Amenorrhea

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Amenorrhea

Amenorrhea: literally, amenorrhea means '*without menses*'. By definition, amenorrhea is the absence of menstruation. Amenorrhea may be primary or secondary.

- ***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

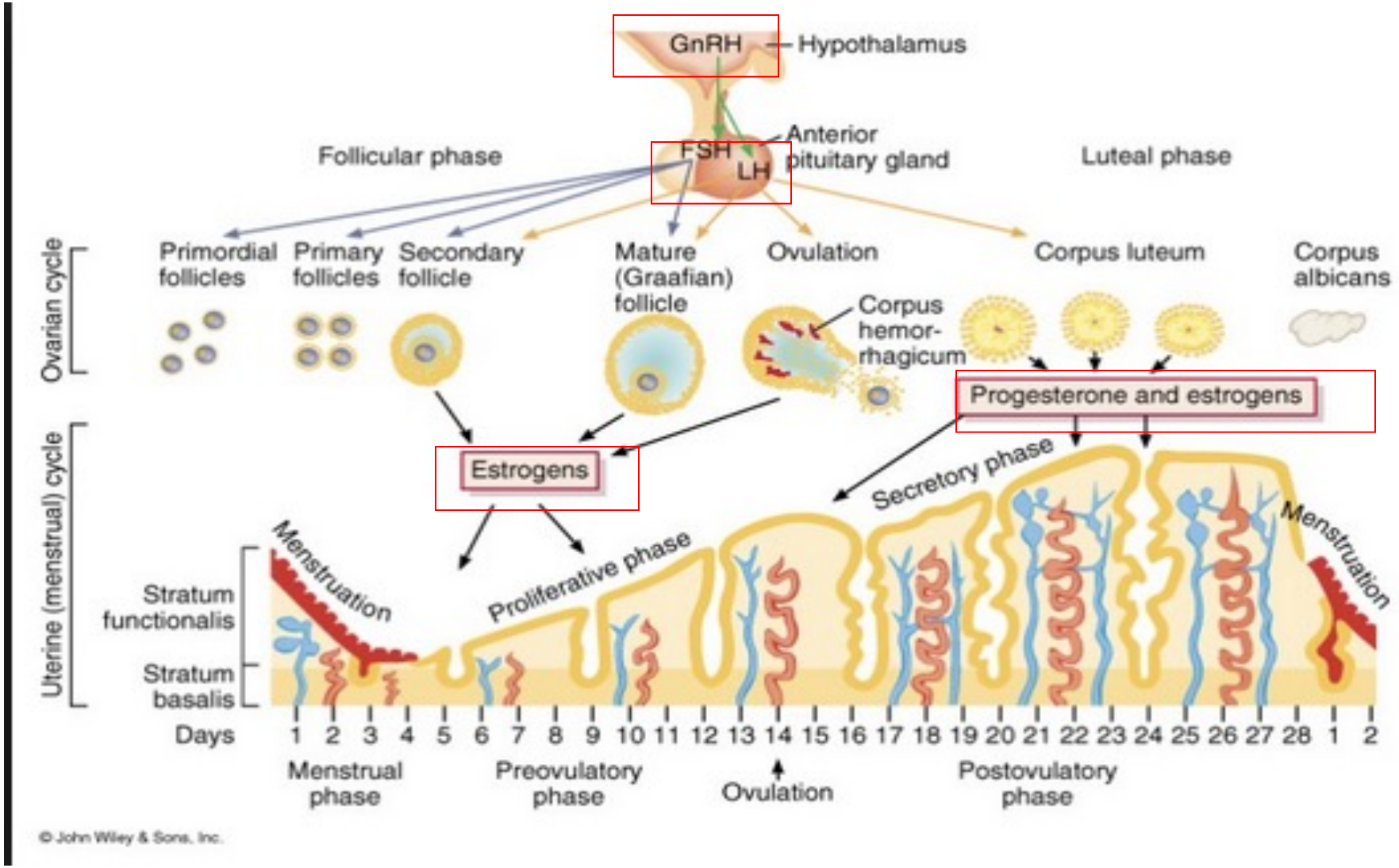
(2) no menstruation by the age of 16 with or without growth or development of secondary sex characters.

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

Physiology of Menstruation

- Hypothalamo-pituitary-ovarian-uterine axis
- Gonadotropin releasing hormone (GnRH)
- Gonadotropins (FSH-LH)- Prolactin H.
- Estradiole (E2), Progesterone (P4), ERs, PRs
- Secondary sex characters; breast,……
- The outflow tract.

