Gonadal Disorders

Male reproductive physiology

Ola Mohammed Al-sallal

Sexual differentiation

- Genetic sex determined by the sex chromosomes, either XX or XY
- Gonadal sex is defined by presence of testes or ovaries
- Phenotypic sex is defined by the hormonal output of the gonads

Male phenotype <<

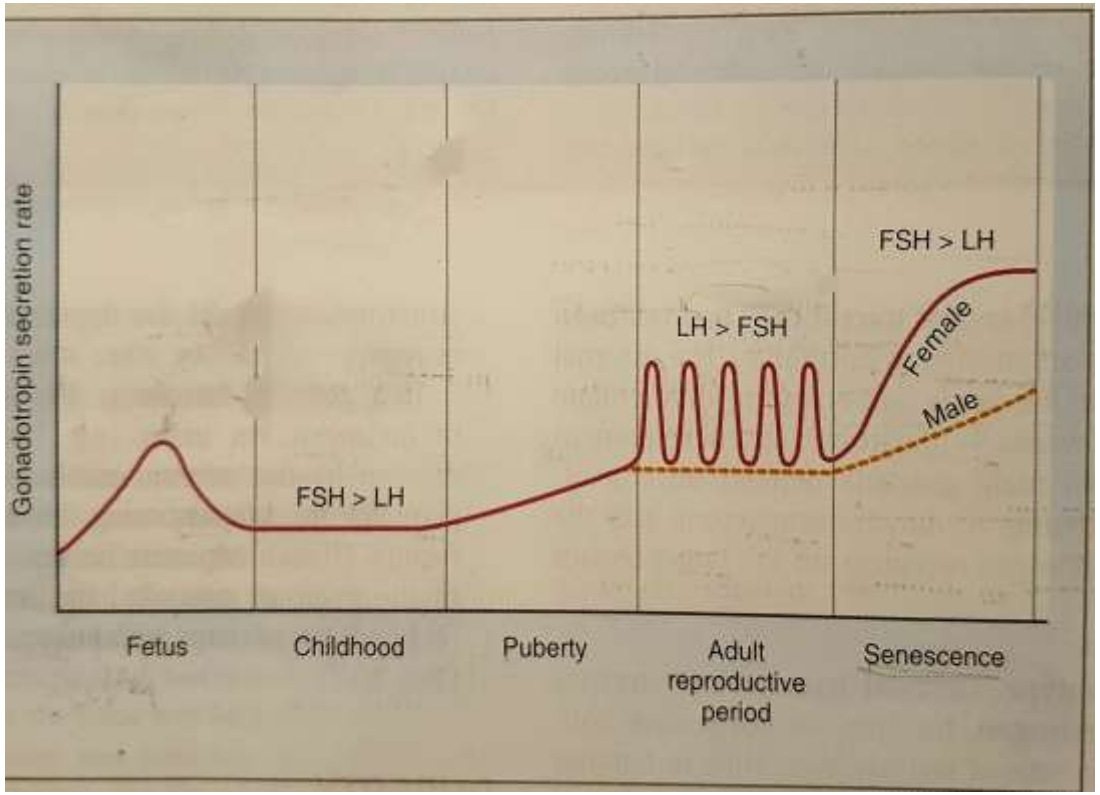
testes secretes testosterone which stimulate differentiation of wolffian ducts

AMH secreted by sertoli cells in testes cause mullerian ducts atrophy

Female phenotype<<

Differentiation of wolffian ducts into the internal female genital tract

Development of external genital tract dosen’t require any hormones



The male gonads are testes which have 2 functions :

1. Spermatogenesis

80% of testes is seminiferous tubules and 20% is connective tissue

Sertoli cells

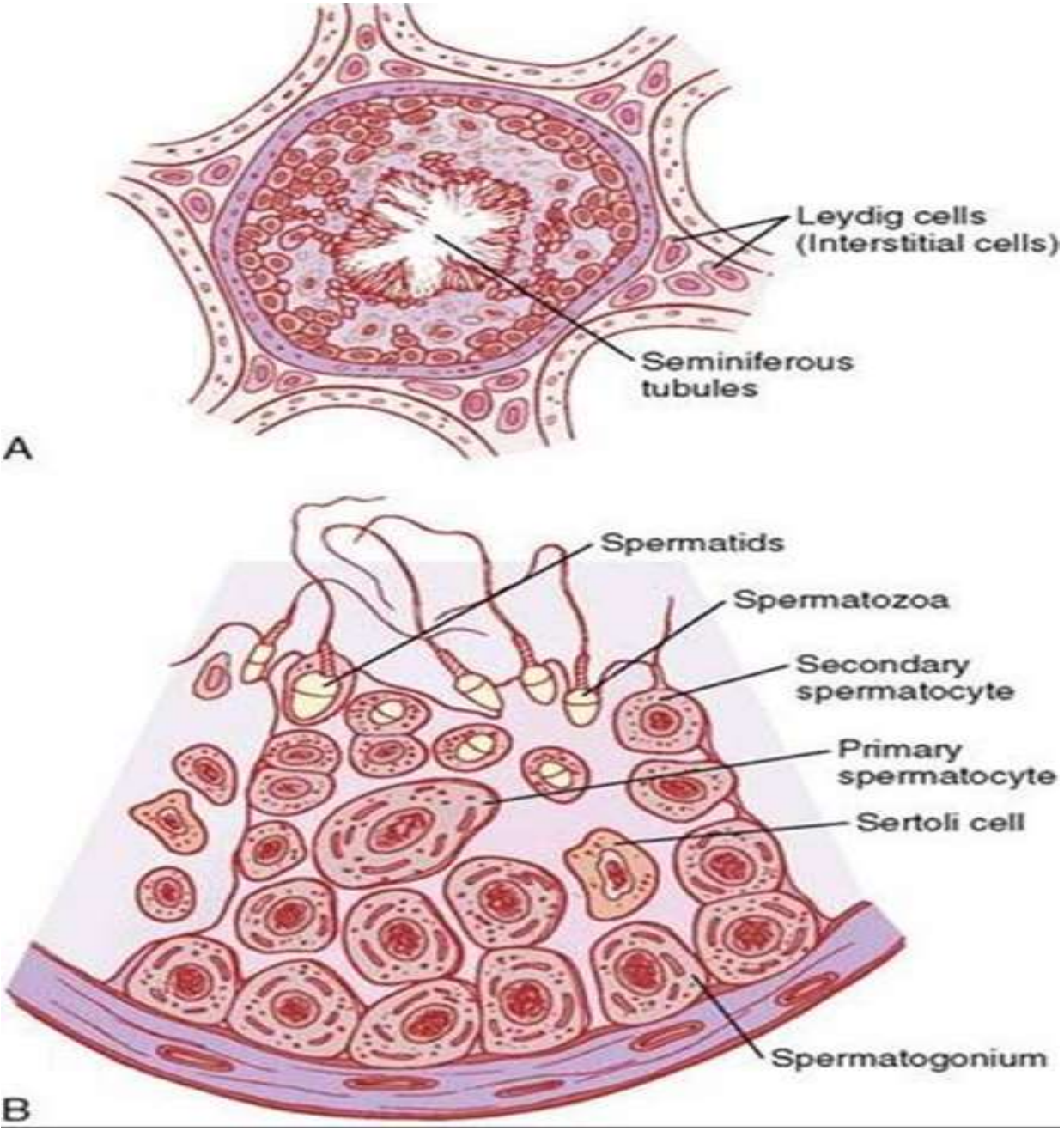
spermatogonia

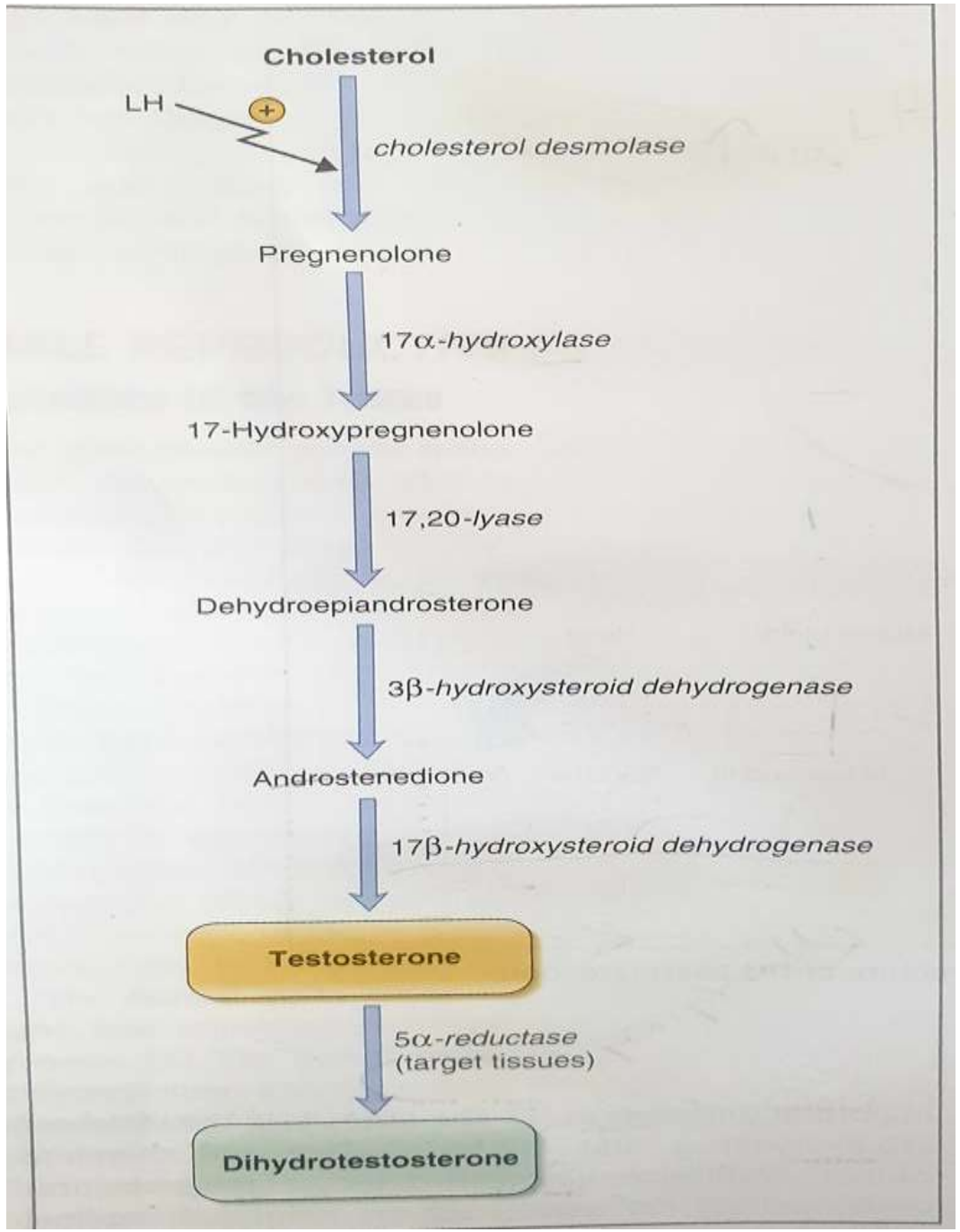
spermatocytes

Leyding cells

1. Provide nutrition to sperm
2. Blood testes barrier
3. Secrete aqueous fluid which help transporting sperms
4. Secrete androgen binding protein

Synthesize and secrete testosterone which has endocrine and paracrine effects


Leydig cells
(Interstitial cells)
Seminiferous
tubules
A
Spermatids
Spermatozoa
Secondary
spermatocyte
Primary
spermatocyte
Sertoli cell
Spermatogonium
B


Cholesterol
LH
+
cholesterol desmolase
Pregnenolone
17α-hydroxylase
17-Hydroxypregnenolone
17,20-lyase
Dehydroepiandrosterone
3β-hydroxysteroid dehydrogenase
Androstenedione
17β-hydroxysteroid dehydrogenase
Testosterone
5α-reductase
(target tissues)
Dihydrotestosterone

2. Synthesis and secretion of testosterone

The steroidogenic pathways in testes similar to those in adrenal cortex except:

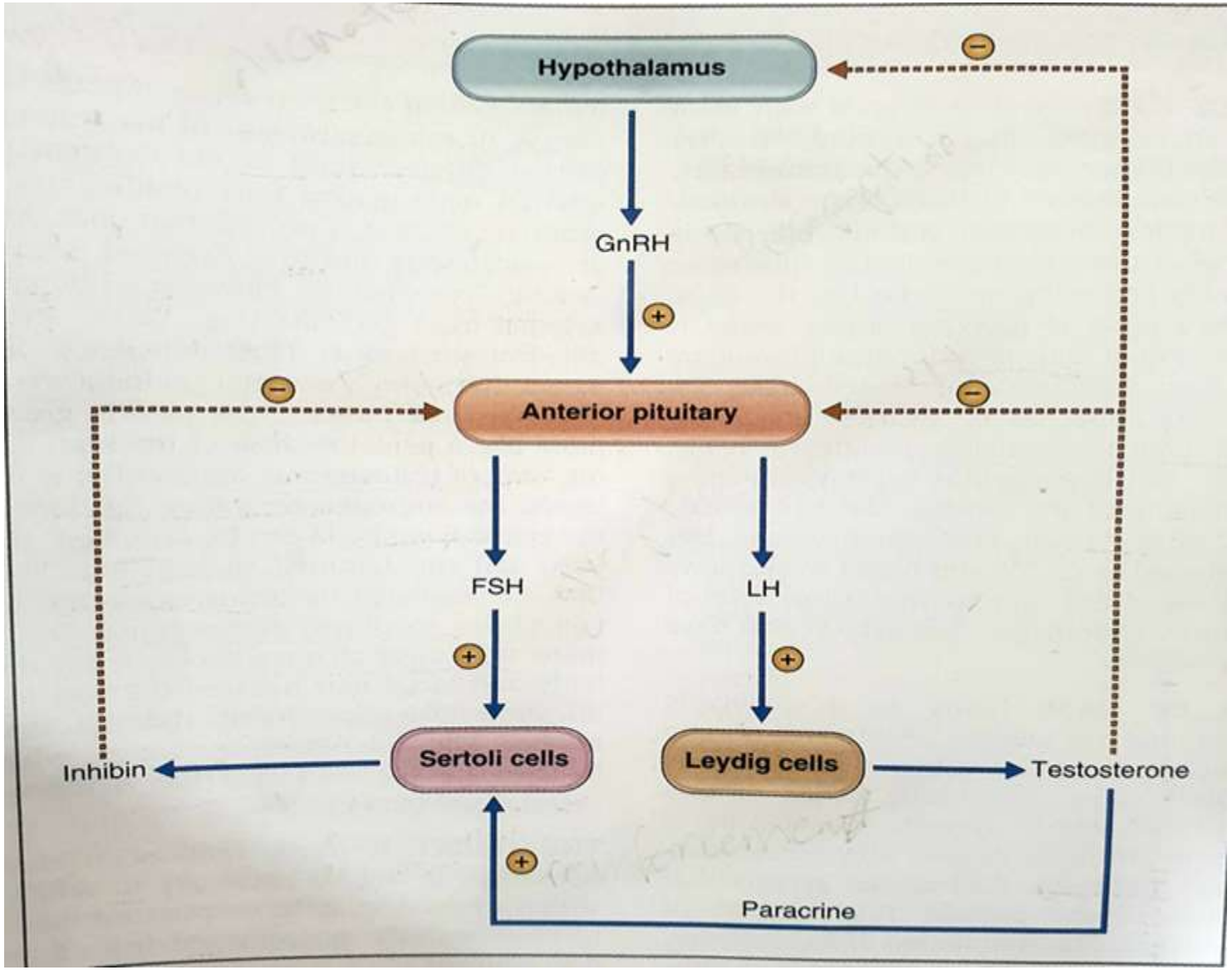
<testes lack 21-B hydroxylase and 11-B hydroxylase for MC and GC synthesis

<testes has additional enzyme 17B-hydroxysteroid dehydrogenase that converts androstenedione to testosterone

* In some tissues dihydrotestosterone is the active androgen(alpha reductase convert testosterone to Dihydrotestosterone)

Mediated by Testosterone	Mediated by Dihydrotestosterone
Differentiation of epididymis, vas deferens, and seminal vesicles	Differentiation of penis, scrotum, and prostate
Increased muscle mass	Male hair pattern
Pubertal growth spurt	Male pattern baldness
Cessation of pubertal growth spurt (epiphyseal closure)	Sebaceous gland activity
Growth of penis and seminal vesicles	Growth of prostate
Deepening of voice	
Spermatogenesis	
Negative feedback on anterior pituitary	
Libido	

Regulation of the testes



Female reproductive physiology

- The female gonads are the ovaries, which, together with the uterus and fallopian tubes constitute the female reproductive tract

