

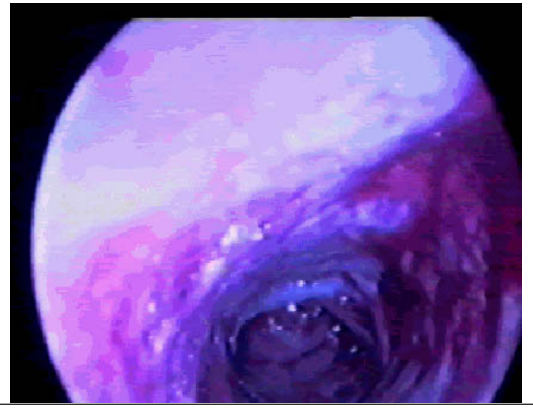
1. Disorders associated with a high prolactin level make up 13% of cases.
2. Anatomic disorders (ie, Asherman syndrome) account for 7%.

Asherman's Syndrome









APPROACH TO A CASE OF SECONDARY AMENORRHEA

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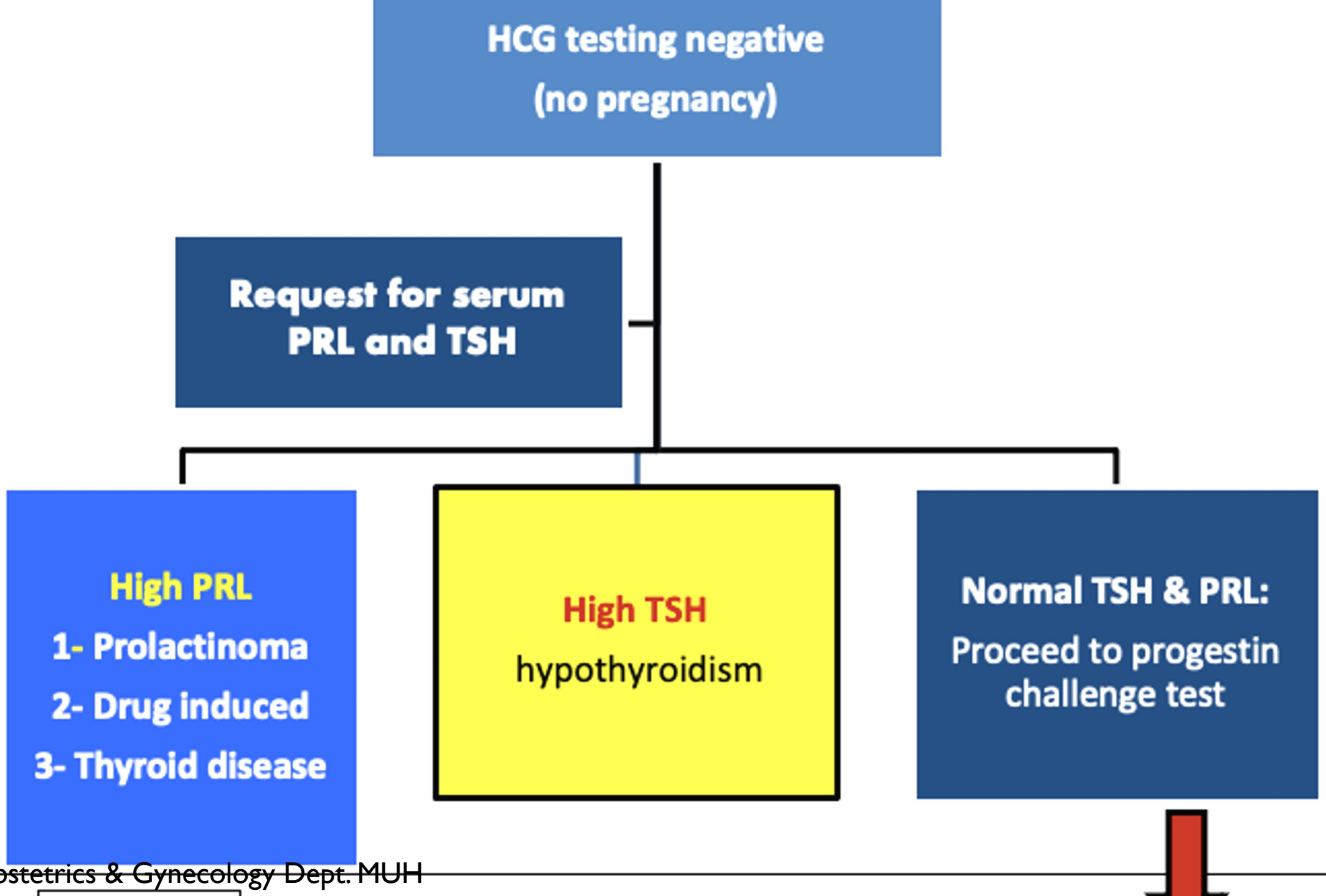
① The 1st step is to exclude pregnancy

② The second step (if not pregnant) is to evaluate Prolactin and TSH→ if abnormal treat accordingly; →

③ If both revealed normal, then

④ test the endometrial responsiveness by progestin withdrawal test as follows…..