PHYSIOLOGY


GnRH
Hypothalamus
Anterior pituitary gland
FSH
LH
Follicular phase
Luteal phase
Ovarian cycle
Primordial follicles
Primary follicles
Secondary follicle
Mature (Graafian) follicle
Ovulation
Corpus hemor-rhagicum
Corpus luteum
Corpus albicans
Progesterone and estrogens
Estrogens
Uterine (menstrual) cycle
Menstruation
Proliferative phase
Secretory phase
Menstruation
Stratum functionalis
Stratum basalis
Days
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 1 2
Menstrual phase
Preovulatory phase
Ovulation
Postovulatory phase
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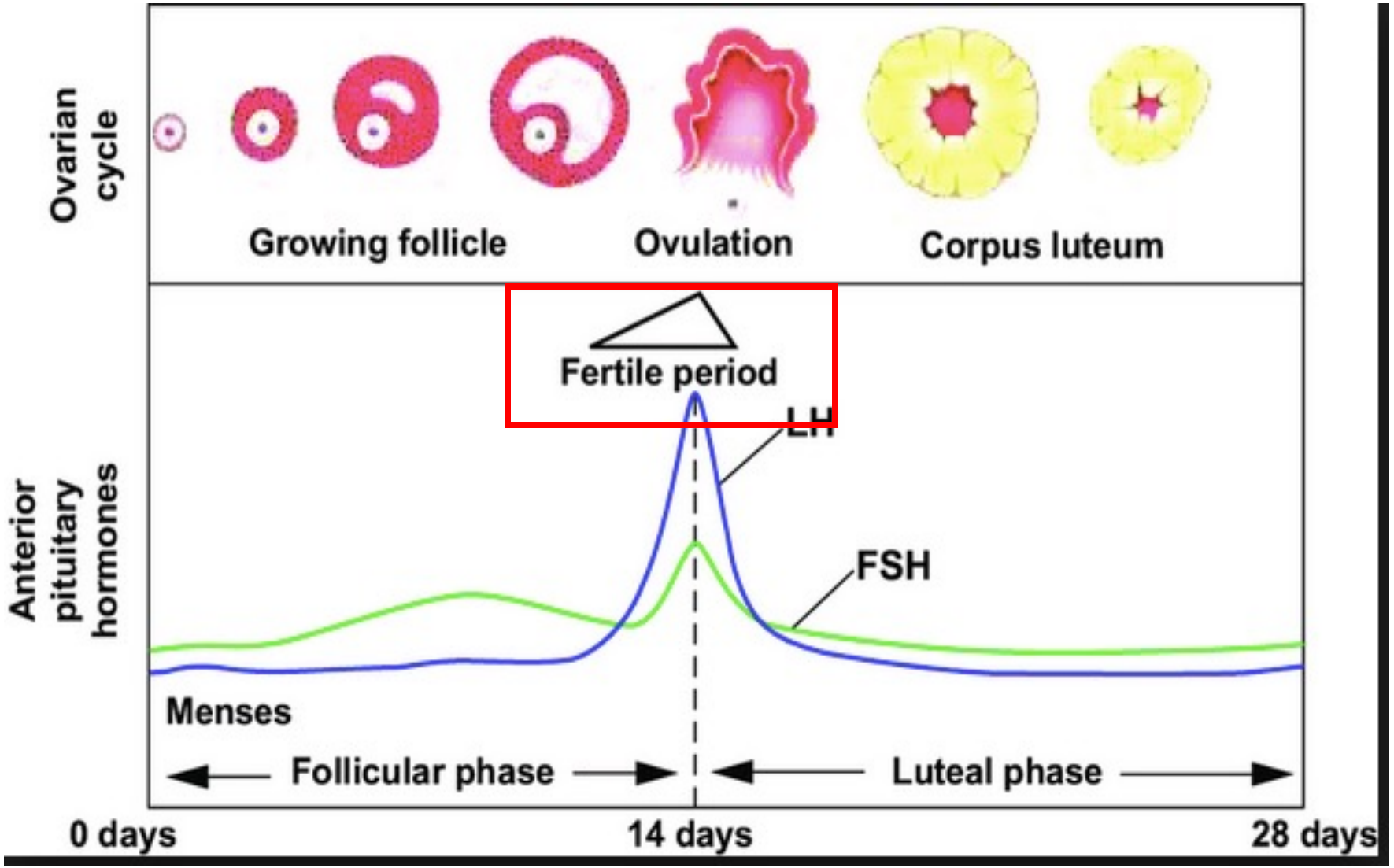
PHYSIOLOGY


Ovarian cycle
Growing follicle
Ovulation
Corpus luteum
Fertile period
LH
FSH
Anterior pituitary hormones
Menses
Follicular phase
Luteal phase
0 days
14 days
28 days

Physiology

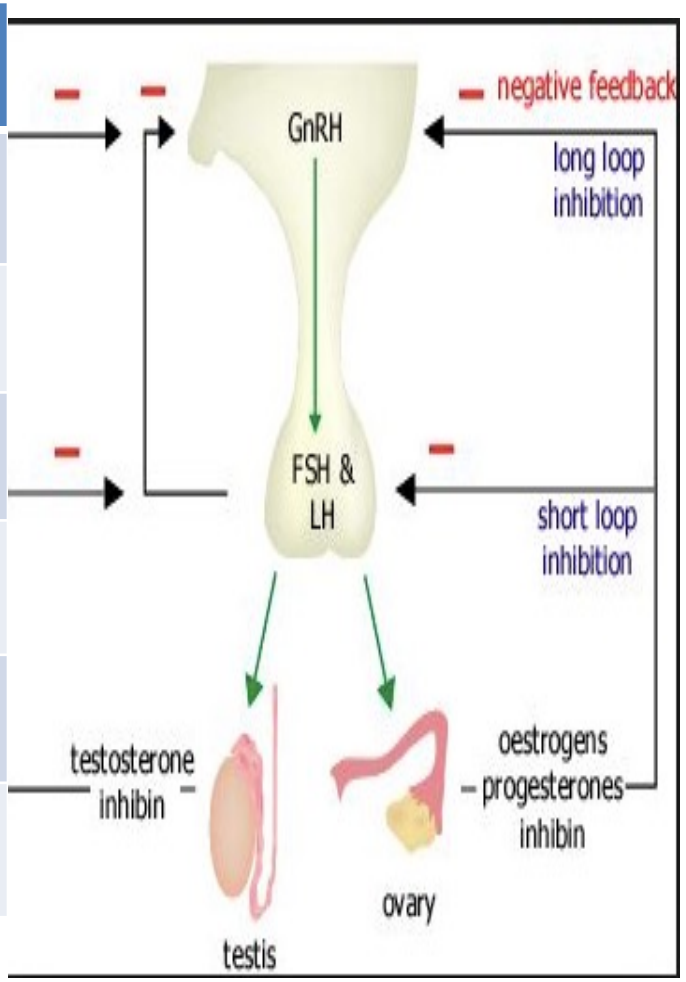
- Development of the breast and feminine constitution depends on E_2 secreted by the granulosa cells of the developing ovarian follicles. E_2 exerts its action via estrogen receptors in the target organ.

- 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 Causes

The cause	%
1-Chromosomal abnormalities (gonadal dysgenesis):	50%
2-hypothalamic hypogonadism	20%
3-Müllerian agenesis:	15%
4-transverse vaginal septum/imperforate hymen	5%
5-pituitary disease	5%
6- others (androgen insensitivity, CAH, PCOS):	5%



Primary Amenorrhea: Causes(detailed)

A. Hypothalamic/pituitary

1. **Hyper/hypothyroidism**
2. **Functional hypothalamic amenorrhea**: abnormal GnRH secretion by hypothalamus →abnormal LH/FSH secretion
   - Very common
   - Normal FSH levels, low E2
   - Can be caused by extreme wt loss/gain, excessive exercise, stress but usually unknown etiology
3. **Congenital GnRH deficiency** (rare)
   - When associated with anosmia = Kallmann's syndrome
4. **Constitutional pubertal delay**
   - Delayed adrenarche and gonadarche
   - NORMAL pubertal development, just at later age
5. **Hyperprolactinemia**
   - Galactorrhea
   - Adenomas are usual cause
6. **Other infiltrative diseases of hypothalamus/pituitary**
   - Consider if associated with primary hypogonadotropic hypogonadism, visual field defects, headaches, known infiltrative disease such as sarcoidosis or hemochromatosis
   - Diagnose by MRI