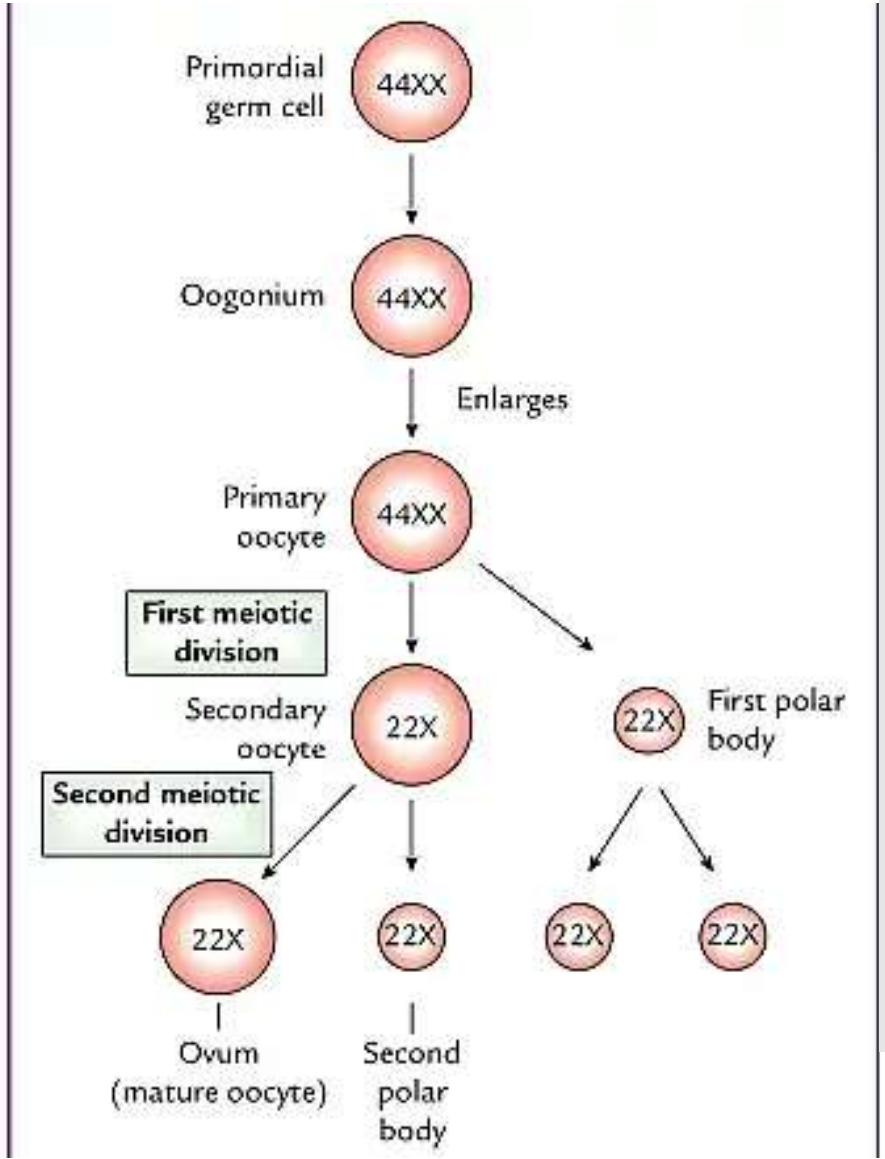
- Ovary has 3 zones>>

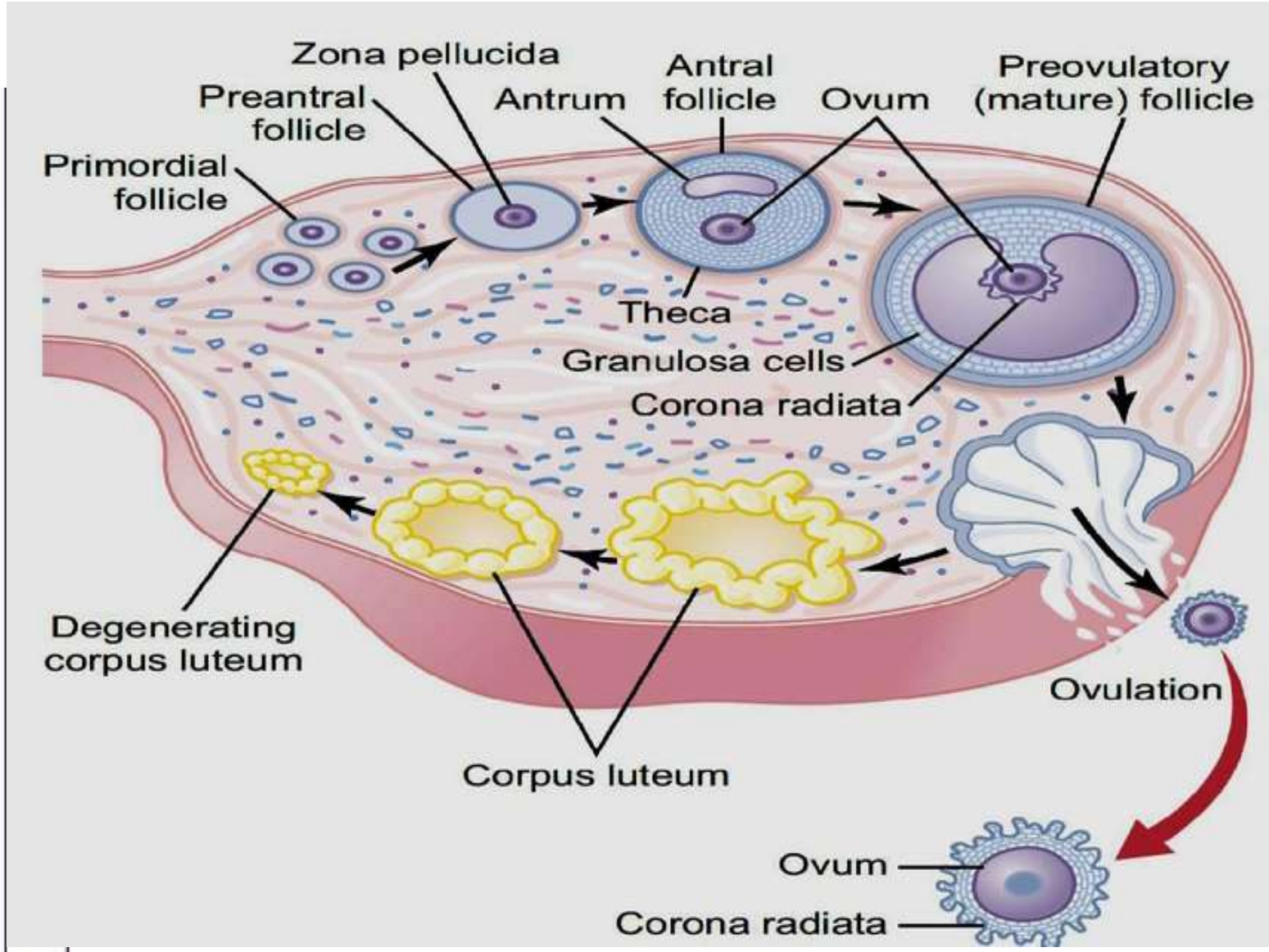
1. The cortex is the outer and largest .it is lined by germinal epithelium and contains all the oocytes which is enclosed in a follicle
2. The medulla is the middle zone and is a mixture of cell types
3. Hilum which contains blood vessels and lymphatics

Functional unit of the ovaries is the single ovarian follicle which compromise one germ cell surrounded by endocrine cells , when fully developed it serves several critical roles

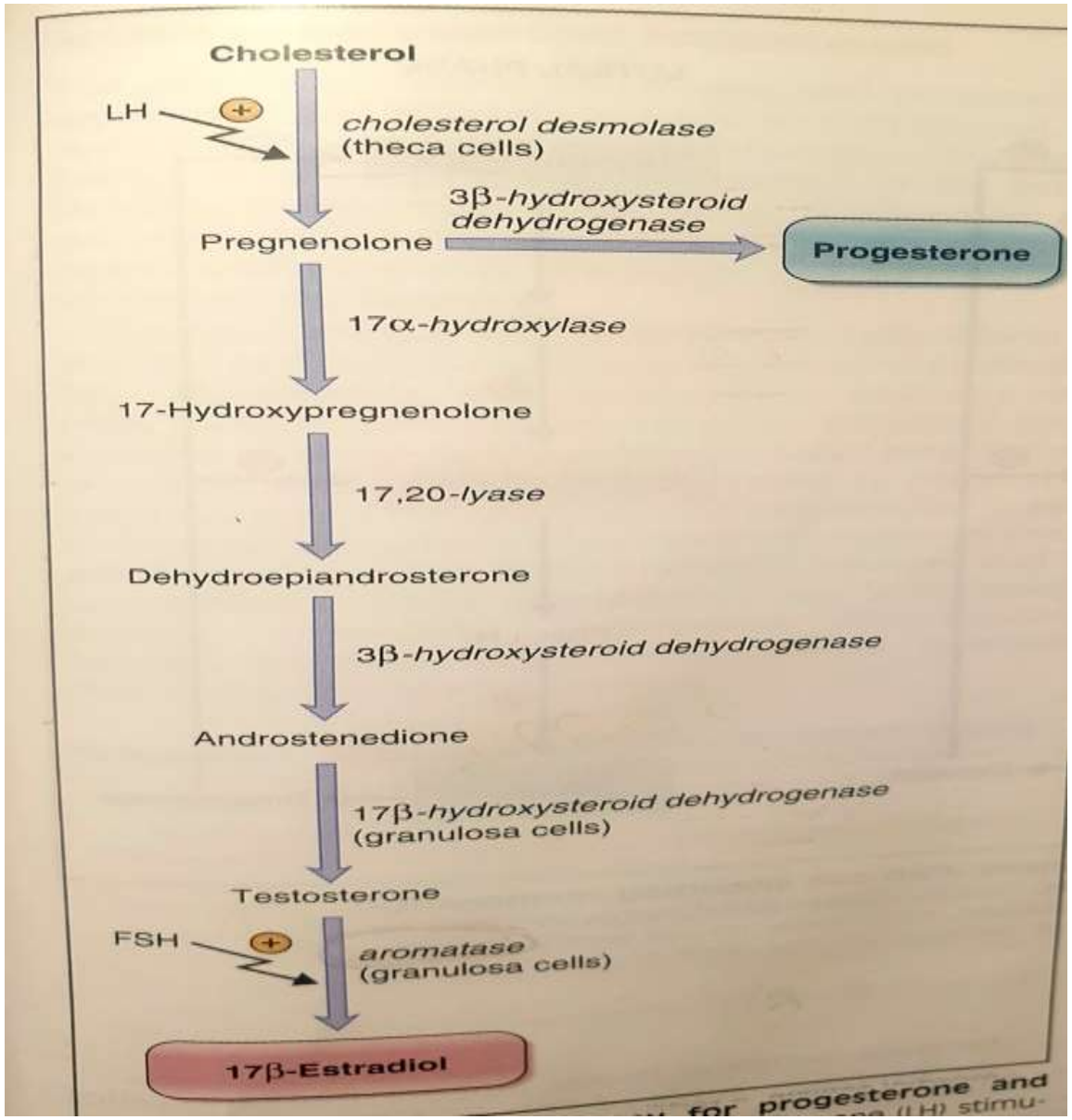
The ovaries have 2 functions :

1.Oogenesis





2.Secretion of female sex hormones



Estrogen and progesterone function in a coordinated fashion to support female reproductive activity including >>development of the ovum, development and maintenance of corpus luteum, maintenance of pregnancy and breast preparation for lactation

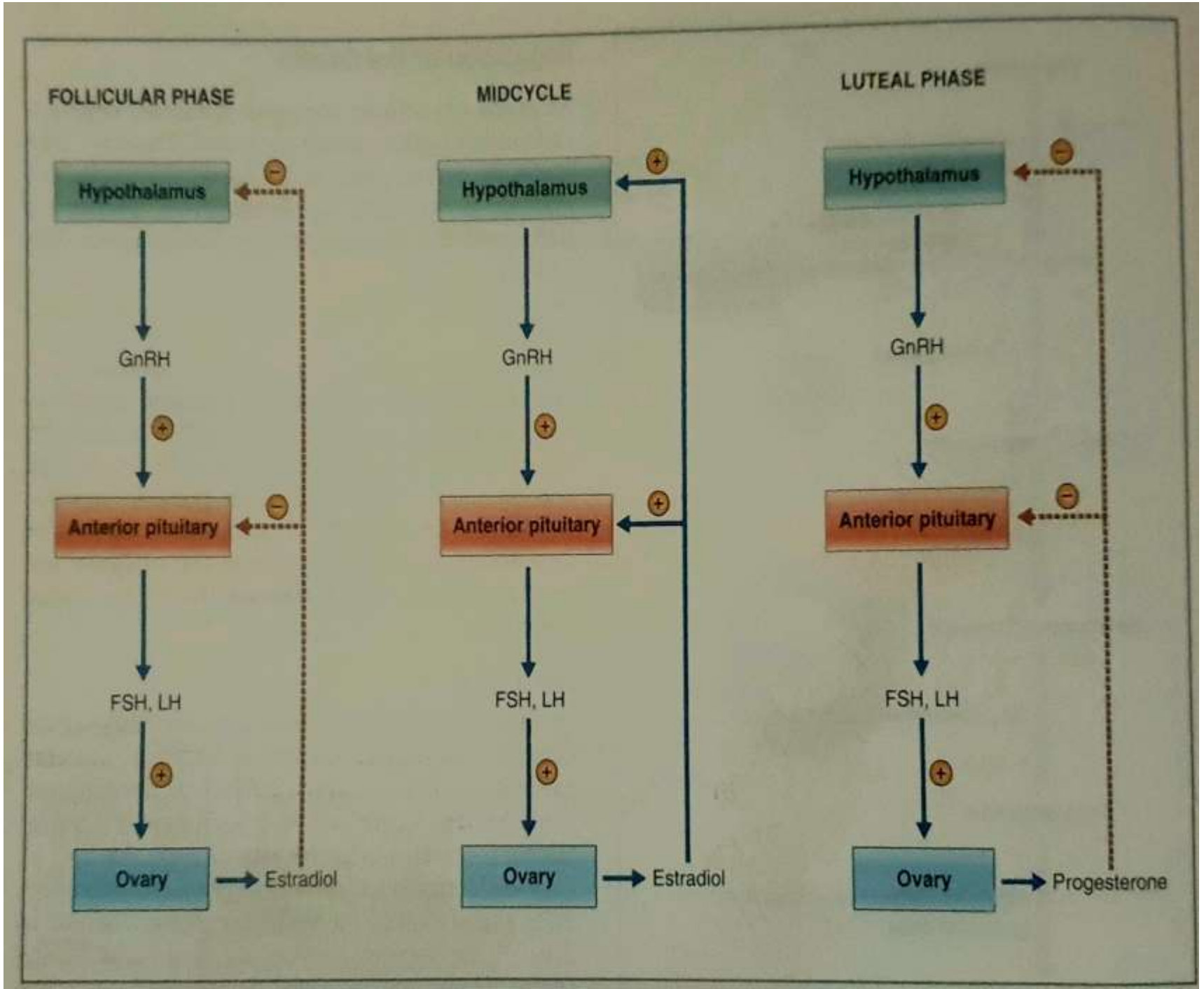
Over the menstrual cycle estrogen secretion precedes progesterone, preparing target tissues to respond to progesterone, as estrogen upregulates progesterone receptors . Conversely progesterone downregulates estrogen receptors

Regulation of the ovaries

- Like testicular function in male, ovarian function in female is driven by pulsatile activity of hypothalamic pituitary axis
- Every 28 days a sequence of :

follicular development (First 14 days)>>ovulation (In between)>>formation and degeneration of corpus luteum (Last 14 days) is repeated in menstrual cycle

- ❑Granulosa cells are the only ovarian cells with FSH receptors. FSH stimulates growth of granulosa cells in 1ry follicles and stimulate estradiol synthesis
- ❑LH levels in blood increase sharply just prior to ovulation inducing rupture of the dominant follicle .Also stimulates luteinization



- Inhibin is produced by granulosa cells. As in the testes it inhibit FSH secretion

- Activin is also produced by granulosa cells and stimulate FSH secretion

Actions of estrogen and progesterone

TABLE 10.2 Actions of Estrogens on Target Tissues

- Maturation and maintenance of uterus, fallopian tubes, cervix, and vagina
- Responsible at puberty for the development of female secondary sex characteristics
- Required for development of the breasts
- Responsible for proliferation and development of ovarian granulosa cells
- Up-regulation of estrogen, progesterone, and LH receptors
- Negative *and* positive feedback effects on FSH and LH secretion
- Maintenance of pregnancy
- Lowering uterine threshold to contractile stimuli
- Stimulation of prolactin secretion
- Blocking the action of prolactin on the breast
- Decreasing LDL cholesterol
- Anti-osteoporosis

TABLE 10.3 Actions of Progesterone on Target Tissues

- Maintenance of secretory activity of uterus during luteal phase
- Development of the breasts
- Negative feedback effects on FSH and LH secretion
- Maintenance of pregnancy
- Raising uterine threshold to contractile stimuli during pregnancy

Menstrual cycle

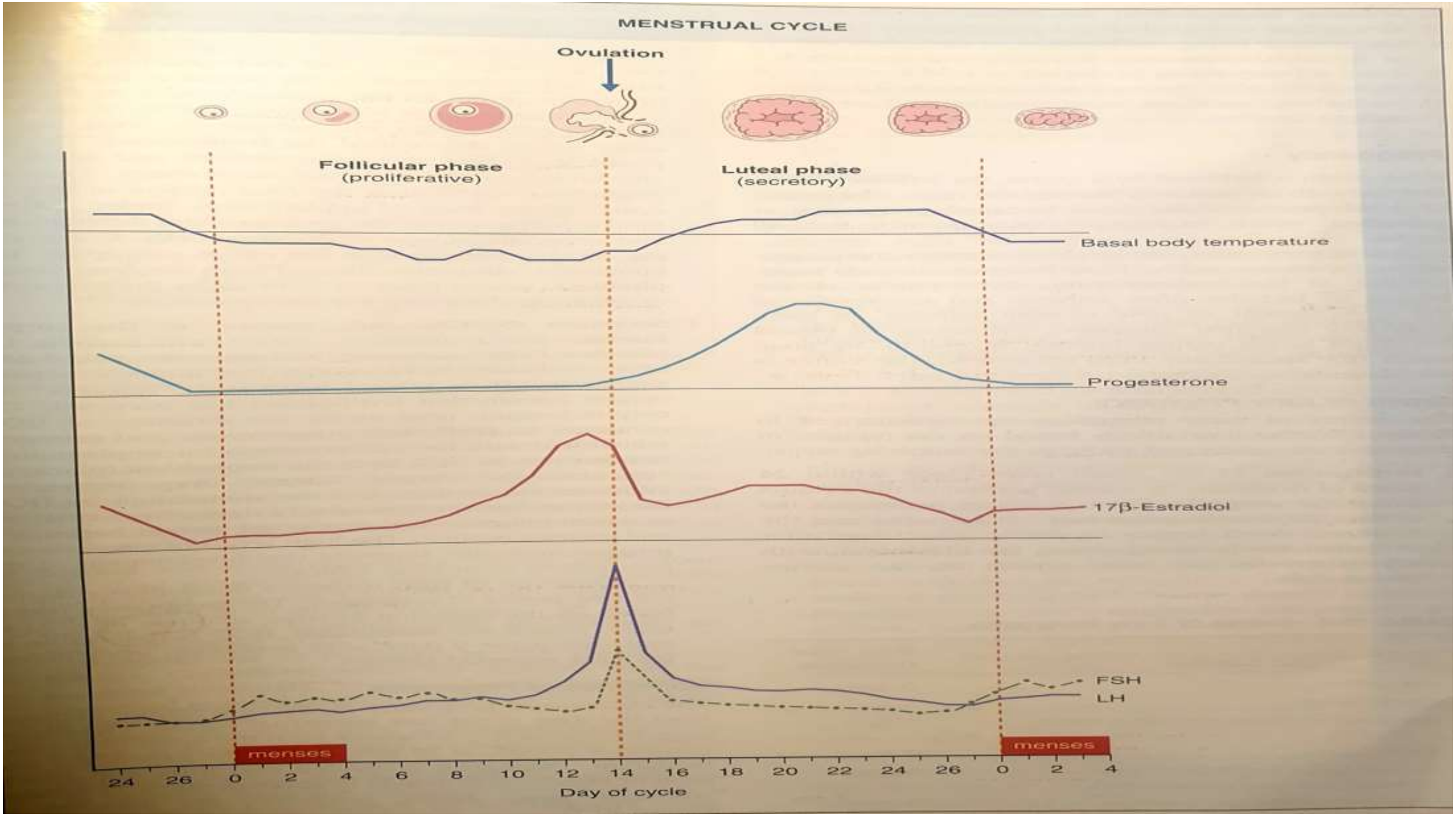
- Recurs approximately every 28 days (21-35). The events include :