HCG testing negative
(no pregnancy)
Request for serum
PRL and TSH
High PRL
1- Prolactinoma
2- Drug induced
3- Thyroid disease
High TSH
hypothyroidism
Normal TSH & PRL:
Proceed to progestin
challenge test

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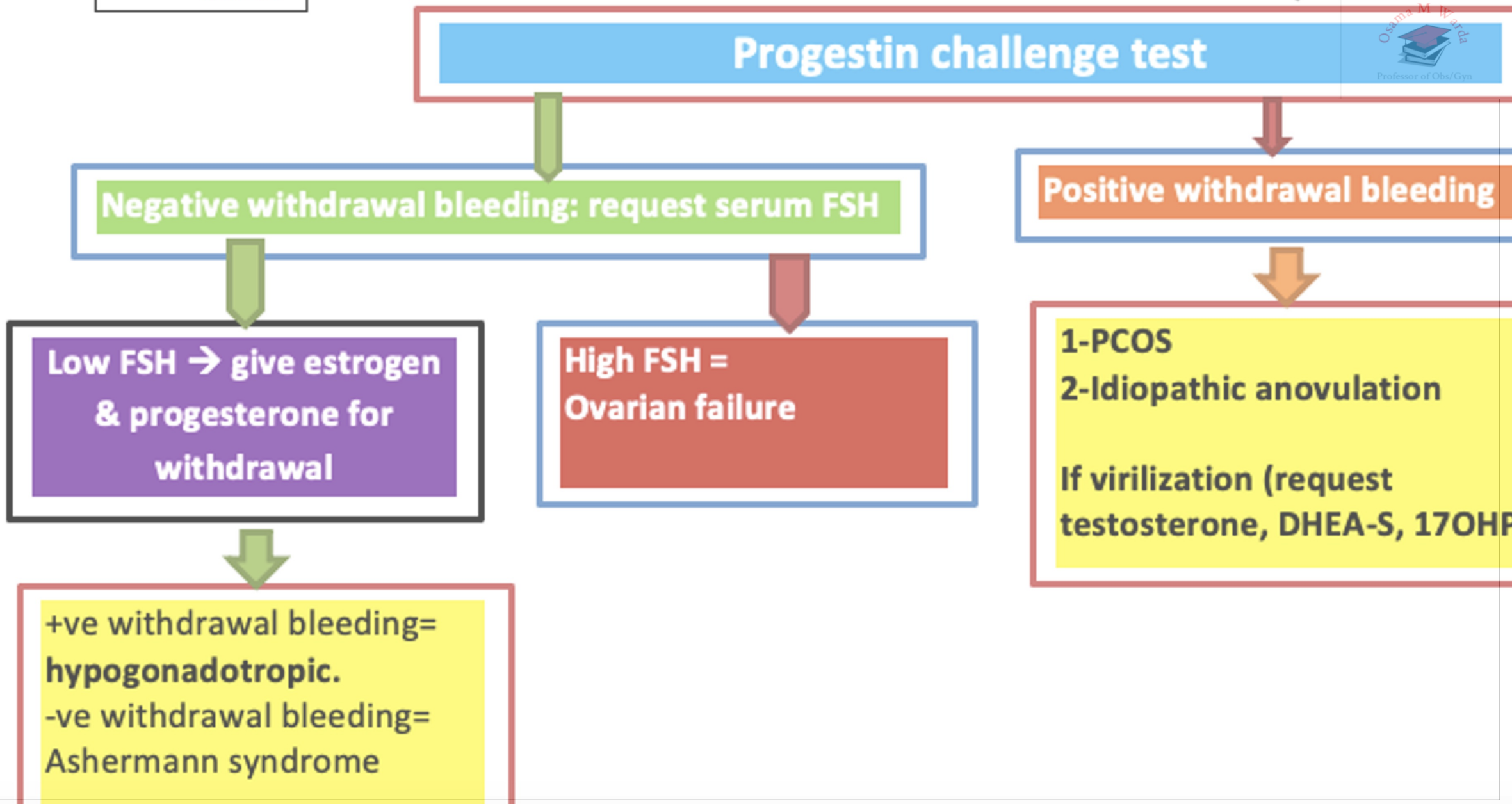
Progestin challenge test
Negative withdrawal bleeding: request serum FSH
Positive withdrawal bleeding
Low FSH → give estrogen & progesterone for withdrawal
High FSH = Ovarian failure
1-PCOS
2-Idiopathic anovulation
If virilization (request testosterone, DHEA-S, 17OHP
+ve withdrawal bleeding= hypogonadotropic.
-ve withdrawal bleeding= Ashermann syndrome