Primary Amenorrhea: Causes(detailed)

B. Ovarian causes

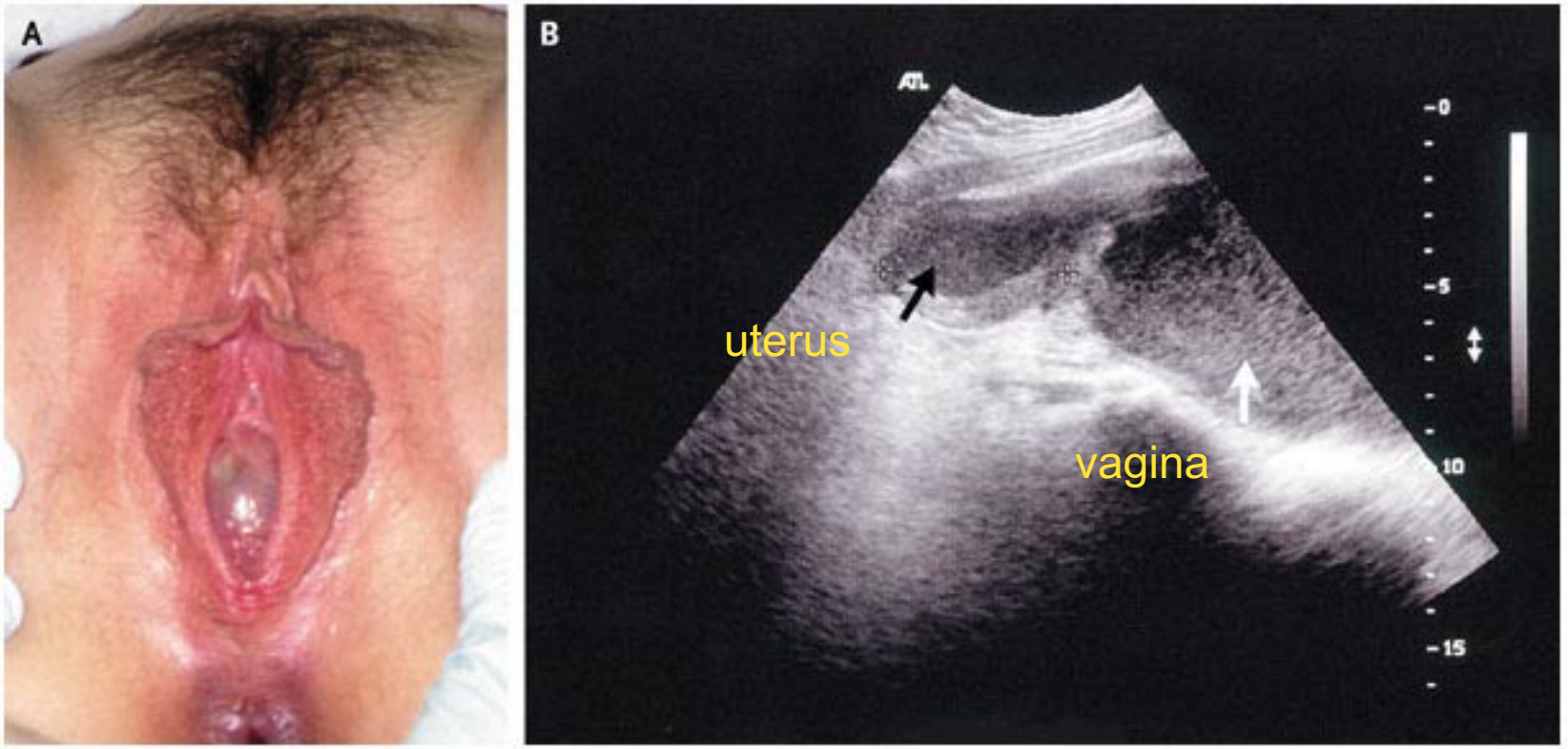
1. **Gonadal dysgenesis →** most common cause!
   - Elevated FSH
   - 45X (most common), 46XX, 46XY (complete =Swyer's syndrome, or incomplete)→rare
2. **Turner syndrome (= 45X0)**
   - External female genetalia, uterus and tubes develop normally until puberty
   - Estrogen and cyclic progesterone supplementation at puberty
   - Growth hormone supplementation
3. **PCOS**
   - Usually delayed menarche with irregular cycles not usually primary amenorrhea
4. **Other causes of ovarian failure:** autoimmune oophoritis, chemo/radiation, fragile X premutation carriers (generally secondary amenorrhea)

Primary Amenorrhea: Causes(detailed)