Development of ovarian follicle and it’s oocyte

Ovulation

Preparation of the reproductive system to receive fertilized ovum

shedding of the endometrial lining if fertilization didn’t occur


MENSTRUAL CYCLE
Ovulation
Follicular phase
(proliferative)
Luteal phase
(secretory)
Basal body temperature
Progesterone
17β-Estradiol
FSH
LH
menses
menses
24 26 0 2 4 6 8 10 12 14 16 18 20 22 24 26 0 2 4
Day of cycle

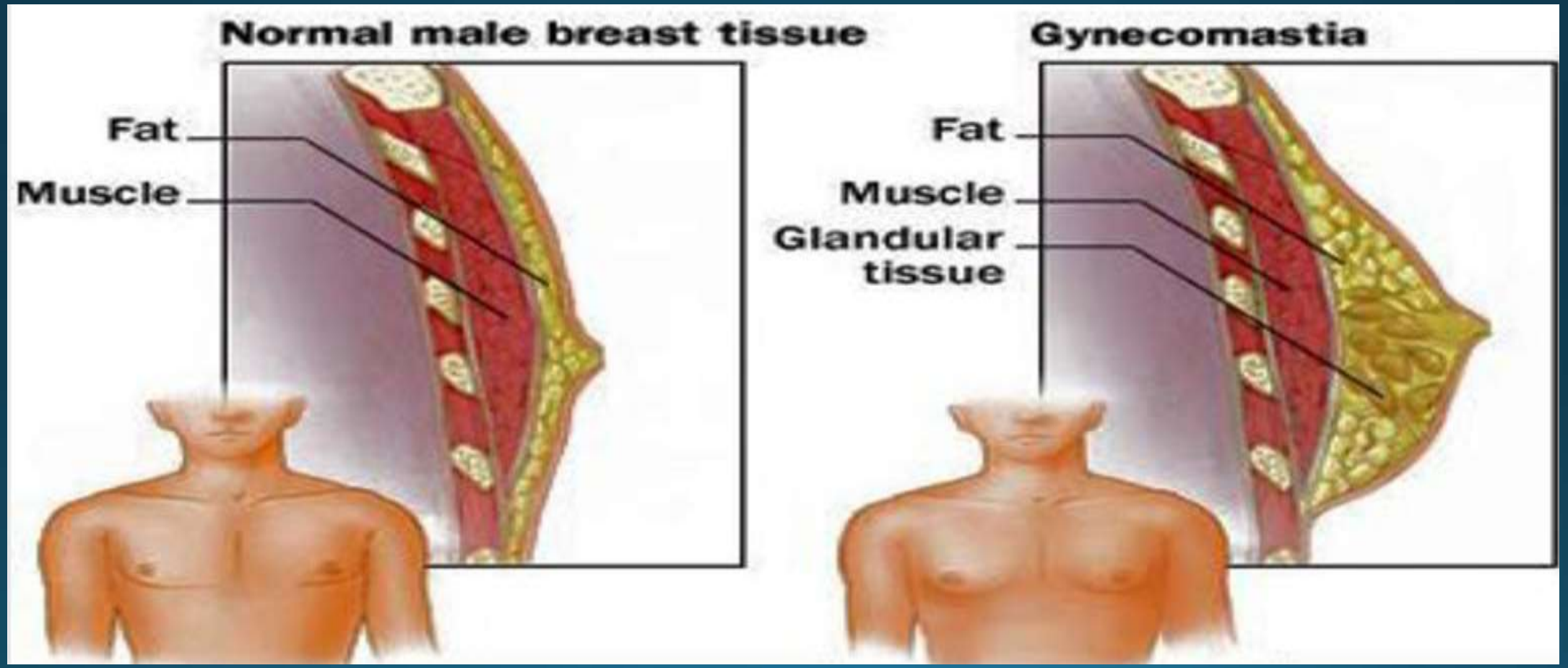
Gynecomastia

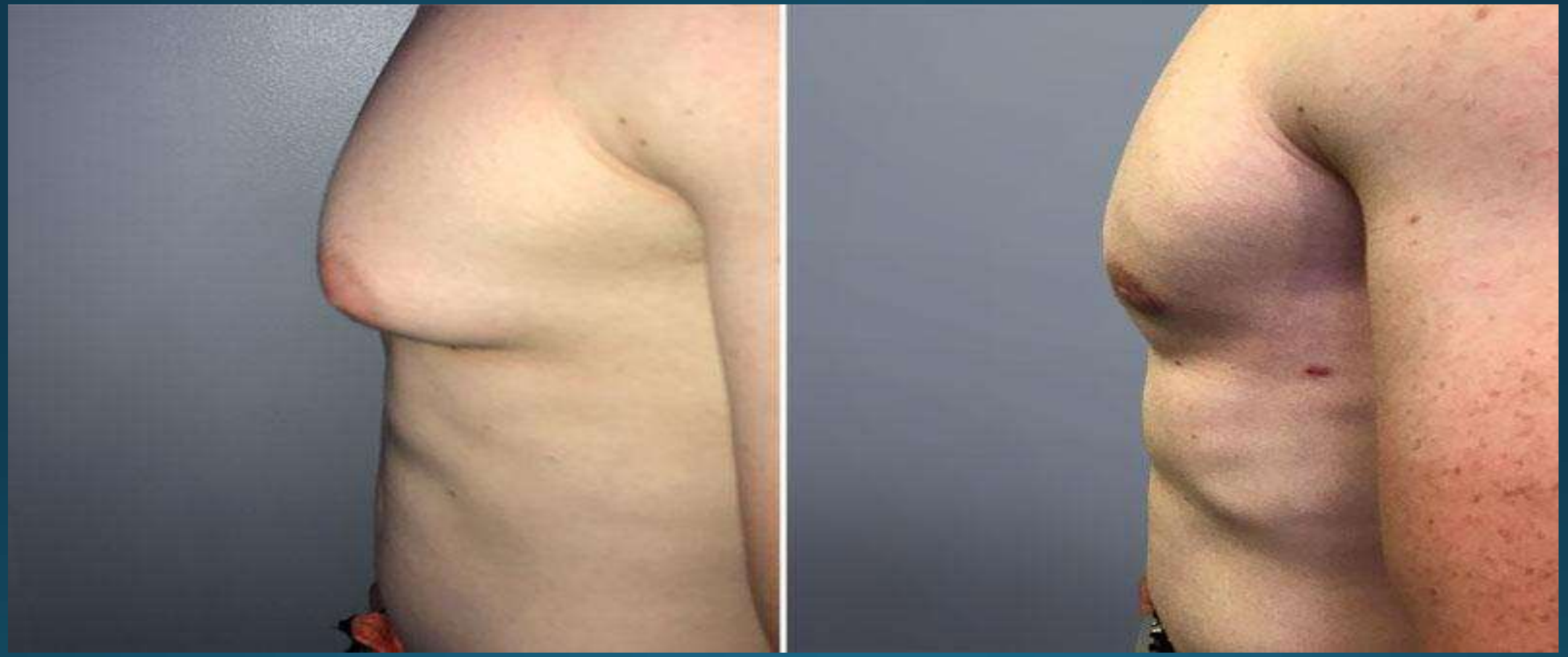
Done By: Yara Al-Hazaimeh

Gynecomastia

Is benign proliferation of the glandular tissue of the male breast, is caused by an increase in the ratio of estrogen to androgen activity.

- At least 30% of males will be affected during their life. Since it causes anxiety, psychosocial discomfort and fear of breast cancer, early diagnostic evaluation is important and patients usually seek medical attention.


Normal male breast tissue
Fat
Muscle
Gynecomastia
Fat
Muscle
Glandular tissue



Gynecomastia

Associated with increased levels of estradiol and decreased levels of testosterone

- Physiologic changes at puberty senescence
- Endocrine and hormonal disorders
- Systemic disease
- Neoplasm
- drugs

Table 2. Etiology of gynecomastia

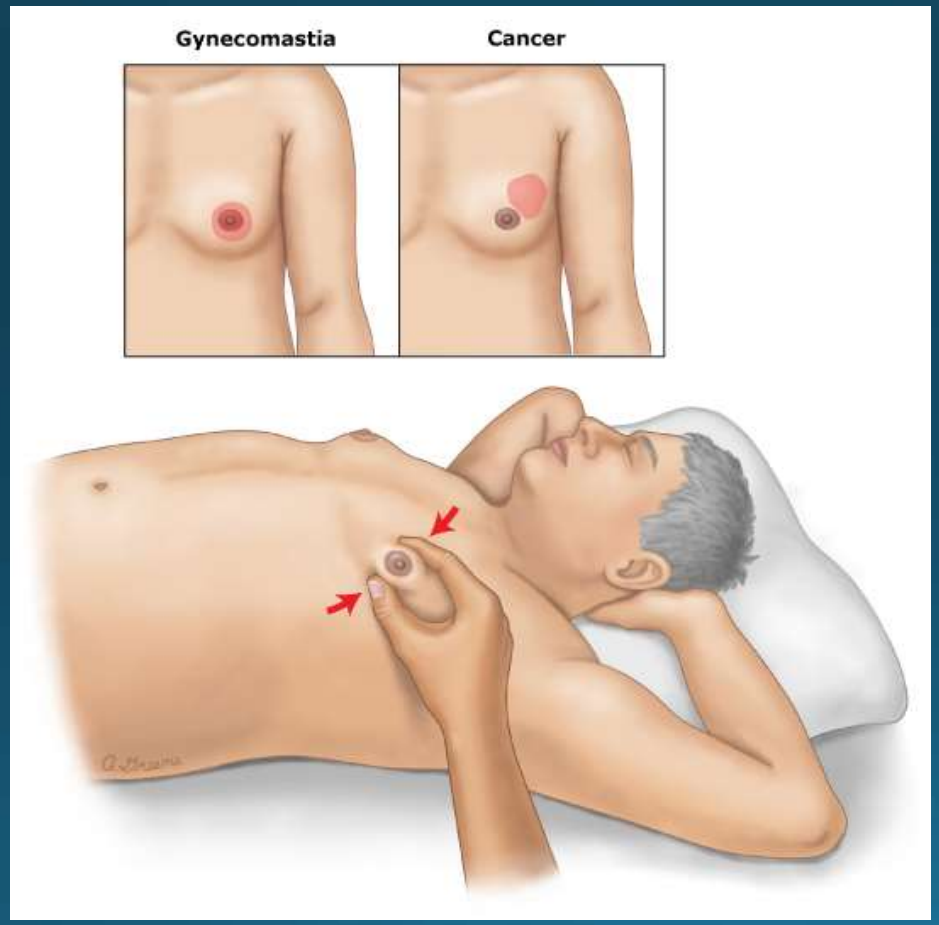
Causes	
Physiological factors	Puberty or aging
Endocrine tumors	Testicular, adrenocortical or pituitary tumors, or ectopic hCG-secretion
Endocrine dysfunctions	Hypogonadism, hyperthyroidism, obesity or refeeding
Non-endocrine diseases	Cirrhosis, renal failure or HIV
Drug-induced factors	Medications, anabolic steroids or illicit drugs
Idiopathic factors	

Table 3. Common medications causing gynecomastia[41]

Type of agent	Medications
Antiandrogens	Bicalutamide, cyproterone, flutamide, finasteride, spironolactone
Antibiotics	Isoniazid, ketoconazole, metronidazole
Antihypertensives	Amlodipine, captopril, enalapril, nifedipine, reserpine, verapamil
Chemotherapeutic agents	Cyclophosphamide, methotrexate
Diuretic	Spironolactone
Gastrointestinal agents	Cimetidine, omeprazole, metoclopramide, ranitidine
Hormones	Androgens, anabolic steroids, estrogens, growth hormone
Psychiatric agents	Diazepam, haloperidol, phenothiazine, tricyclic antidepressants
Others	Amiodarone, antiretrovirals, digitalis, domperidone, statins, theophylline

Diagnosis of gynecomastia

- 1) Palpable mass of tissue at least 0.5 cm in diameter (usually underlying the nipple).
- 2) The pt position: Patient lies on his back with his hands behind his head.
- 3) The examiner then places his or her thumb and forefinger on each side of the breast and slowly brings them together.


Gynecomastia
Cancer

Pubertal gynecomastia

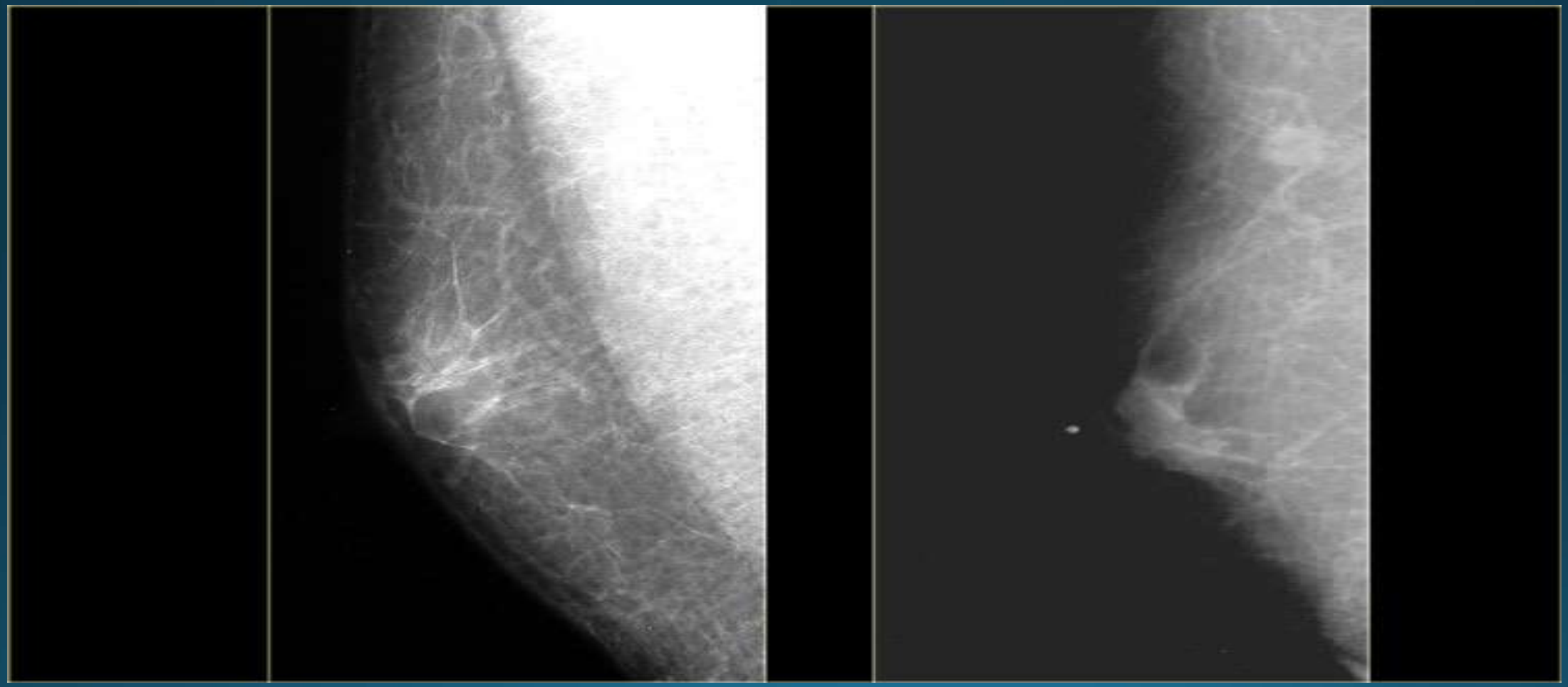
- Occurs in normally-growing infant and pubertal boys that resolves on its own with time is known as physiologic gynecomastia.
- During puberty, *levels of these hormones may fluctuate and rise at different levels*, resulting in a temporary state in which estrogen concentration is relatively high.
- Gynecomastia caused by transient changes in hormone levels with growth usually disappears on its own within six months to two years.