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Case Senarios

Case 1

- **A 20 years old virgin presented with primary amenorrhea, on examination the breast was Tanner's stage 5 (= well developed), the uterus was palpated of average normal size by combined recto-abdominal examination .**
- **Questions**:
- ***A- Three possible causes.***
- ***B- Two important hormone estimations for diagnosis.***

Case 2

A 20 years old lady with primary amenorrhea, well-developed breast and P/R examination revealed absence of the uterus;

Questions:

A- Two Differential diagnoses

B- Three important investigations to confirm diagnosis

CASE -3

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History

A 32-year-old woman complains that she has not had a period for 3 months. Four home pregnancy tests have all been negative. She started her periods at the age of 15 years and until 30 years she had a normal 27-day cycle. She had one daughter by normal delivery 2 years ago, following which she breast-fed for 6 months. After that she had normal cycles again for several months and then her periods stopped abruptly. She was using the progesterone only pill for contraception while she was breast-feeding and stopped 6 months ago as she is keen to have another child. She reports symptoms of dryness during intercourse and has experienced sweating episodes at night as well as episodes of feeling extremely hot at any time of day. There is no relevant gynaecological history. The only medical history of note is that she has been hypothyroid for 10 years and takes thyroxine 100 μg per day. She does not take any alcohol, smoke or use recreational drugs.

Examination

Examination findings are unremarkable

CASE -3

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Examination

Examination findings are unremarkable

INVESTIGATIONS

		Normal range
Haemoglobin	12.2 g/dL	11.7–15.7 g/dL
White cell count	5.1 × 10^9/L	3.5–11 × 10^9/L
Platelets	203 × 10^9/L	150–440 × 10^9/L
Thyroid-stimulating hormone	3.6 mu/L	0.5–7 mu/L
Free thyroxine	28 pmol/L	11–23 pmol/L
Follicle-stimulating hormone	45 IU/L	Day 2–5 1–11 IU/L
Luteinizing hormone	30 IU/L	Day 2–5 0.5–14.5 IU/L
Prolactin	401 mu/L	90–520 mu/L
Oestradiol	87 pmol/L	Day 2–5 70–510 pmol/L
Testosterone	2.3 nmol/L	0.8–3.1 nmol/L

Questions

- What is the diagnosis?
- What further investigations should be performed?
- What are the important points in the management of this woman?

ANSWER 3

This woman has symptoms of amenorrhoea as well as hypo-oestrogenic vasomotor symptoms and vaginal dryness. The diagnosis is of premature menopause, confirmed by the very high gonadotrophin levels. High levels occur because the ovary is resistant to the effects of gonadotrophins, and negative feedback to the hypothalamus and pituitary causes increasing secretion to try and stimulate the ovary. Sheehan's syndrome (pituitary necrosis after postpartum haemorrhage) would also cause amenorrhoea but would have inhibited breast-feeding and all menstruation since delivery.

Premature menopause (before the age of 40 years) occurs in 1 per cent of women and has significant physical and psychological consequences. It may be idiopathic but a familial tendency is common. In some cases it is an autoimmune condition (associated with hypothyroidism in this case). Disorders of the X chromosome can also be associated.

Effects of premature menopause

- *Hypo-oestrogenic effects:*
  - vaginal dryness
  - vasomotor symptoms (hot flushes, night sweats)
  - osteoporosis
  - increased cardiovascular risk
- *Psychological and social effects:*
  - infertility
  - feeling of inadequacy as a woman
  - feelings of premature ageing and need to take hormone-replacement therapy (HRT)
  - impact on relationships

Further investigations

Repeat gonadotrophin level is required to confirm the result and exclude a midcycle gonadotrophin surge or fluctuating gonadotrophins. Bone scan is necessary for baseline bone density and to help in monitoring the effects of hormone replacement. Chromosomal analysis identifies the rare cases of premature menopause due to fragile X syndrome or Turner's syndrome mosaicism.

Management

Osteoporosis may be prevented with oestrogen replacement, with progesterone protection of the uterus. Traditional HRT preparations or the combined oral contraceptive pill are effective, the latter making women feel more 'normal', with a monthly withdrawal bleed and a 'young person's' medication.

Her options are adoption, accepting childlessness and in vitro fertilization (IVF) with donor oocytes.

Occasionally premature menopause is a fluctuating condition (resistant ovary syndrome) whereby the ovaries may function intermittently. Contraception should therefore be used if it would be undesirable to become pregnant.

Patient support organizations are a good source for women experiencing such an unexpected and stigmatizing diagnosis.

KEY POINTS

- Premature menopause (<40 years) occurs in 1 per cent of women.
- Oestrogen replacement is essential for bone and cardiovascular protection.
- It may be possible to conceive with IVF using donor oocytes.

Thank You