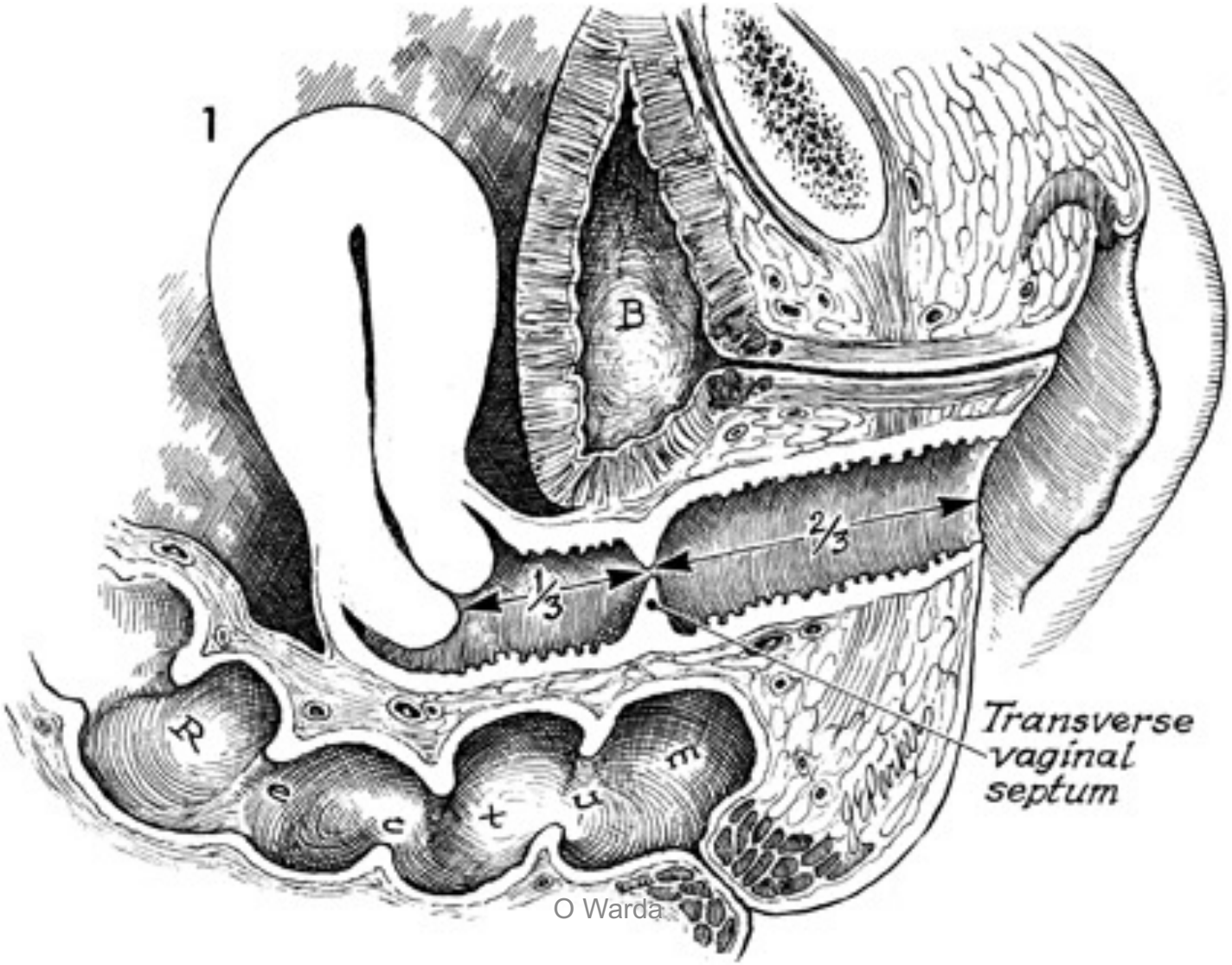
C. Anatomical causes

1. **Imperforate hymen**
   - Cyclic pelvic pain
   - Perirectal mass (hematocolpos)
2. **Transverse vaginal septum** (between hymeneal ring and cervix)
3. **Vaginal agenesis** = Mayer-Rokitansky-Kuster-Hauser (MRKH) Syndrome
   - Congenital absence of vagina with variable uterine development
   - Agenesis/hypoplasia of mullerian system
   - Unknown etiology
   - Differentiate from androgen insensitivity by normal testosterone in MRKH, and definitely by karyotyping

Imperforate Hymen



Transverse Vaginal Septum



Primary Amenorrhea: Causes(detailed)

D. Receptors/enzymes

1. **Androgen Insensitivity**
   - X-linked recessive
   - 46XY looks like normal external phenotypic female
     - Testes palpable in labia/inguinal area
     - Testes make Mullerian inhibiting substance (MIS)
       - » Regression of tubes, uterus, upper 1/3 of vagina
     - At puberty: breasts develop but absence of pubic/axillary hair
   - Defect in androgen receptor
   - High serum testosterone (normal range for men)
   - Testes should be removed after puberty due to risk of testicular cancer after age 25
2. **5-α-reductase deficiency** (can't convert testosterone to more active DHT)
   - 46XY
   - Phenotypically female or ambiguous genitalia (DHT needed for penile growth)
   - Virilization at puberty (normal increase in testosterone secretion)
     - Testosterone (not DHA) stimulates normal hair growth, muscle mass, voice deepening
3. **17-α-hydroxylase deficiency - rare**
   - Decreased cortisol and adrenal/gonadal sex steroid secretion
   - Phenotypic females or ambiguous genitalia
   - Hypertension (mineralocorticoid excess)

Primary Amenorrhea: Causes(detailed)

D. Enzymes, (continued…)

4- Vanishing testes syndrome

- 46XY, gonads fail to develop
- Variable phenotype depending on when in development failure occurs
- Elevated FSH and LH
- Remove testes due to risk of gonadoblastoma/dysgerminoma in 30%

5- Absent testis determining factor = Ullrich-Turner Syndrome

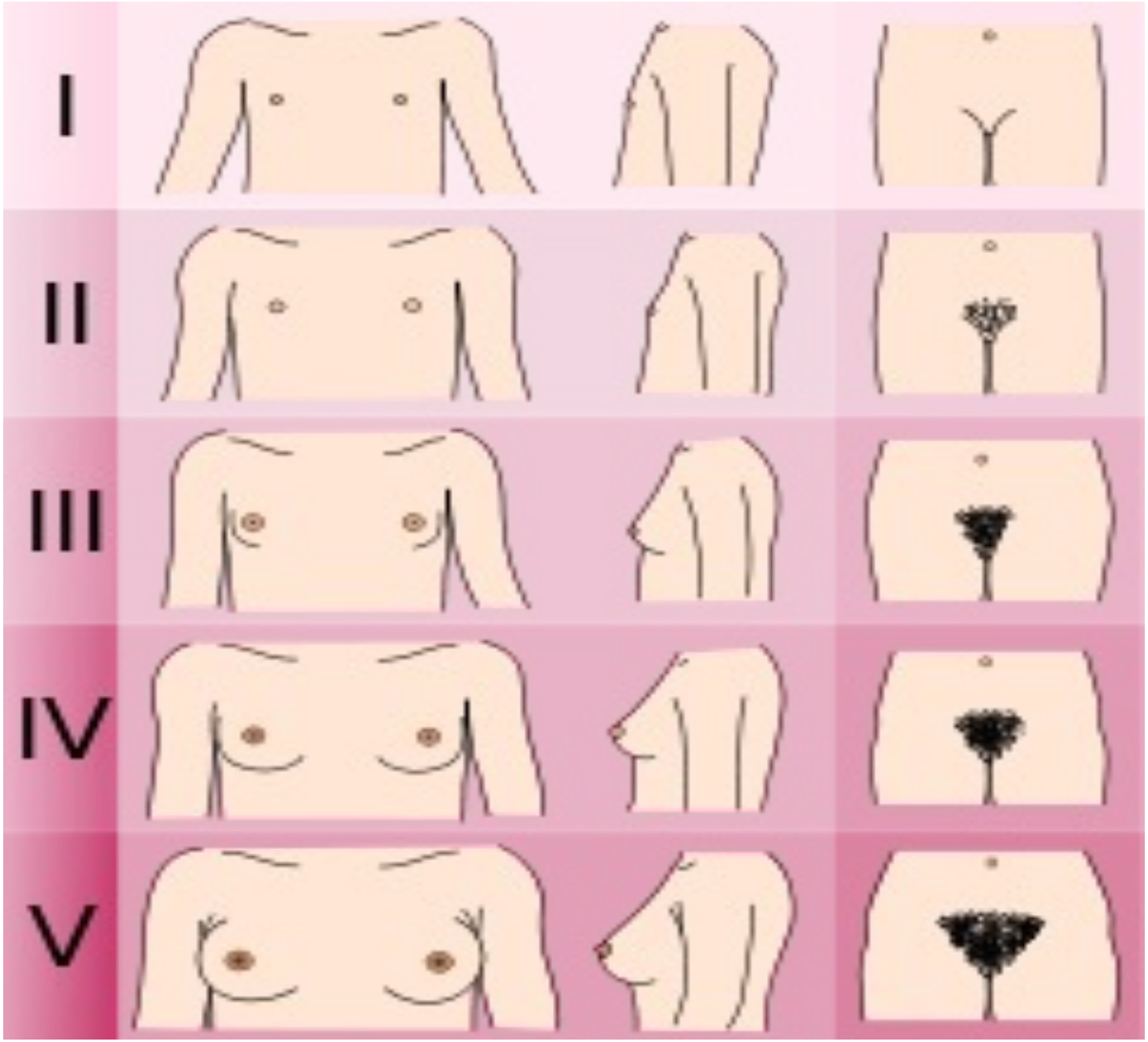
- Deletion/mutation of testis determining factor on Y chromosome (no MIS or testosterone)
- Female internal and external genitalia