Gynecomastia

3- mammographic patterns -representing various degrees and stages of ductal and stromal proliferation

- Nodular
- Dendritic
- Diffuse glandular

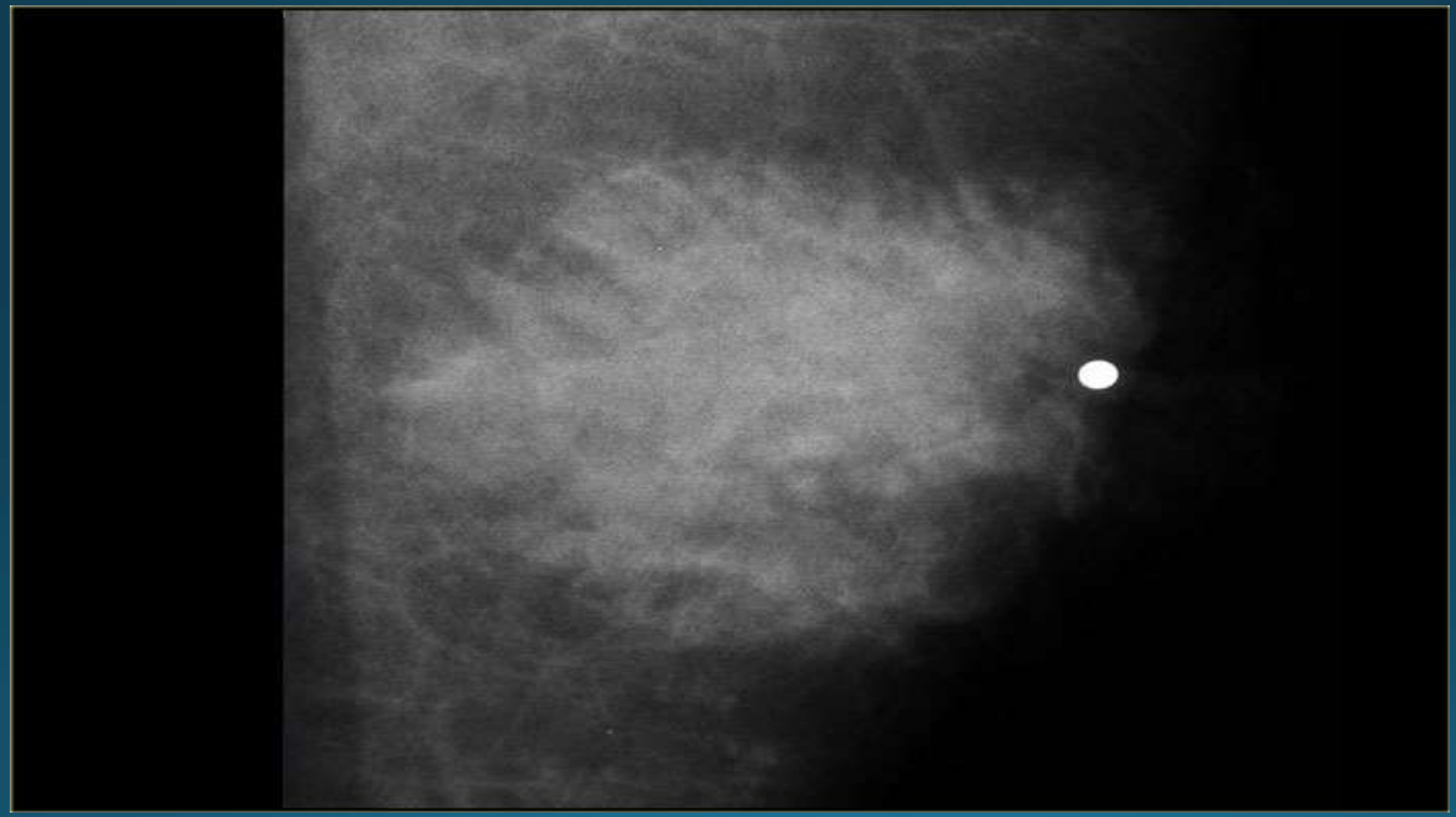
normal



Nodular pattern

- The nodular pattern of gynecomastia is seen in the florid early phase.
  It begins as an increased number of ducts and epithelial proliferation with edema and cellular fibroblastic stroma.
  This phase is reversible.

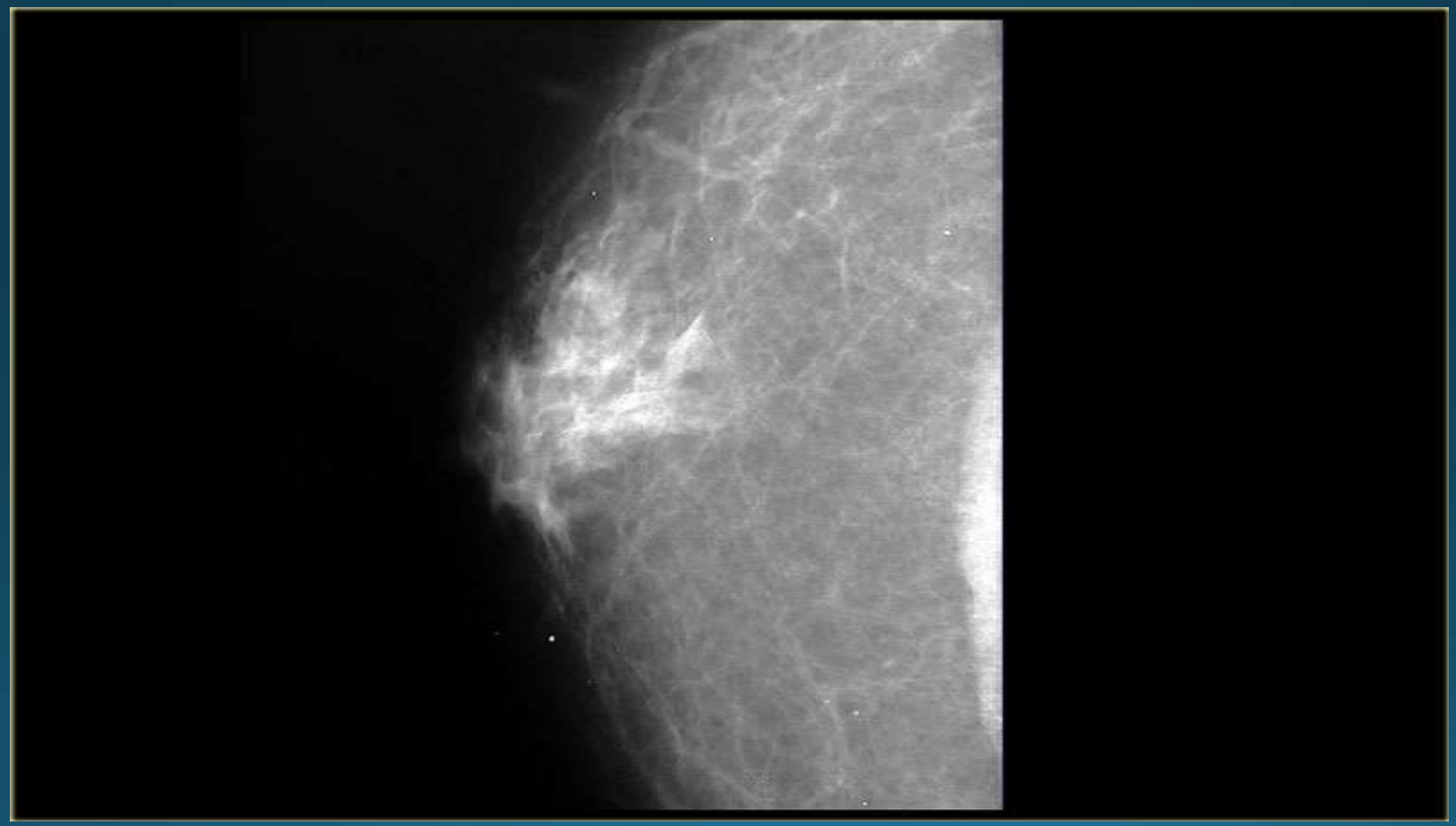
Nodular pattern



Dendritic Pattern

- The dendritic pattern is seen in the fibrotic or late phase.
  There are dilated ducts, moderate epithelial proliferation and fibrosis.

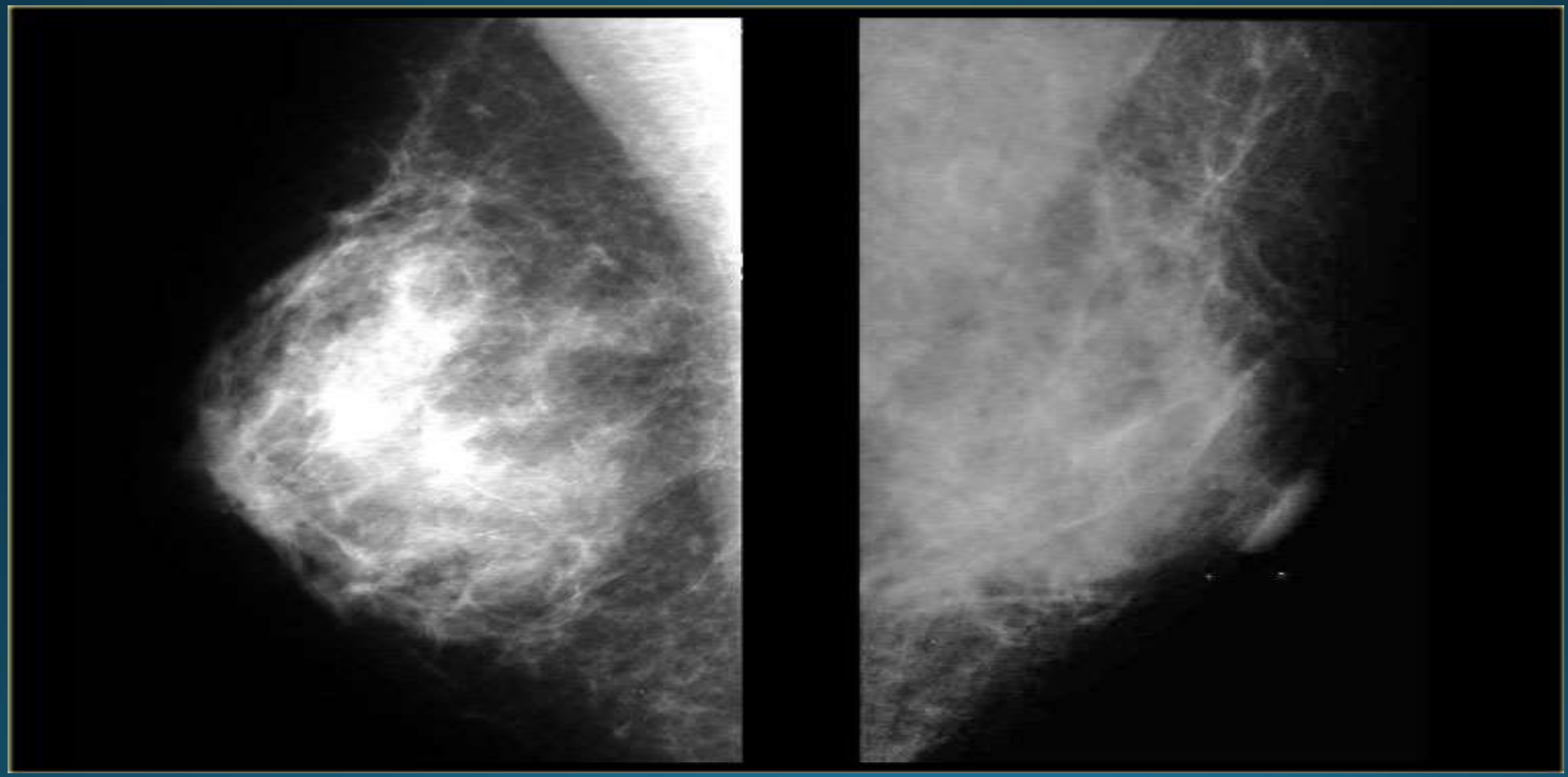
Dendritic Pattern



Diffuse glandular pattern

- This pattern is seen in males with very high estrogen levels.
- The image simply looks like small female breasts. .

Diffuse glandular pattern

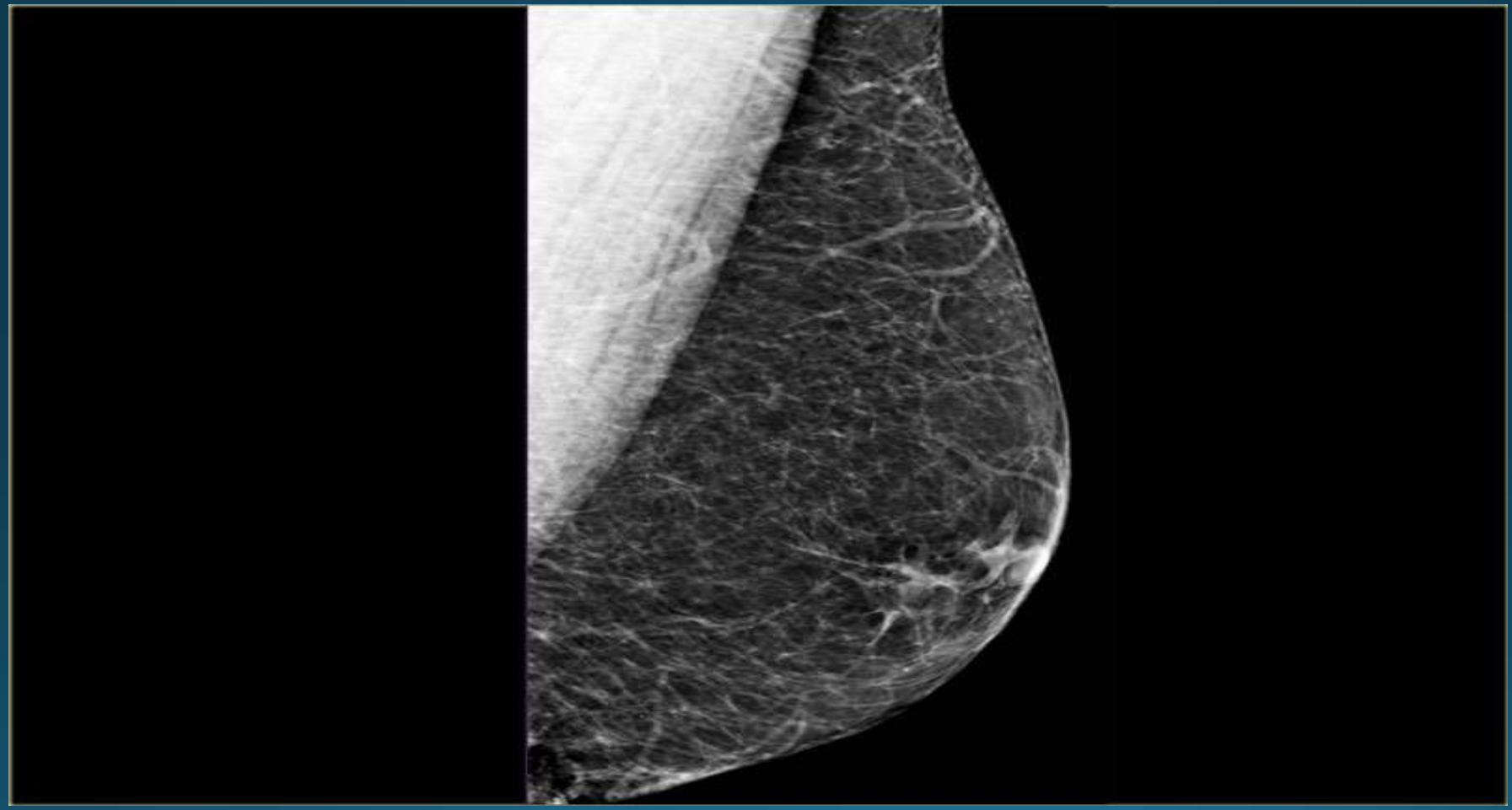


Pseudogynecomastia - a fatty proliferation of the breasts, without proliferation of glandular tissue.

- **Physical findings:**

Fingers will not meet any resistance until they reach the nipple. (no discrete mass)

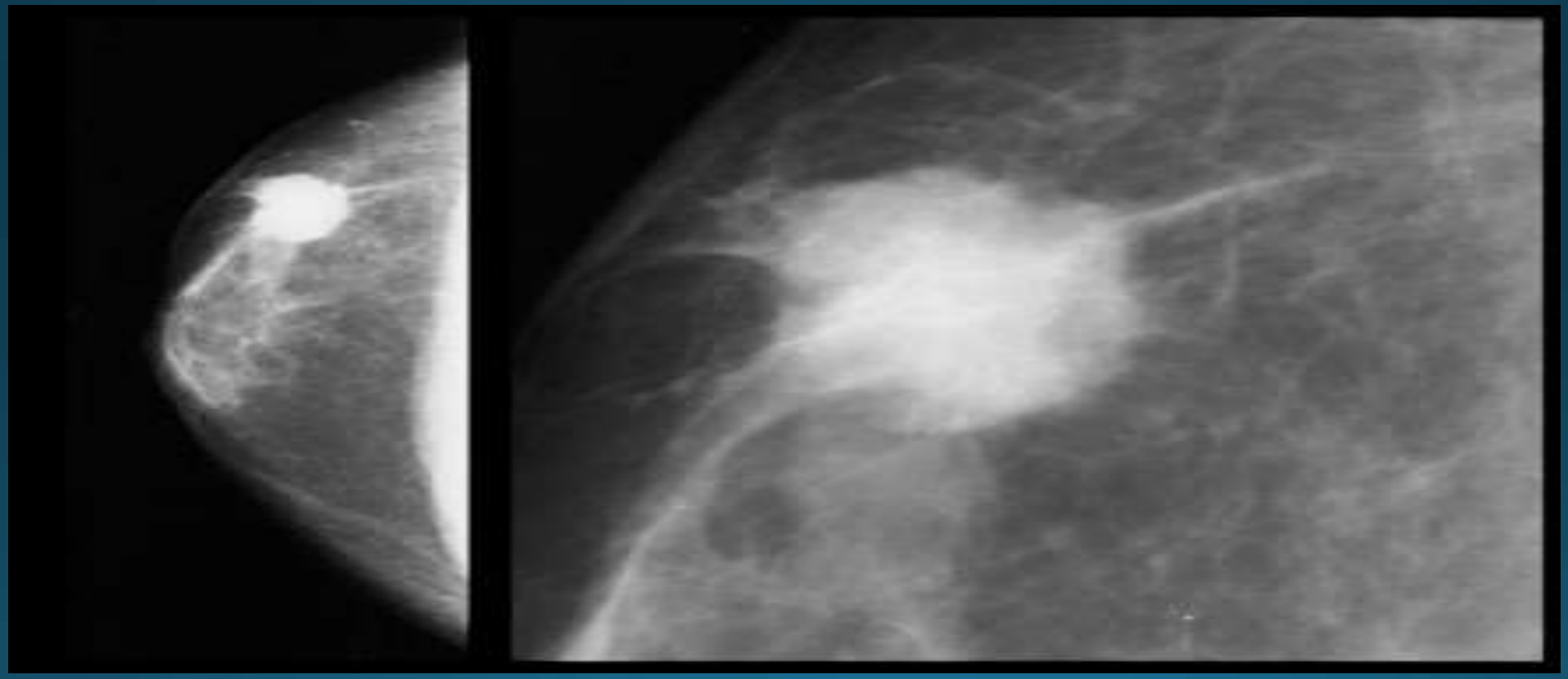
Pseudogynecomastia



DDX of gynecomastia

	Gynecomastia	Pseudogynecomastia	Breast cancer
Pathology:	Proliferation of the glandular tissue	Increase in breast fat	Mutation(BRCA1 or BRCA2)
Shape:	unilateral/bilateral(+), concentric, rubbery-to-firm disk, mobile, located beneath the areolar area	Diffuse breast enlargement without any subareolar glandular tissue	Unilateral, nontender, fixed, firm to hard, eccentric to the nipple-areolar complex
Physical findings:	A palpable mass of tissue at least 0.5 cm in diameter	Fingers will not meet any resistance until they reach the nipple. (no discrete mass)	Skin dimpling, nipple discharge & retraction, and regional lymphadenopathy
Imaging	Not routinely recommended	None	Ultrasonography or Mammography

Male breast cancer



Biochemical testing for gynecomastia

Test	Indication
-Morning serum total testosterone	Middle-aged to older men (2-5%)
-luteinizing hormone (LH) levels -Free or bioavailable testosterone	1)Obese {low sex hormone-binding globulin (SHBG)} 2)Low Morning serum testosterone
-Human Chorionic Gonadotropin (hCG) -LH -Estradiol	1)Recent onset 2)Painful or tender 3)Greater than 5 cm

Treatment of gynecomastia

Line of treatment	Indication
Stop offending drugs	If the drug is identified as the cause of gynecomastia during the early, proliferative, and often painful phase, stopping it may result in regression of glandular tissue
Androgens	Male with hypogonadism
Selective estrogen receptor modulators (SERMs)	Tamoxifen (most common agent) This type of therapy is most often used for severe or painful gynecomastia.
Surgical intervention	1) In the late fibrotic stage (after 12 months). 2) Persistent pubertal gynecomastia (lasts until adulthood)

HYPOGONADISM

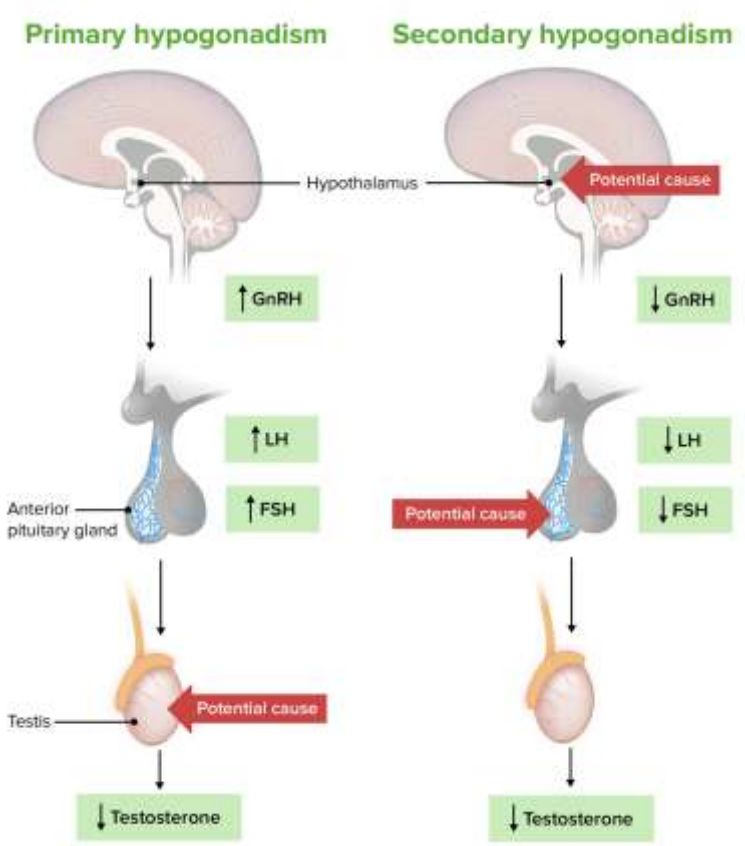
Male

Done By: Aya Al-Ajlouni

Hypogonadism

- **Hypogonadism** in a male refers to a decrease in one or both of the two major functions of the testes:
  sperm production (impaired gamete production)or testosterone production (diminished sex hormone biosynthesis).
  These abnormalities can result from disease of the testes (**primary hypogonadism**) or disease of the hypothalamus or pituitary (**secondary hypogonadism**).

- May be a presenting complaint or an incidental finding such as during investigation for subfertility.



Causes of male Hypogonadism

- **Causes of Primary Hypogonadism (Hypergonadotrophic hypogonadism) in males :**

1. **<u>Congenital abnormalities</u>:**

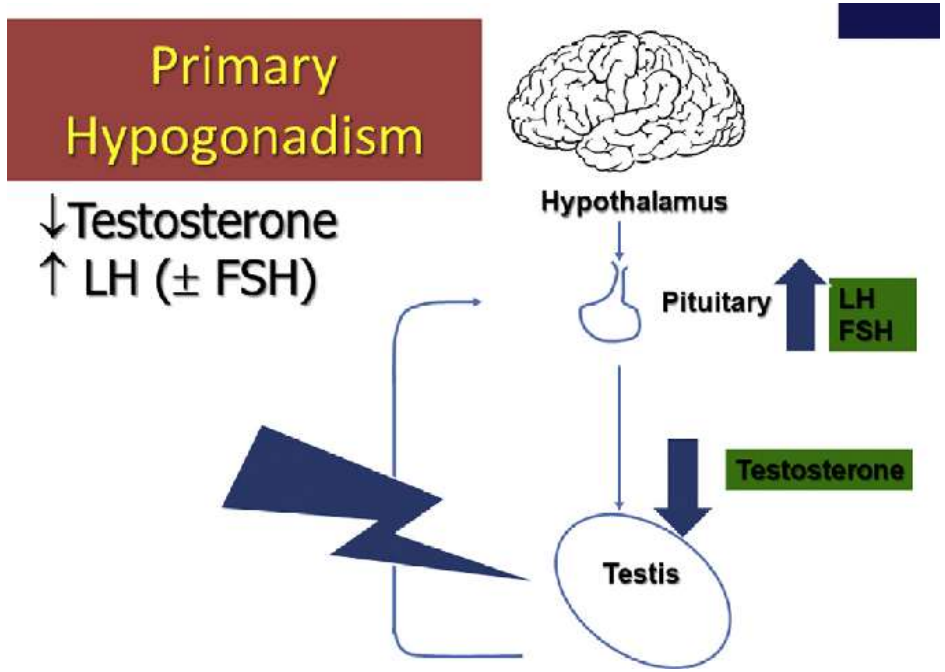
➢Klinefelter syndrome .

➢Mutation in the FSH and LH receptor genes .

➢Cryptorchidism .

➢5^{α}- reductase deficiency.

➢Anorchia /Leydig cell agenesis.



Causes of male Hypogonadism

- **Causes of Primary Hypogonadism (Hypergonadotrophic hypogonadism) in males :**

2. <u>Acquired diseases</u>:

- Infections, especially mumps orchitis .
- Testicular torsion .
- Trauma .
- Radiation .
- Environmental toxins .
- Orchidectomy .
- Autoimmune damage .
- Sickle Cell Anemia .
- Chronic systemic illnesses (Hepatic cirrhosis /Chronic renal failure /AIDS) .

Causes of male Hypogonadism

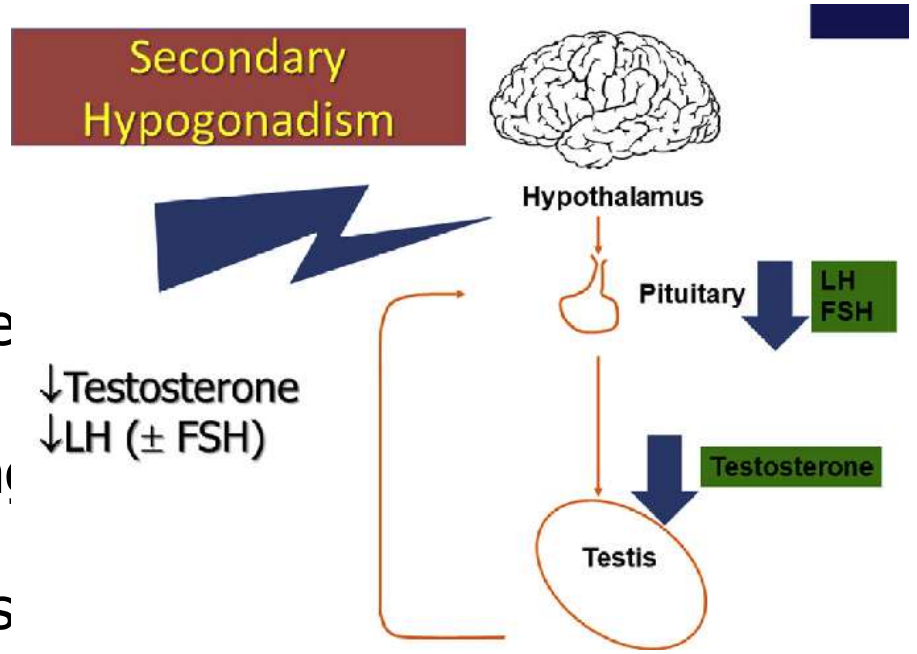
- **Causes of Secondary Hypogonadism (Hypogonadotrophic hypogonadism) in males :**

1. **Acquired:**

➢ Tumors

➢ "Functional" gonadotropin deficiency
-Chronic systemic disease (Asthma / Malabsorption/ cystic fibrosis / renal failure
-Anorexia nervosa, bulimia.
-Hyperprolactinemia
-Hypothyroidism, diabetes mellitus, Cushing disease.

➢ Infiltrative diseases (Granulomatous diseas Hemochromatosis)



Causes of male Hypogonadism

- **Causes of Secondary Hypogonadism (Hypogonadotrophic hypogonadism) in males :**

2. **Congenital:**

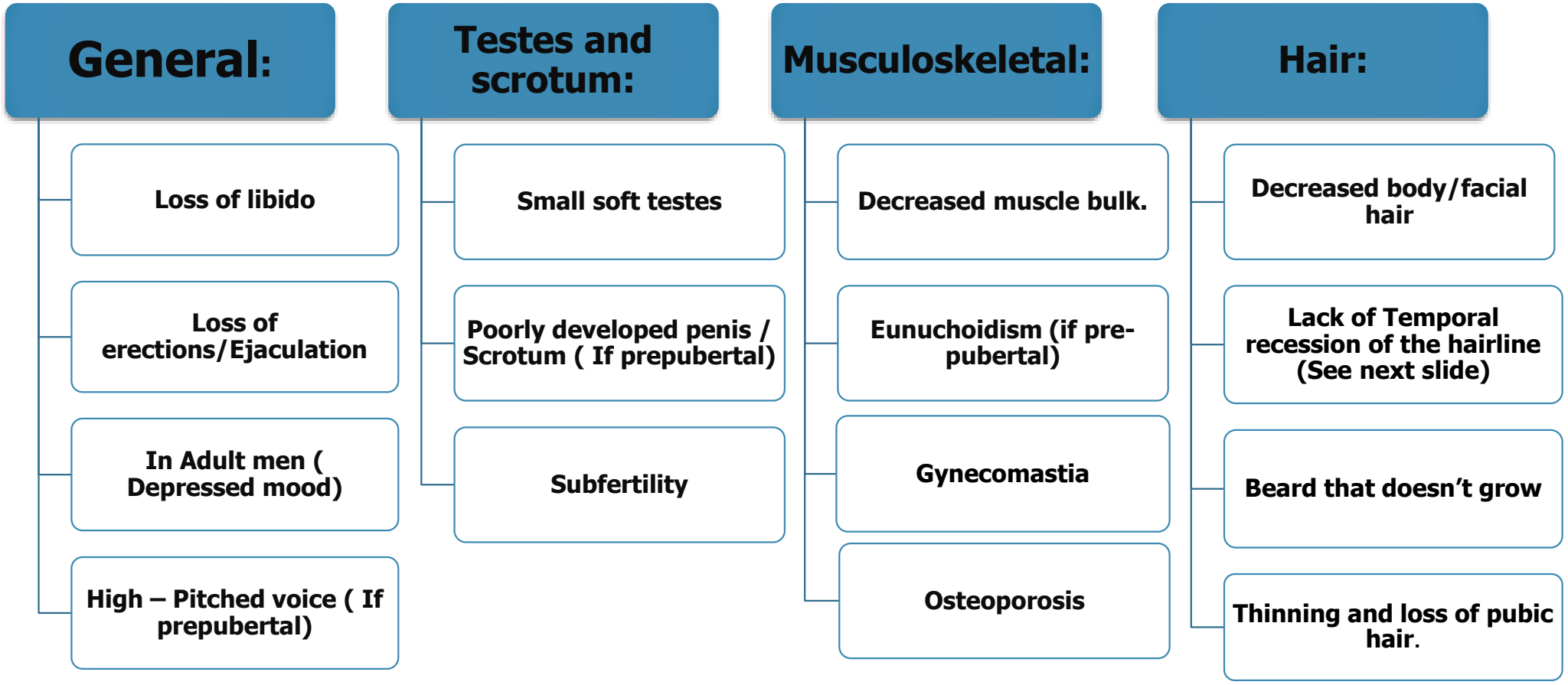
- Isolated GnRH deficiency:
  -Kallmann syndrome.
- Congenital malformations often associated with craniofacial anomalies.
- Idiopathic forms of multiple anterior pituitary hormone deficiencies.

Clinical features of Hypogonadism

- The clinical features of male hypogonadism depend upon the age of onset, severity of testosterone deficiency, and whether there is a decrease in one or both of the two major functions of the testes: sperm production and testosterone production.

1. Decreased sperm production ☐ Infertility.
2. Symptoms are usually related to testosterone deficiency ☐ Low energy / Low Libido / Erectile Dysfunction / Decreased body/facial hair .

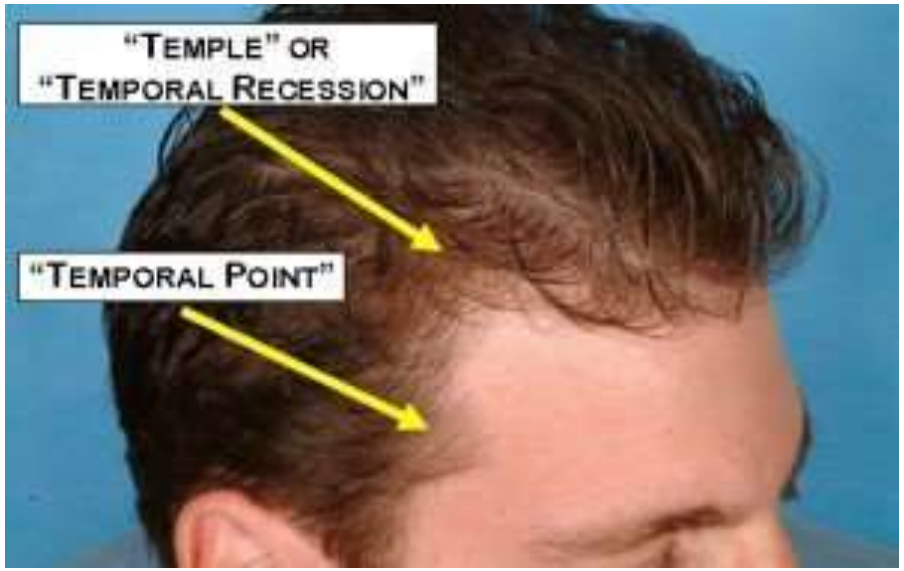
Clinical features of Hypogonadism



***Gynecomastia, tender or not, is more likely to occur in primary than secondary hypogonadism, as is infertility.

Clinical features of Hypogonadism

- **<u>Lack of Temporal recession of the hairline.</u>**



Investigations for Hypogonadism

1. Testicular disease may be immediately apparent but basal **levels of testosterone ,LH and FSH** should be measured to distinguish between primary testicular failure and hypothalamic-pituitary disease

2. **Depending on the causes**, **semen analysis, chromosomal analysis, pituitary MRI scan, prolactin levels and bone age estimation** are required.

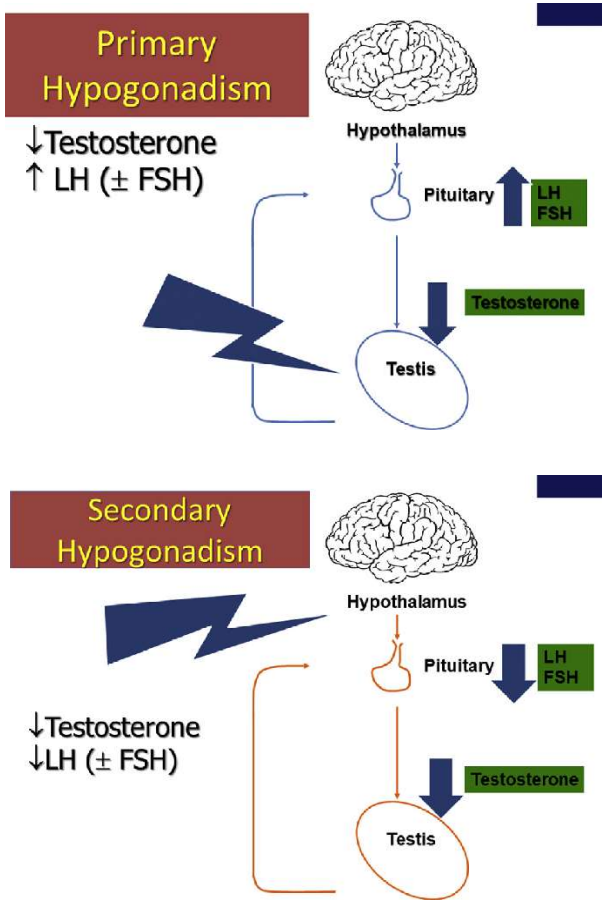
* Patients with Hypogonadotrophic (Secondary) Hypogonadism should be investigated for pituitary disease.
* Patients with Hypergonadotrophic (Primary) Hypogonadism should have the testes examined for cryptorchidism or atrophy, and a karyotype should be performed (to identify Klinefelter's syndrome)

Investigations for Hypogonadism

- **Hypogonadism** can result from disease of the testes (primary hypogonadism) or disease of the hypothalamus or pituitary (secondary hypogonadism).
  The **distinction** between these disorders, is made by measurement of the serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH):

- 1) The patient has **primary hypogonadism** if the serum testosterone concentration and/or the sperm count are **below normal** and the serum LH and/or FSH concentrations are **above normal**.

- 2) The patient has **secondary hypogonadism** if the serum testosterone concentration and/or the sperm count are **below normal** **and** the serum LH and/or FSH concentrations are **normal** or **low.**



Treatment of Hypogonadism

- **Treatment is testosterone.**
- **Testosterone replacement** is clearly indicated in younger men with significant hypogonadism to **prevent osteoporosis and restore muscle power and libido.**
- Replacement is usually **transdermal gel** or **intramuscular injection**.
- In gonadotropin deficiency LH and FSH or **pulsatile GnRH** may be used when fertility is desired.

*The role of testosterone replacement to treat the decline in serum testosterone concentration that occurs with aging in men, in the absence of identifiable pituitary or hypothalamic disease, has been unclear. However, results from the Testosterone Trials suggest that testosterone has a beneficial effect on sexual function, mood, possibly walking, bone density, and anemia .

Patient monitoring recommendations

1. **Prostate specific antigen (PSA)** should be measured in patients older than 50, because testosterone can aggravate prostatic carcinoma.
2. **Hemoglobin** concentration should be monitored in older men, as androgen replacement can cause polycythemia.
3. Testosterone therapy impairs spermatogenesis further by suppressing pituitary gonadotropin secretion.