Diagnosis: History

- Other stages of puberty reached?
  - Lack of any pubertal development suggests ovarian/pituitary cause
- Family history?
- Short compared to other family members?
- Neonatal/childhood health?
- Symptoms of virilization?
- Recent stress/weight change/exercise?
- Drugs? (heroin/methadone can affect hypothalamus)
- Galactorrhea? **(antipsychotics and reglan can cause hyperprolactinemia)**
- Headaches, vision problems, fatigue, polyuria, polydipsia? **(hypothalamic/pituitary disorders)**

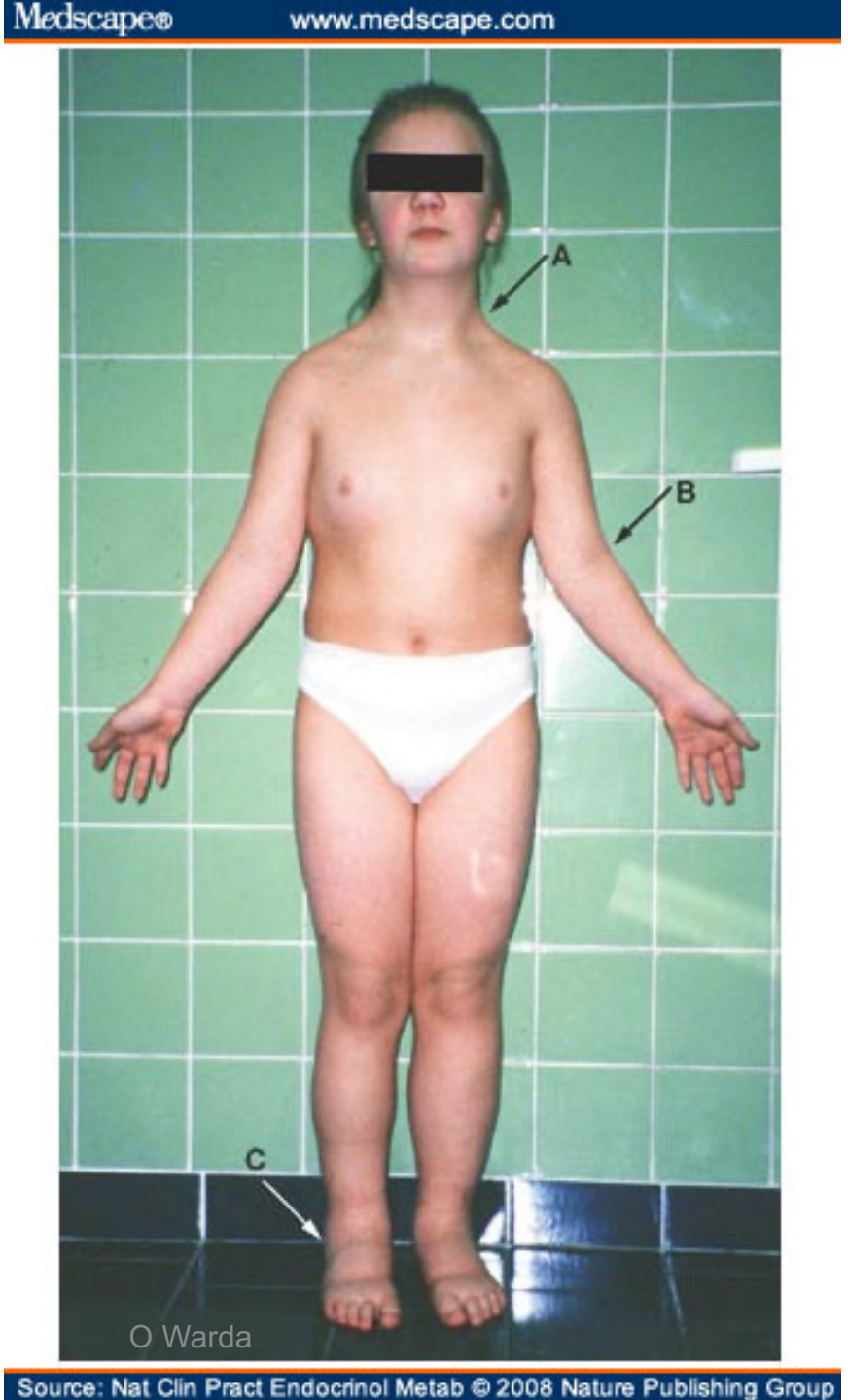
Diagnosis: Physical Examination

- Height, weight, arm span, growth chart
- Blood pressure
  - Turner Syndrome: co-arctation of aorta
  - Adrenal issues
- Breast development? (Tanner staging)
  - Marker of estrogen action/ovary function
- Genital exam
  - Clitoral size - Tanner staging of pubertal hair
  - Hymen - Vaginal depth
  - Vaginal or rectal exam to eval internal organs
- Skin: hirsutism, acne, striae, increased pigmentation, vitiligo
- Features of Turner Syndrome: low hair line, web neck, shield chest, widely spaced nipples



Tanner staging

Turner Syndrome



Diagnosis…

- **Uterus absent**
  - Karyotype, serum testosterone
  - Mullerian anomalies: 46XX with normal testosterone
  - Androgen insensitivity: 46XY with male testosterone levels (distinguish from 5-alpha-reductase defined by virilization at puberty).