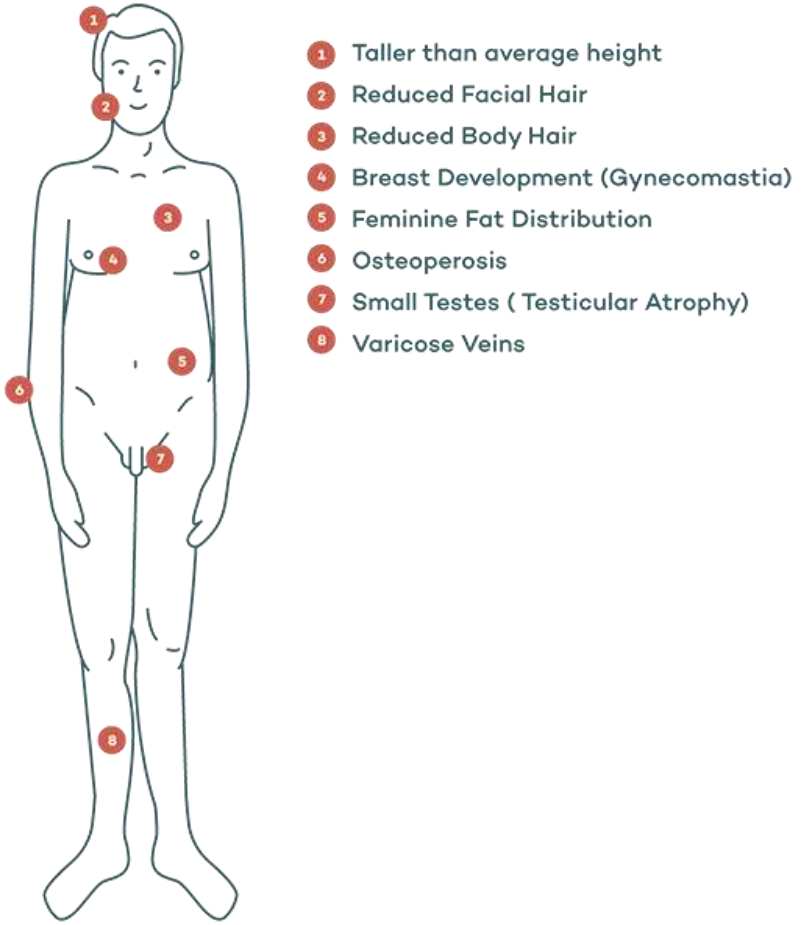
Klinefelter's syndrome (Hypergonadotropic Hypogonadism)

- **Klinefelter's syndrome :** is the most common primary developmental abnormality causing hypogonadism, affecting 1 of every 400-500 males . It's caused by one or more supernumerary X chromosomes.

- usually associated with a **47xxy karyotype**.
- There is both a impairment of Leydig cells function and seminiferous tubular dysgenesis.
- Usually presents in adolescence with poor sexual development, small or undescended testes, gynecomastia or infertility
- Characteristic long leg length associated with 47xxy,and may be exacerbated by androgen deficiency with lack of epiphyseal closure in puberty.
- Learning difficulties and behavioral disorders.
- Increased **risk** of breast cancer and type 2 diabetes in later life.
- Predisposition for emphysema and bronchiectasis.

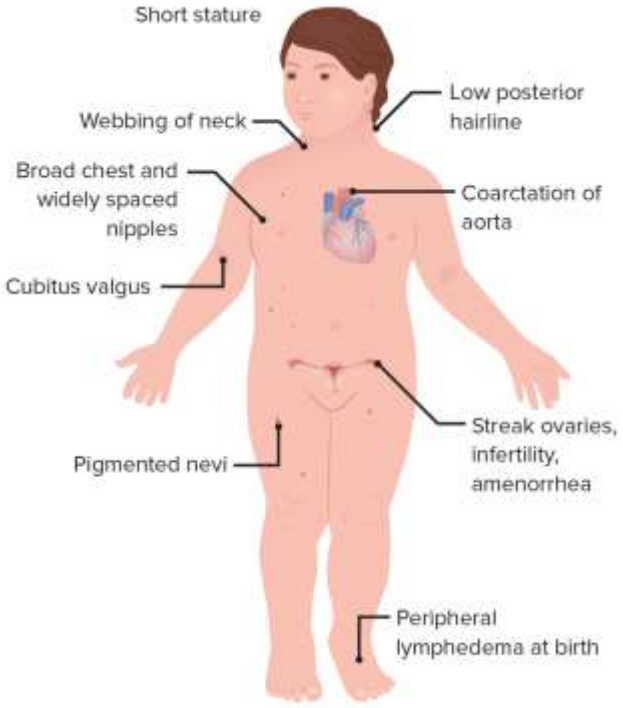
Klinefelter's syndrome (Hypergonadotropic Hypogonadism)

1. Infertility is the most common symptom.
2. Confirmation by chromosomal analysis.
3. Treatment is androgen replacement unless testosterone levels are normal.
4. No treatment is possible for the abnormal seminiferous tubules and infertility.



Turner syndrome
Hypergonadotropic Hypogonadism(female)

- Genetic condition that only affects **females**.
- The condition is caused by **an abnormal chromosome** and affects about one in every 2,500 baby girls.
- Turner syndrome is typically caused by **nondisjunction**.
- A pair of sex chromosomes fails to separate during the formation of an egg (or sperm), so, when an abnormal egg unites with a normal sperm to form an embryo, that embryo may end up missing one of the sex chromosomes **(X rather than XX).**
- **45,X.**

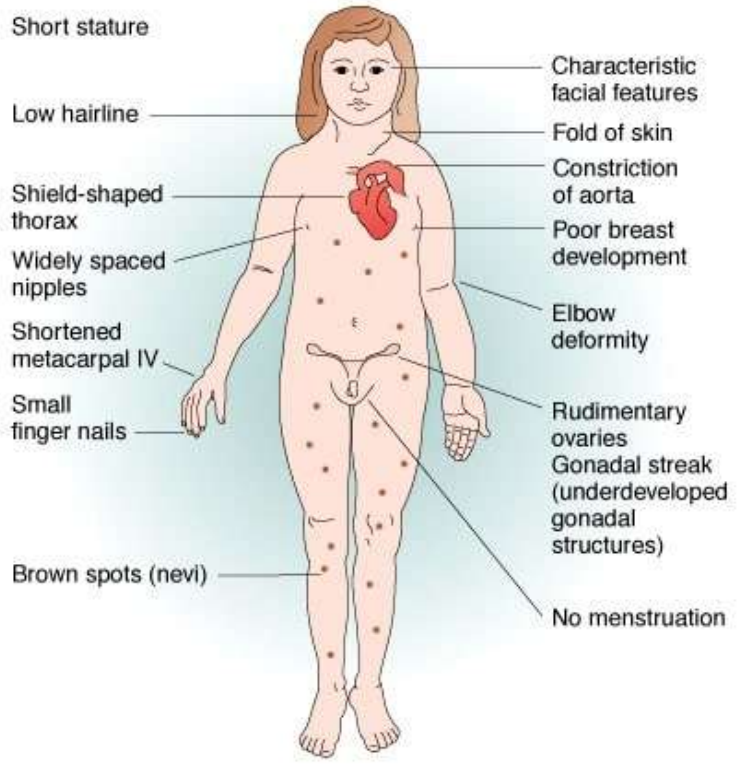


Turner syndrome
Hypergonadotropic Hypogonadism(female)

- Two characteristics that occur in almost all cases of TS. They are:

1. Being shorter than average in height.
2. A lack of development of the ovaries, leading to infertility.

- One of the missing genes on the X chromosome is the SHOX gene, which is responsible for long bone growth.
- The missing SHOX gene is the reason girls who have the disorder are unusually short.
- Other missing genes regulate ovarian development, which influences sexual characteristics.



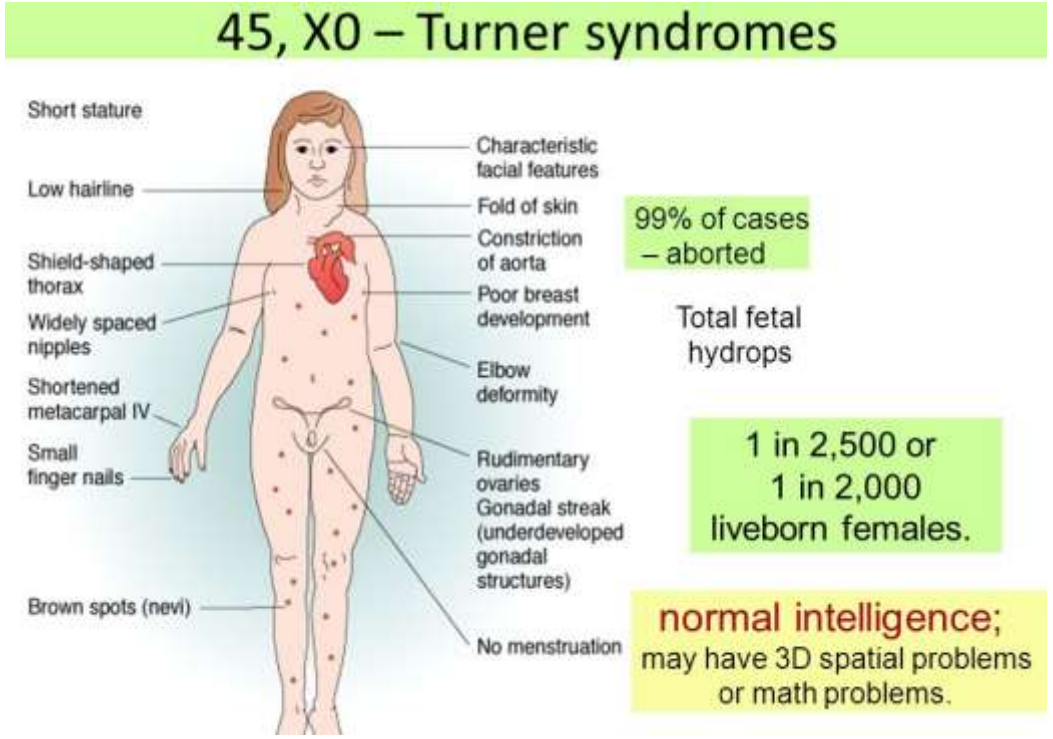
Turner syndrome
Hypergonadotropic Hypogonadism(female)

- **Possible symptoms in young infants include:**

1. Swollen hands and feet.
2. Wide and webbed neck and a low or indistinct hairline.

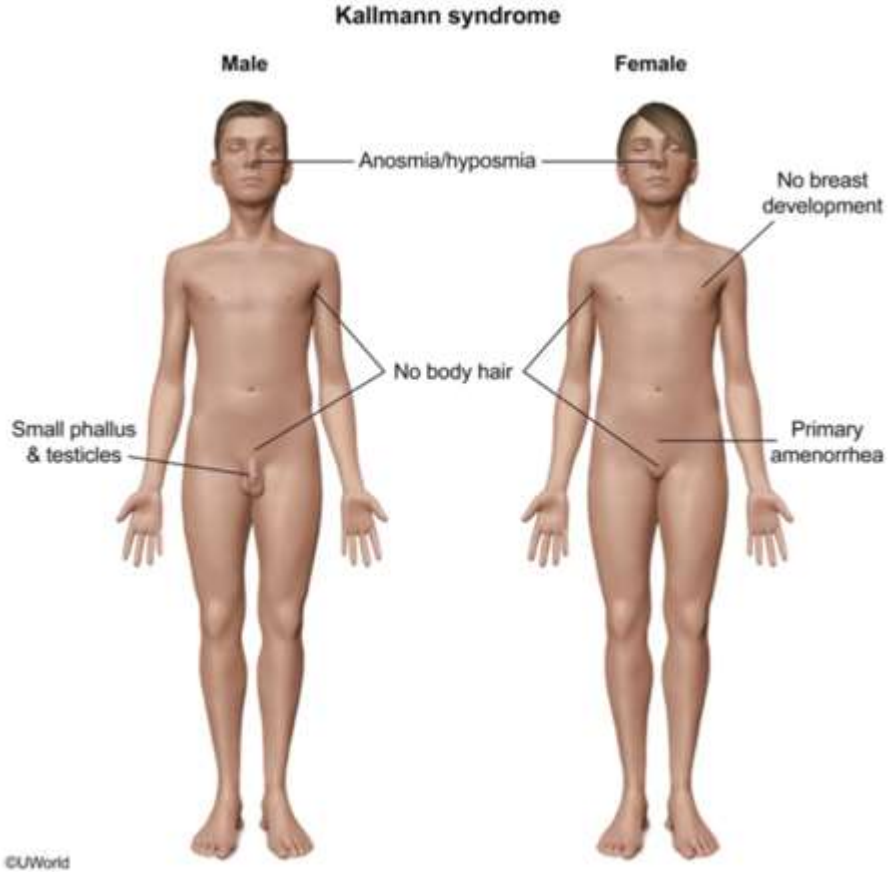
- **A combination of the following symptoms may be seen in older females:**

1. Absent or incomplete development at puberty.
2. A broad chest and widely spaced nipples.
3. Drooping eyelids , Dry eyes.
4. Infertility.
5. No periods (absent menstruation).
6. Short height.
7. Vaginal dryness.
8. Arms that turn out slightly at the elbow.

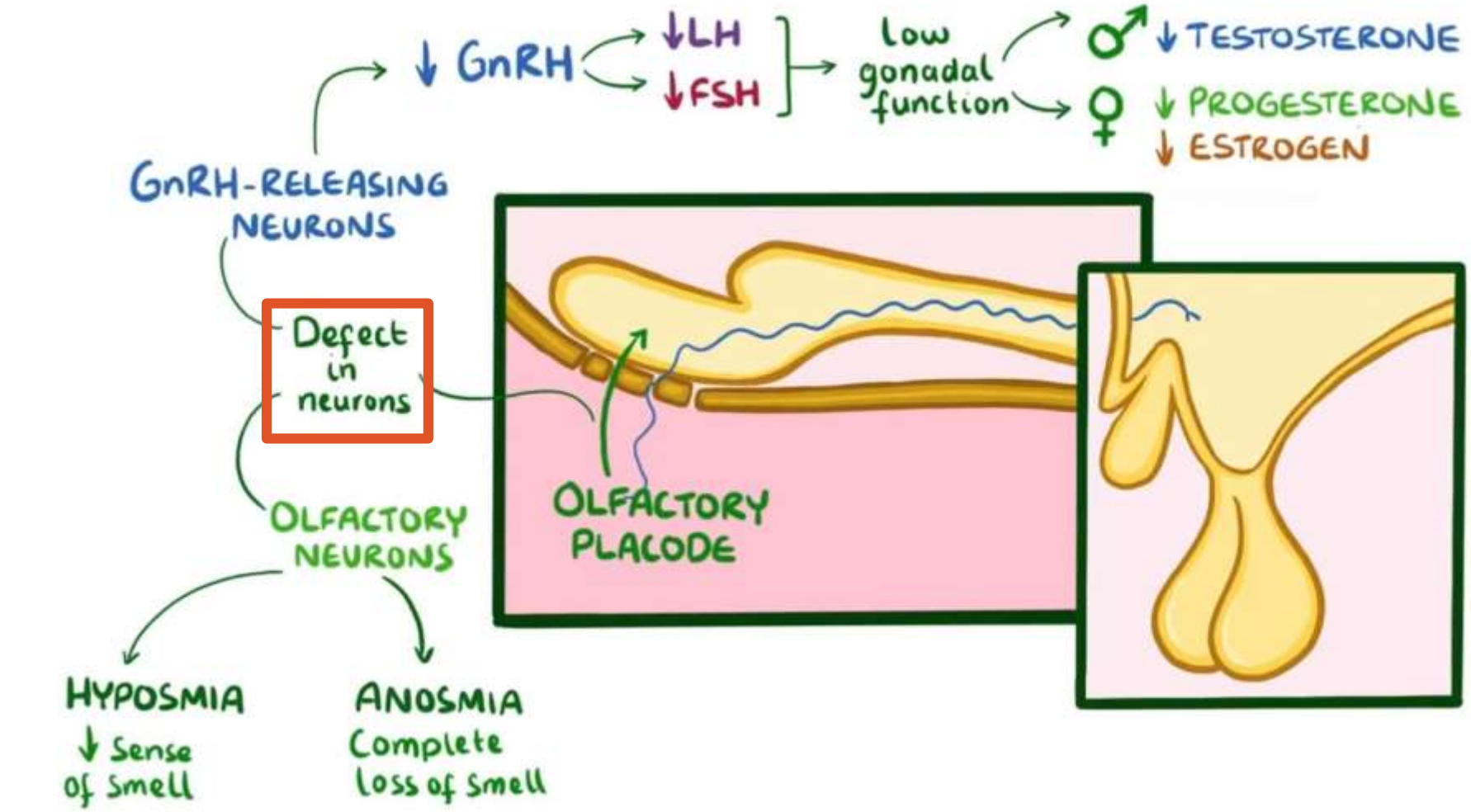


Kallmann's syndrome (Hypogonadotropic Hypogonadism)

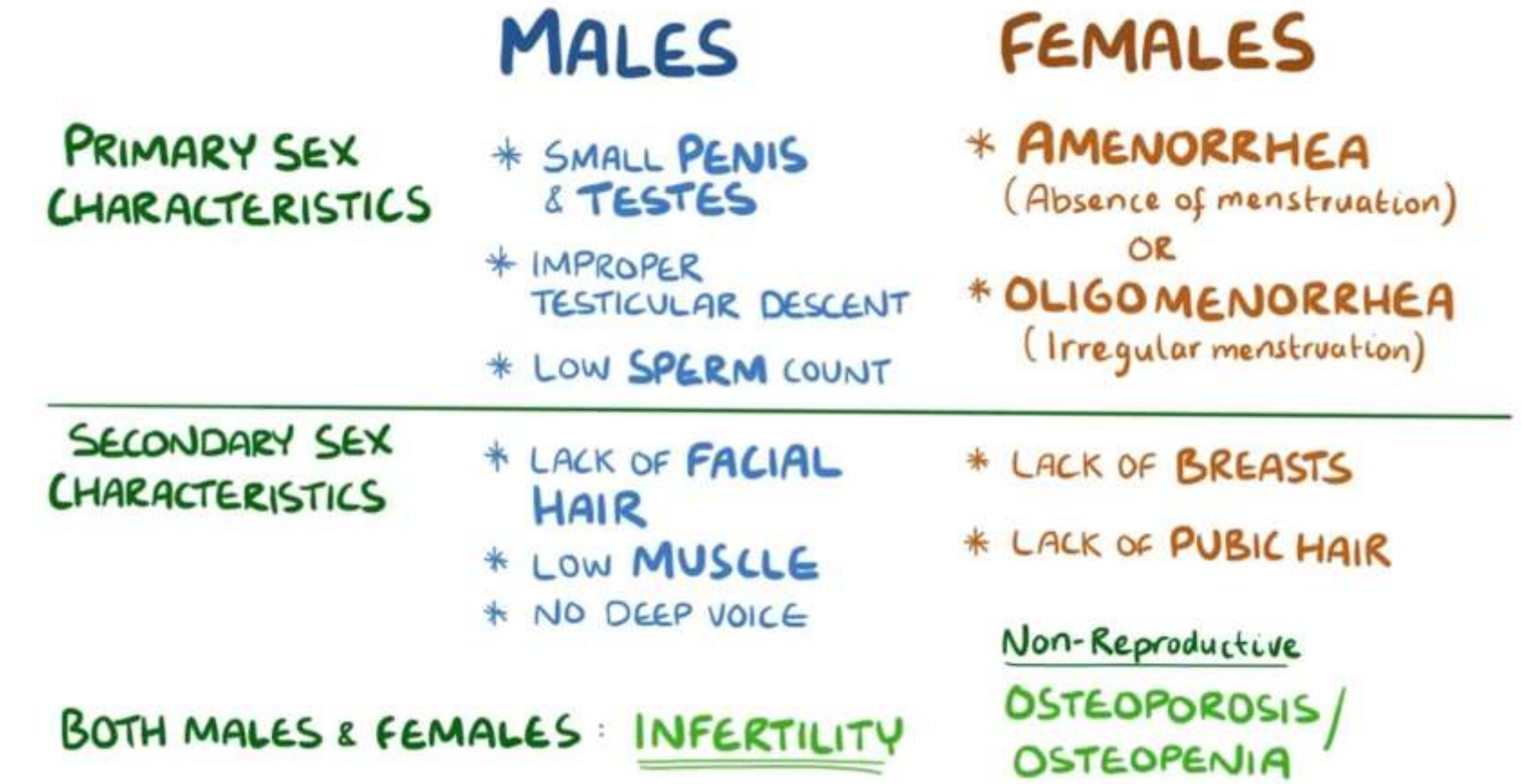
- **Happens in females or males.**
- Congenital hormonal condition characterized by the failure of an individual to enter pubert
- It is a form of **Hypogonadotrophic Hypogonadism** (HH). In particular it is a failure of communication between the hypothalamus and the anterior pituitary glan
- It results in the sex organs or **gonads** (teste or ovaries) **not maturing** in the usual manner during puberty.



Kallmann's syndrome (Hypogonadotropic Hypogonadism)



Kallmann's syndrome (Hypogonadotropic Hypogonadism)



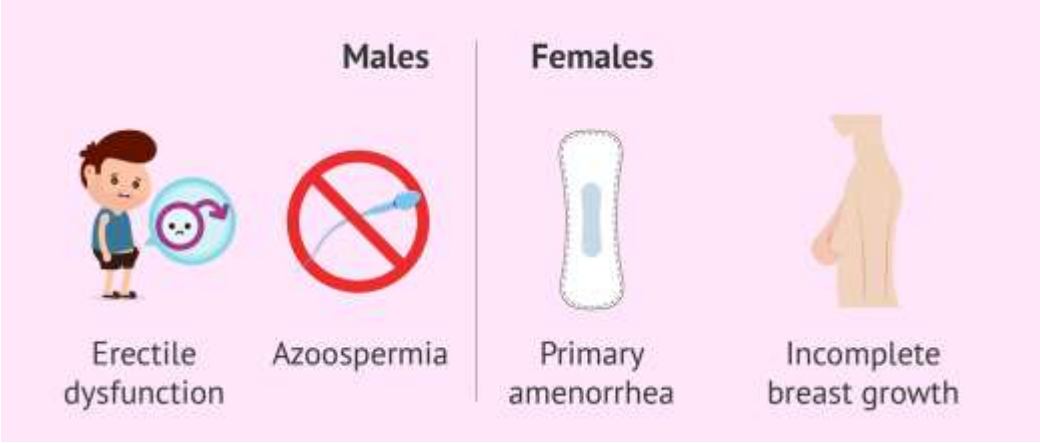
Kallmann's syndrome (Hypogonadotropic Hypogonadism)

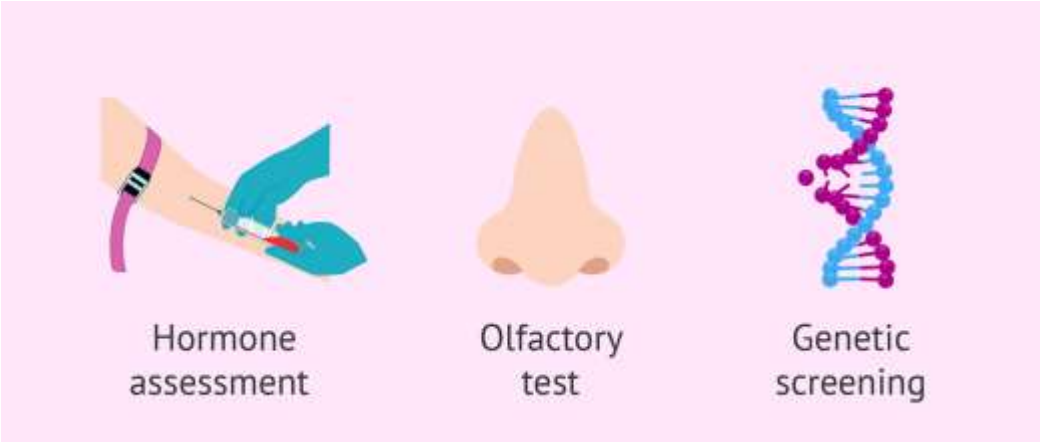
Hypothalamic neurons that are responsible for releasing gonadotropin-releasing hormone (GnRH neurons) fail to migrate into the hypothalamus during embryonic development.

1. **Failure to start or fully complete puberty in both men and women**
2. **Lack of testicle development in men**; size < 3 cm^3. The normal range is between 12 and 30 cm^3
3. **Primary amenorrhea** or failure to start menstruation in women
4. **Poorly defined secondary sexual characteristics** in both men and women.
5. **Infertility**
6. **Hypogonadotropic hypogonadism (↓LH /↓FSH)**
7. **Congenital** (present from birth)
8. Total lack of sense of smell (**anosmia**) or markedly reduced sense of smell (**hyposmia**).

Kallmann's syndrome (Hypogonadotropic Hypogonadism)

1. **Isolated GnRH deficiency.**
2. Associated with decreased or absent sense of smell (**anosmia**), and sometimes with other bony, renal and cerebral abnormalities.
3. **Management is that of secondary hypogonadism.**
4. Fertility is possible.





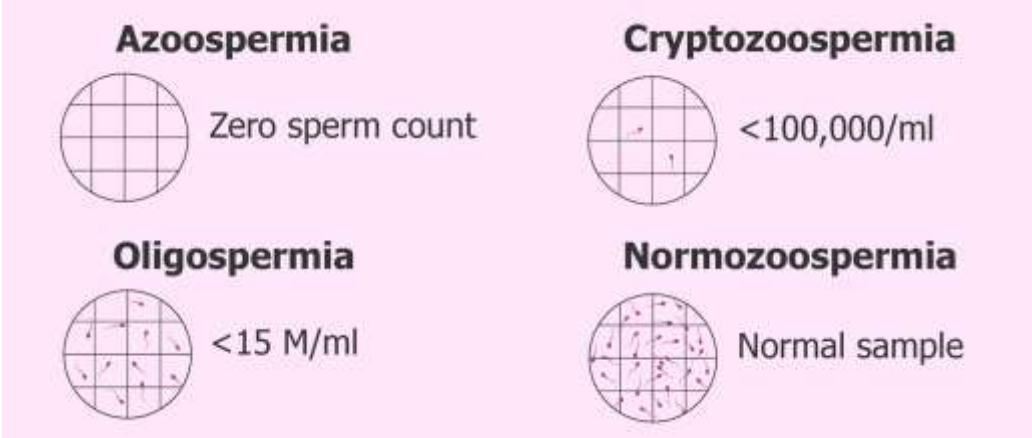
Normosmic idiopathic Hypogonadotropic Hypogonadism

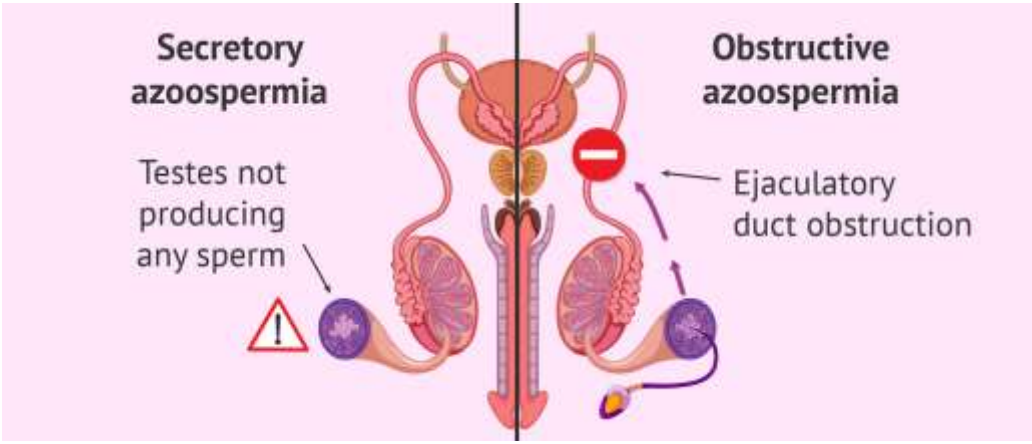
1. Idiopathic hypogonadotropic hypogonadism (IHH) with **normal sense of smell (normosmic IHH)**) is a rare genetic disorder caused by an **isolated defect in the secretion of GnRH** by the hypothalamus or the action of GnRH on the pituitary gonadotrophins.
2. Hypogonadism, infertility, absent ,incomplete or partial pubertal maturation.

Diseases	Klinfelter syndrome	Turner syndrome	Kallmman syndrome
Karyotype	Xxy 47	Xo 45	Normal 46 xx or xy
FSH/LH	high	high	low
Testosterone	low	-	Low in males
Estrogen	-	low	Low in females
Treatment	Hormonal replacement	Hormonal replacement	Hormonal replacement Gonadotropins or GNRH pulsatile therapy

Oligospermia or Azoospermia

1) These **may be secondary** to gonadotrophin deficiency and can be corrected by gonadotrophin therapy.
2) **More often they result from primary testicular diseases**, in which case they are rarely treatable.
3) **Azoospermia** with normal testicular size and low FSH levels suggests a vas deferens block, which is sometimes reversible by surgical intervention.





Amenorrhea

Mariam Fakhouri

Primary Amenorrhea:

- Female patient who has never menstruated-

Is the absence of menstrual bleeding and secondary sexual characteristics (for example, breast development and pubic hair) in a girl by age 13 years.

or

the absence of menstrual bleeding with normal development of secondary sexual characteristics in a girl by age 15 years.

This occurs as a manifestation of delayed puberty or a consequence of anatomical defect of the female reproductive system, such as endometrial hypoplasia or vaginal agenesis

Agenesis : Absence or incomplete development of an organ.

Hypoplasia : the underdevelopment , incomplete development or atrophy of a tissue or organ

The causes of primary amenorrhea

1- in the absence of secondary sexual characteristics development:

Hypogonadotropic hypogonadism (low FSH and LH levels)

- constitutional delay of growth and puberty

Hypergonadotropic hypogonadism (elevated FSH and LH levels)

- gonadal dysgenesis .. Turner syndrome
- premature ovarian failure

2- in the presence of the secondary sexual characteristics development:

Müllerian agenesis (the congenital absence of a vagina and abnormal uterine development)

An imperforate hymen or a transverse vaginal septum

Secondary Amenorrhea:

-cessation of menstruation-

It is defined as the absence of menses for three months in a woman with previously normal menstruation

The causes of secondary amenorrhea :

1)Physiological

-Pregnancy

-Menopause

2)Hypogonadotrophic hypogonadism

(hypothalamic/pituitary dysfunction)

Causes of secondary amenorrhea (cont.):

3)Ovarian dysfunction

Polycystic ovarian syndrome

Hypergonadotrophic hypogonadism

Androgen-secreting tumor

4)Uterine dysfunction

Asherman's syndrome

(adhesions and/or fibrosis of the endometrium)

5)Premature ovarian failure (premature menopause)

6)Hyperprolactenemia

7)Hypothyroidism

Clinical assessment :

History:

- Age of the patient
- Date of onset
- Age of menarche
- Sudden or gradual onset
- General health
- Weight changes in recent past:

Weight gain :

may suggest hypothyroidism, Cushing's syndrome or, very rarely, a hypothalamic lesion

Weight loss : of any cause can cause amenorrhea by suppression of gonadotrophins

-anorexia

History:

- Stress (job, lifestyle, exams, relationships).
- Excessive exercise.
- Hirsutism, acne, virilization.

(Hirsutism, obesity and long-standing irregular periods suggest polycystic ovarian syndrome)

- Headaches/visual symptoms.
- Drugs.
- Chronic or long-term illnesses.
- Family history of amenorrhea & genetic defects or disorders.
- Past history of pregnancies ,gynecological surgery.
- Estrogen deficiency symptoms associated with menopause like: Hot flushes, sweating, Anxiety, Irritability, Emotional lability, Dyspareunia (difficult or painful sexual intercourse).

Physical Examination

:

- General health
- Body shape and skeletal abnormalities
- Weight and height
- Hirsutism and acne
- Evidence of virilization
- Maturity of secondary sexual characteristics
- Galactorrhoea
- Normality of vagina, cervix and uterus

Approach to evaluation :

-Once pregnancy has been ruled out, a logical approach to women with either primary or secondary amenorrhea is to consider disorders based upon the levels of control of the menstrual cycle: pituitary, hypothalamus, ovary, and uterus.

-Determining the site of the defect is important because it determines the appropriate therapeutic regimen.

-While the most common causes of secondary amenorrhea are likely to be functional hypothalamic amenorrhea or polycystic ovary syndrome (PCOS), disorders with an anatomic or pathologic cause must be ruled out .

Investigations :

-**Blood tests** : Serum LH, FSH, estradiol, prolactin, testosterone, T3&4, TSH should be measured.
High LH, FSH with low estradiol suggest primary ovarian failure.
Elevated LH, prolactin, testosterone levels with normal estradiol are common in PCOS.
Low LH, FSH and estradiol suggest hypothalamic or pituitary disease and pituitary MRI is indicated .

-**karyotype** should be performed in younger women to exclude mosaic Turner's syndrome.

-**Ultrasonography** of the pelvis may be performed to assess the abnormalities.

-**Ovarian biopsy** may be needed for primary ovarian failure.

Table 19.25 Amenorrhoea: differential diagnosis and investigation

Hormone results					Possible diagnoses	Secondary tests
LH	FSH	E2	PRL	T		
↑	↑	↓	N	N	**Ovarian failure**	
					Ovarian dysgenesis[a] Premature ovarian failure[a] Steroid biosynthetic defect[a] (Oophorectomy) (Chemotherapy) Resistant ovary syndrome	Karyotype Ultrasound of ovary/uterus Laparoscopy/biopsy of ovary HCG stimulation
↓	↓	↓	N	N	**Gonadotrophin failure**	
					Hypothalamic-pituitary disease[a] Kallmann's syndrome/nIHH[a] Possible hypothalamic causes: Hypothalamic amenorrhoea[a] Weight-related amenorrhoea[a] Exercise-induced amenorrhoea and anorexia[a] Post-pill amenorrhoea General illness[a]	Pituitary MRI if diagnosis unclear Possibly LHRH test Serum free T_4 Possibly full assessment of pituitary function
↓	↓	↓	↑/↑↑	N	**Hyperprolactinaemia**	
					Prolactinoma[a] Idiopathic hyperprolactinaemia[a] Hypothyroidism[a] Polycystic ovarian disease[a] Physiological in lactation Dopamine antagonist drugs	See page 955 (hyperprolactinaemia) Serum free T_4/TSH Pituitary MRI Other tests for PCOS
↑/N	N	N	N/↑	N/↑	**Polycystic ovary syndrome[a]**	
					Rarely Cushing's syndrome	Androstenedione, DHEAS SHBG Ultrasound of ovary Progesterone challenge See page 957 (Cushing syndrome)
N/↓	N/↓	N/↓	N	↑↑	**Androgen excess**	
					Gonadal or adrenal tumour Congenital adrenal hyperplasia[a]	Imaging ovary/adrenal 17a-OH-progesterone
N	N	↑	↑	N	**Pregnancy**	Pregnancy test
N	N	N	N	N	**Uterine/vaginal abnormality**	
					Imperforate hymen[a] Absent uterus[a] Lack of endometrium	Examination findings (?EUA) Ultrasound of pelvis Progesterone challenge Hysteroscopy

[a]These conditions may present as primary amenorrhoea. LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, oestradiol; PRL, prolactin; T, testosterone; DHEAS, dehydroepiandrosterone sulphate; SHBG, sex hormone-binding globulin; HCG, human chorionic gonadotrophin; LHRH, luteinizing hormone-releasing hormone; nIHH, normosmic idiopathic hypogonadotropic hypogonadism; EUA, examination under anaesthesia.

First of all, the underlying cause should be treated! Wherever possible (e.g. hypothyroidism, low weight, stress, excessive exercise).