Diagnosis

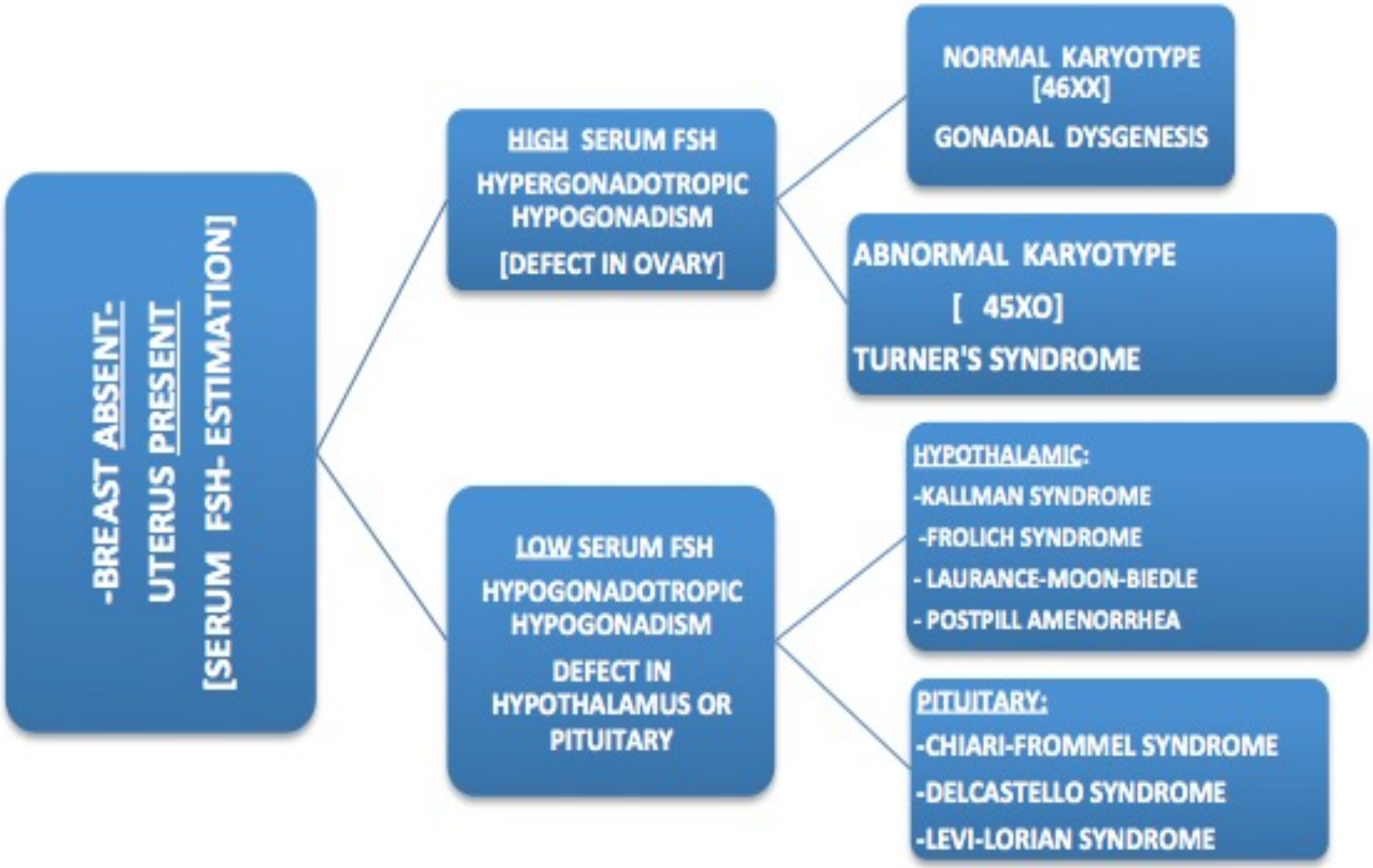
- **Uterus present :**
  - Ultrasound, rarely MRI
  - Cyclic pelvic pain: may have obstructed outflow tract (vaginal septum or imperforate hymen) that can be detected on exam or ultrasound
- **Uterus present, no other anatomic issue**
  - B-HCG to exclude pregnancy
  - FSH

Diagnosis

SERUM FSH LEVEL

- **If high: indicative of primary ovarian failure**
  - Karyotype
    - Turners (46X0) or presence Y chromosome
    - Remove testes if Y chromosome present
  - Other workup based on rest of history/exam and suspected cause of ovarian failure
  - Don't forget evaluation for associated diagnoses (ie: other autoimmune disorders in autoimmune oophoritis or heart disease/HTN/hearing loss in Turners)
- **Low/normal FSH: suggests functional hypothalamic amenorrhea, GnRH defeciency, hypothal/pituitary issues**
  - Cranial MRI to evaluate for infiltrative disease/adenoma
  - Prolactin, TSH
  - Testosterone and DHEA-S if signs of hyperandrogenism
- **Normal FSH with normal breasts and uterus**
  - Workup should focus on causes of secondary amenorrhea

1- BREAST ABSENT- UTERUS PRESENT



2- BREAST DEVELOPED- UTERUS ABSENT

This condition is found only in 2 conditions, androgen insensitivity (=testicular feminization syndrome), and müllerian agenesis; the difference in both conditions are listed in [table 3-1]

Table [3-1]: differences between androgen insensitivity syndrome & mullerian agenesis

Item	Androgen insensitivity	Mullerian agenesis
1- Axillary & pubic hair	Absent	Present
2- Serum testosterone	Male level	Female level
3- Karyotyping *	46XY	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 heriditary

* The most important differentiating point is karyotyping.

3-BREAST ABSENT- UTERUS ABSENT

- 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,

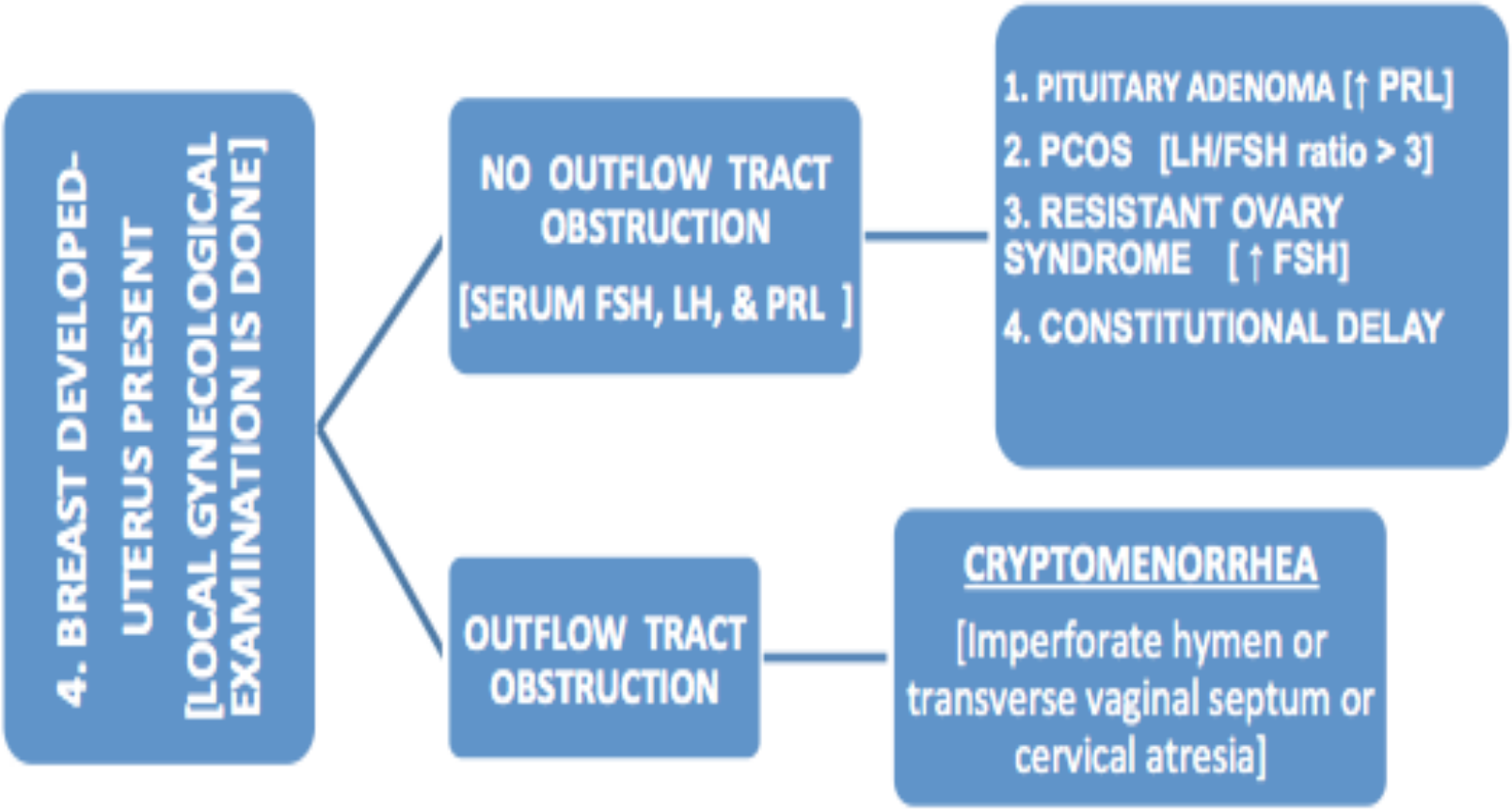
  [b]. 17 alpha- hydroxylase deficiency in 46XY individuals, and

  [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.

4. BREAST DEVELOPED, UTERUS DEVELOPED

4- BREAST DEVELOPED- UTERUS DEVELOPED



Treatment

- ….treat underlying cause, replace deficient hormones or surgically correct underlying anatomic defect

- Many women can achieve pregnancy with IVF and, if necessary, donor eggs

Secondary amenorrhea

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

Secondary amenorrhea causes

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

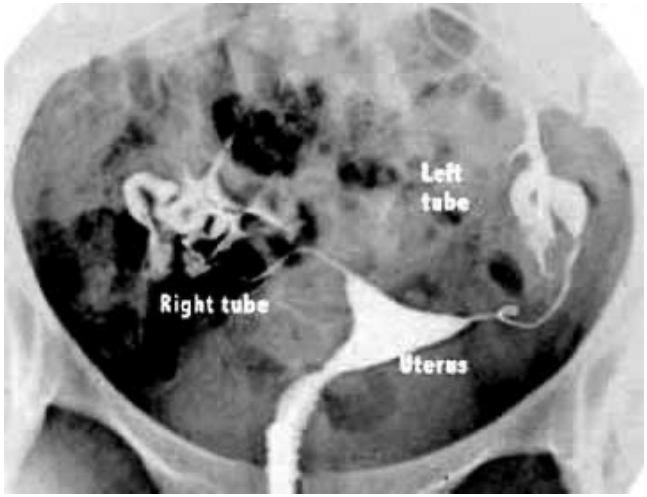
Secondary amenorrhea causes

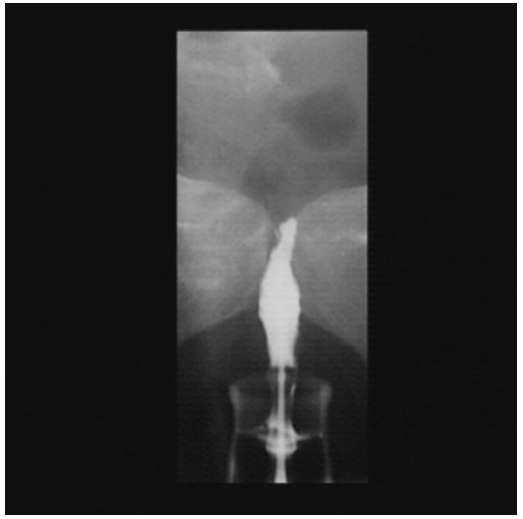
- Pituitary disorders
  - Hyperprolactinemia
    - Prolactinoma
    - Medications
    - PCOS
    - Renal failure
  - Hypoprolactinemia
    - Pituitary resection
    - Sheehan's syndrome
- Thyroid disorders
  - Hyper- or hypothyroidism

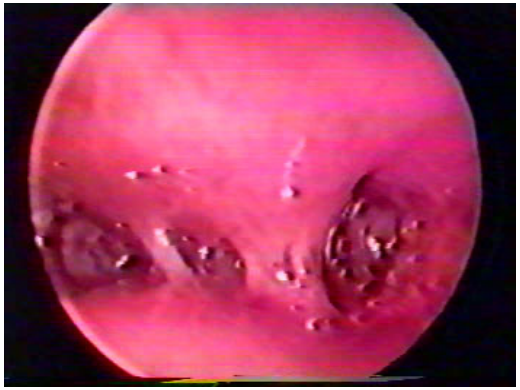
Secondary amenorrhea causes

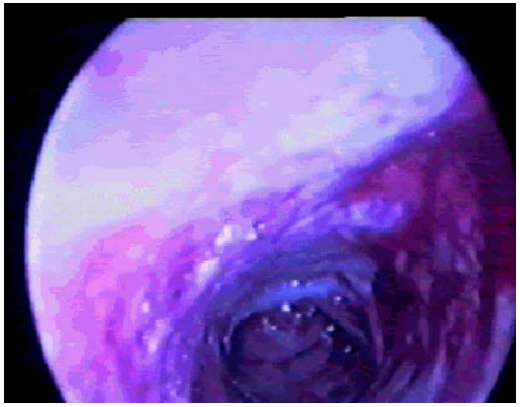
- Ovulation disorders
  - Polycystic ovarian syndrome
  - Premature ovarian failure
- Uterine abnormalities
  - Asherman's syndrome
  - Cervical stenosis
- Drug-induced amenorrhea
  - Hormonal contraceptives
  - GnRH analogues

Asherman's Syndrome







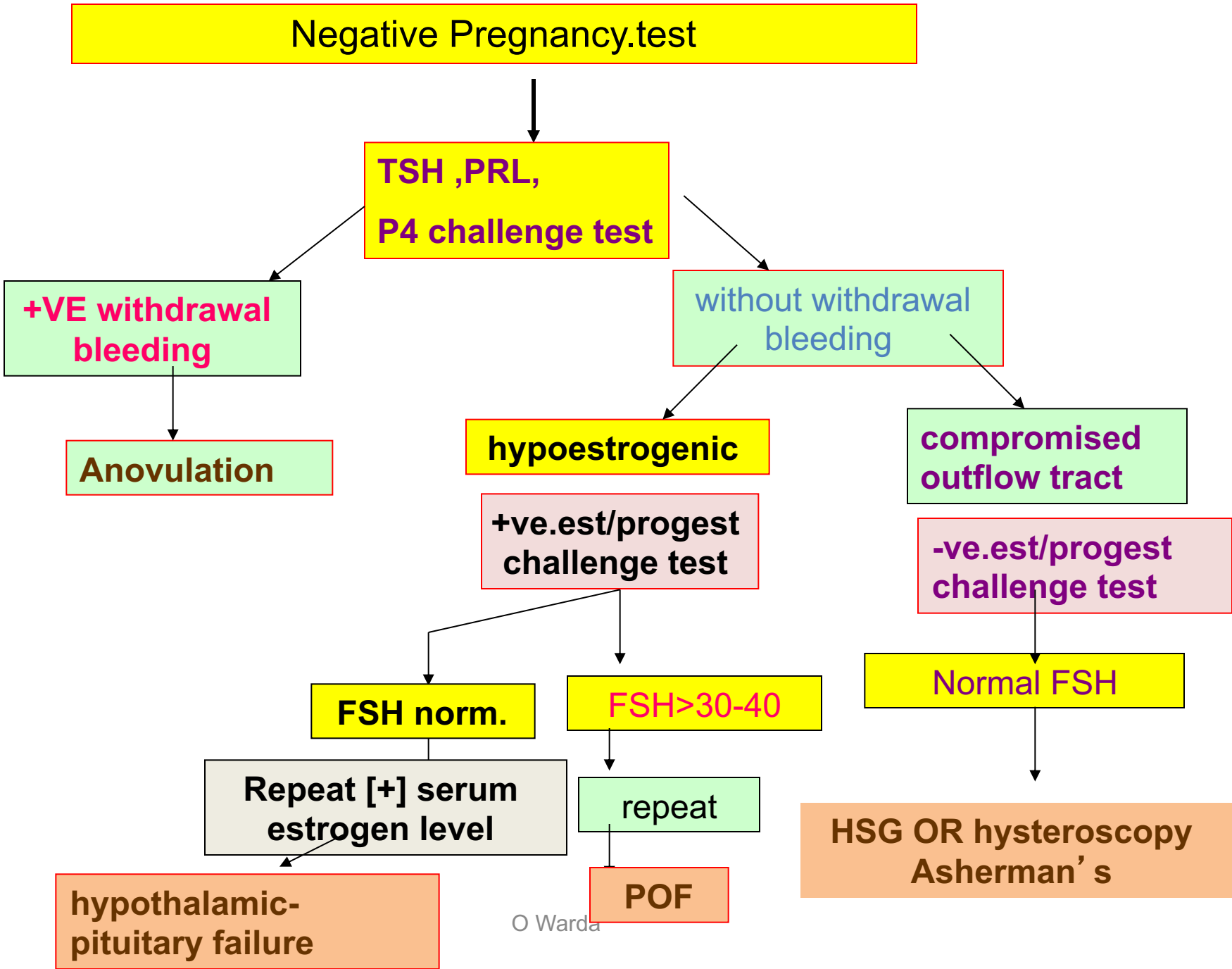


Secondary Amenorrhea diagnosis

History

- Nutrition/exercise habits, weight change
- Sexual/contraceptive practice
- History of uterine/cervical surgery

- Physical exam
  - Height/weight
  - Hirsutism
  - Galactorrhea
  - Estrogen status of tissues
- Laboratory
  - BhCG →PRL & TSH → progesterone challenge → FSH → if high →karyotype


Negative Pregnancy.test
TSH ,PRL,
P4 challenge test
+VE withdrawal bleeding
Anovulation
without withdrawal bleeding
hypoestrogenic
+ve.est/progest challenge test
FSH norm.
Repeat [+] serum estrogen level
hypothalamic-pituitary failure
FSH>30-40
repeat
POF
compromised outflow tract
-ve.est/progest challenge test
Normal FSH
HSG OR hysteroscopy
Asherman's

Secondary Amenorrhea

- Treatment goals
  - Discovery and treatment of underlying disorder
  - Hormone replacement
  - Menses every 1-3 months
  - Pregnancy
    - Ovulation induction
    - GnRH pump
    - FSH/LH

- THANK
- YOU