Goals — The overall goals of management in women with amenorrhea include:

-Correcting the underlying pathology, if possible

-Helping the female patient to achieve fertility, if desired

-Preventing complications of the disease process (eg, estrogen replacement to prevent osteoporosis)

hirsutism

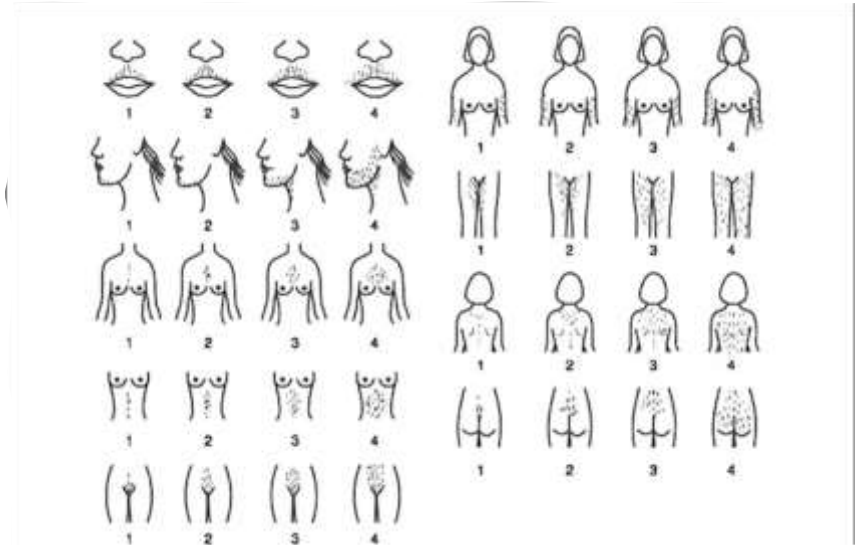
Female

By Sara aljawamis

Definition of hirsutism

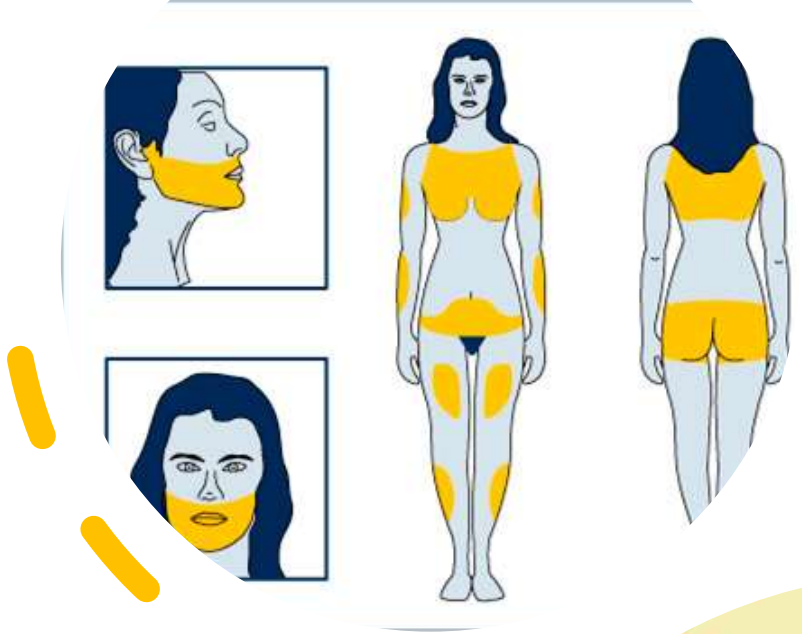
- **Hirsutism is when a women grows coarse hair in places they typically either do not grow hair or only have very fine hair (e.g., moustache, chin, torso, back).**

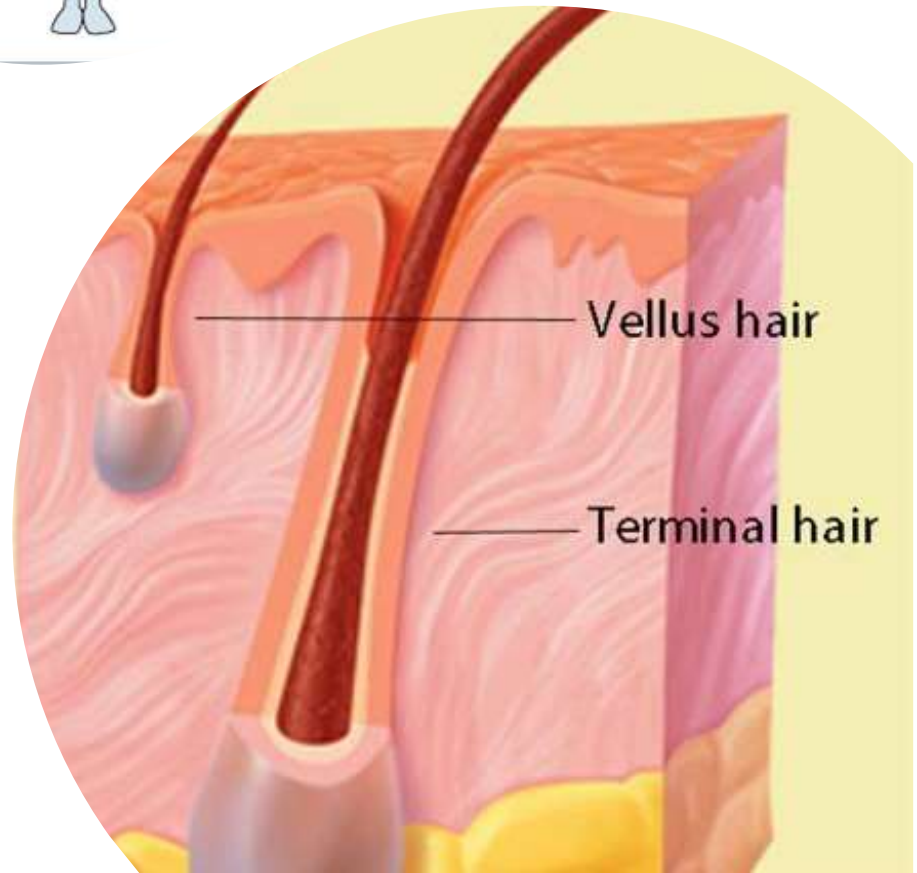
- **It is a medical sign rather than a disease and may be a sign of a more serious medical condition, especially if it develops well after puberty.**



Definition of hirsutism

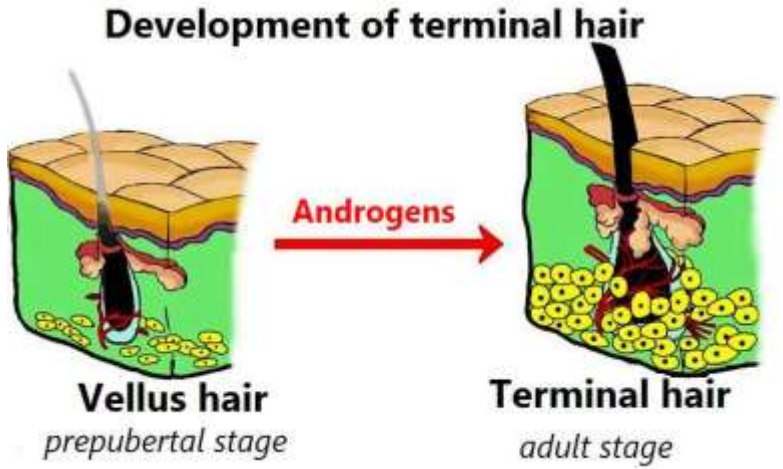
- **Soft vellus hair is normally present all over the body , and this type of hair on the face and elsewhere is normal and not sex hormone dependent .**
- **While terminal (coarse) hair in the beard , moustache , breast, chest , axilla , abdominal midline , pubic and thigh areas is sex hormone dependent , and any excess hair in these regions is a marker of Hirsutism (increased ovarian or adrenal androgen production, most commonly PCOS)**

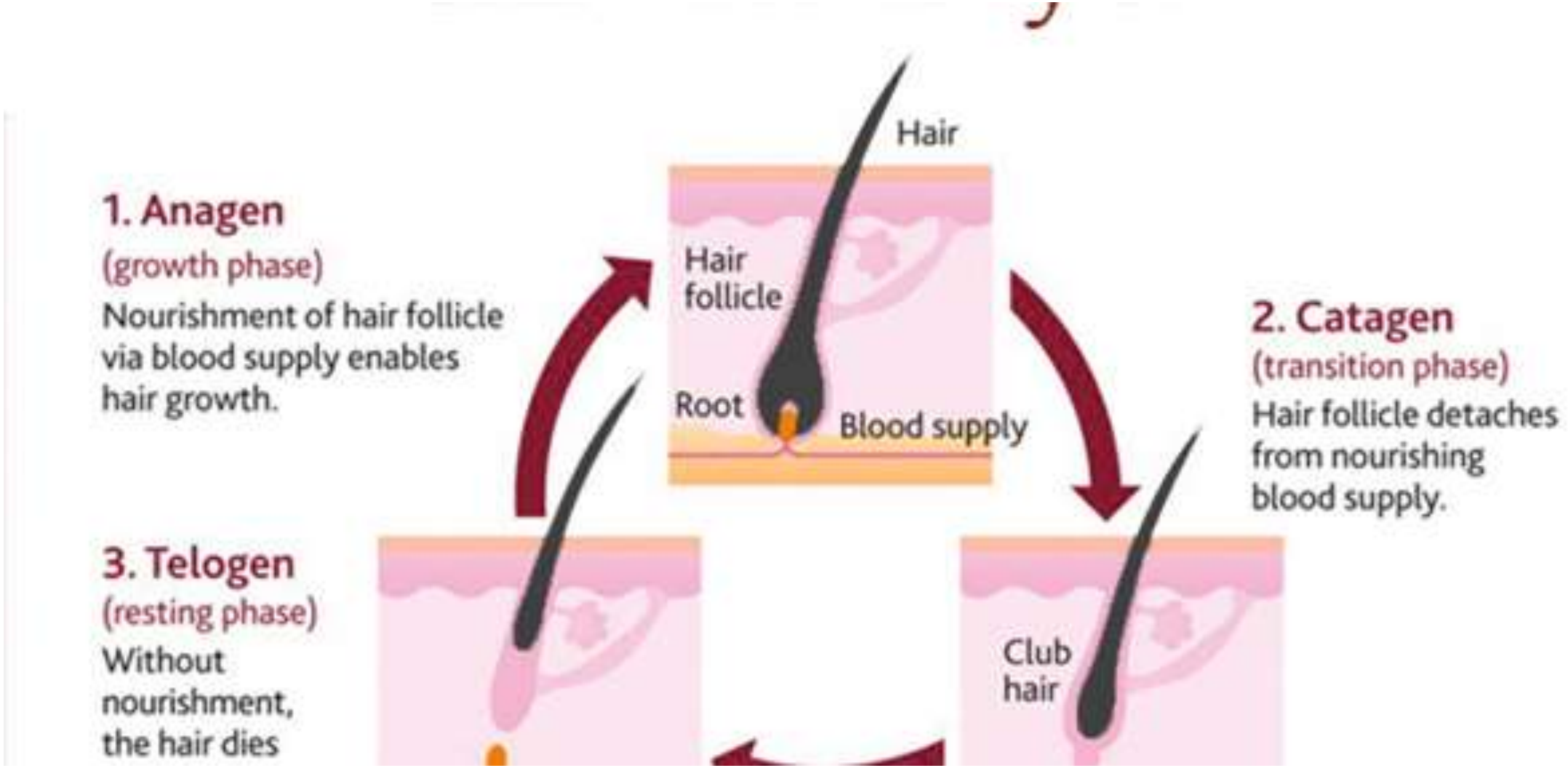




Pathophysiology

- **The number of hair follicles does not change over an individual's lifetime, but the follicle size and type of hair can change in response to numerous factors, particularly androgens.**
- **Depending upon the body site hormonal regulation plays an important role in the hair growth cycle.**
- **Androgens increase hair follicle size, hair fiber diameter, and the proportion of time terminal hairs spend in the anagen phase.**

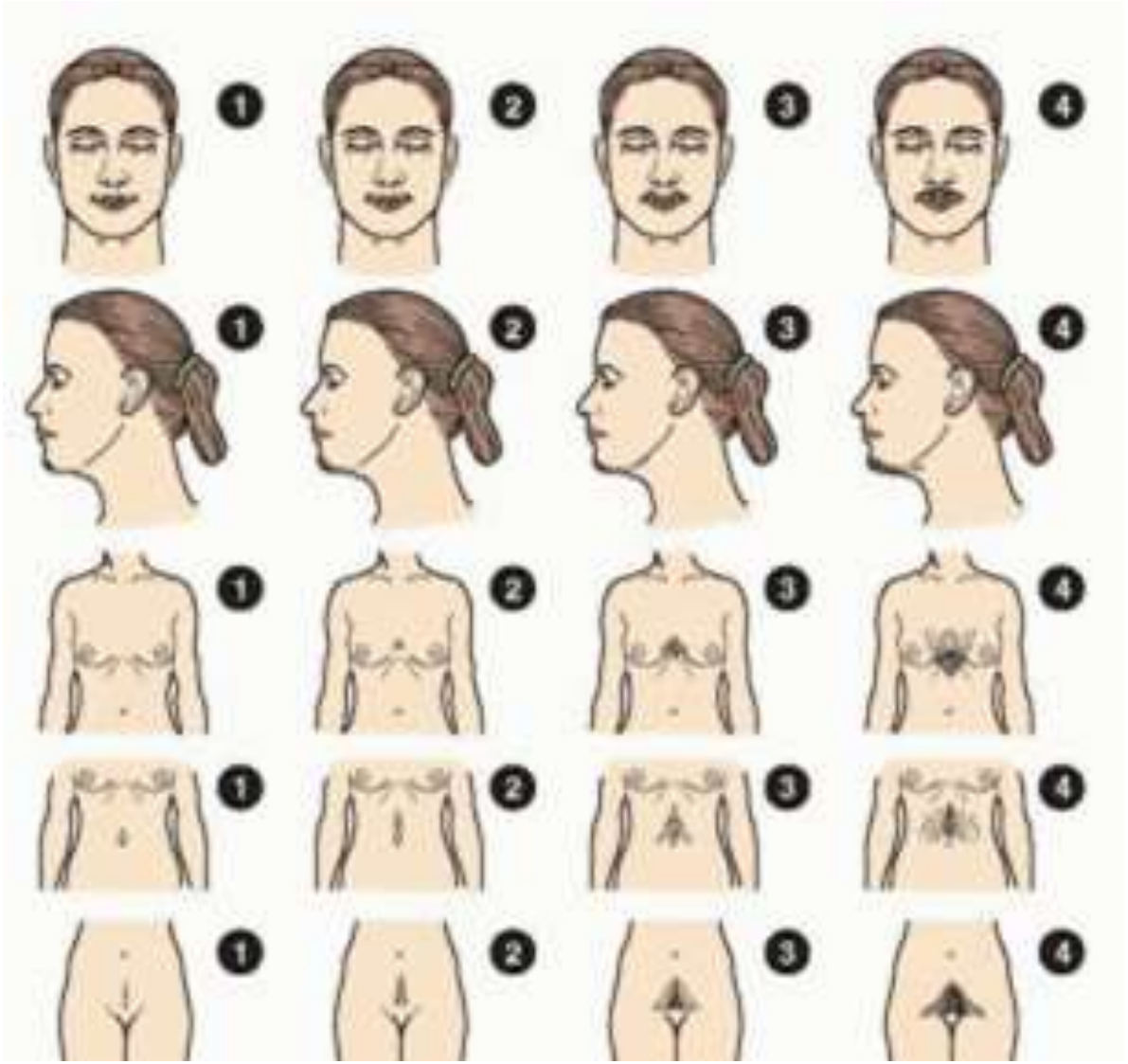



1. Anagen
(growth phase)
Nourishment of hair follicle via blood supply enables hair growth.
Hair
Hair follicle
Root
Blood supply
2. Catagen
(transition phase)
Hair follicle detaches from nourishing blood supply.
Club hair
3. Telogen
(resting phase)
Without nourishment, the hair dies

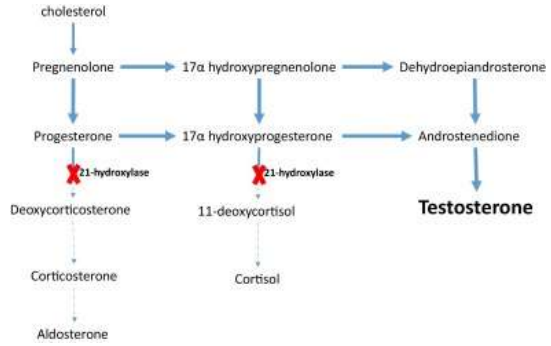
Causes

- **1) an increased level of androgens, the male hormones.**

- **2) an oversensitivity of hair follicles to androgens. Male hormones such as testosterone stimulate hair growth, increase size and intensify the growth and pigmentation of hair.**

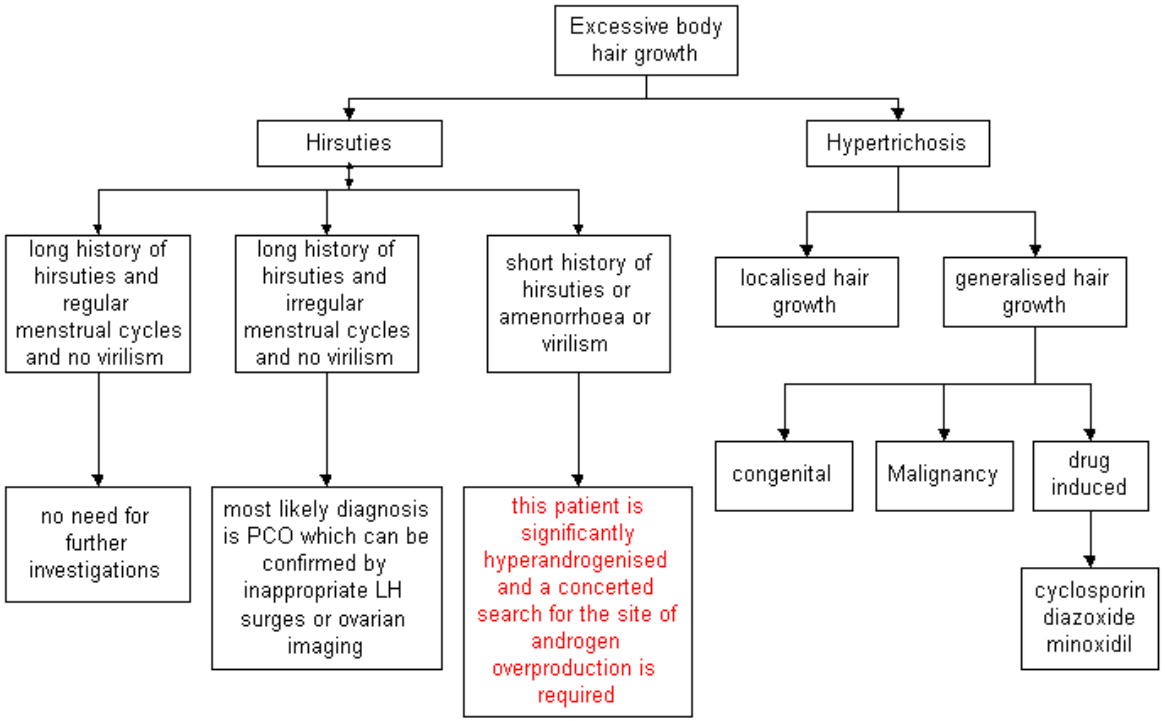


Causes



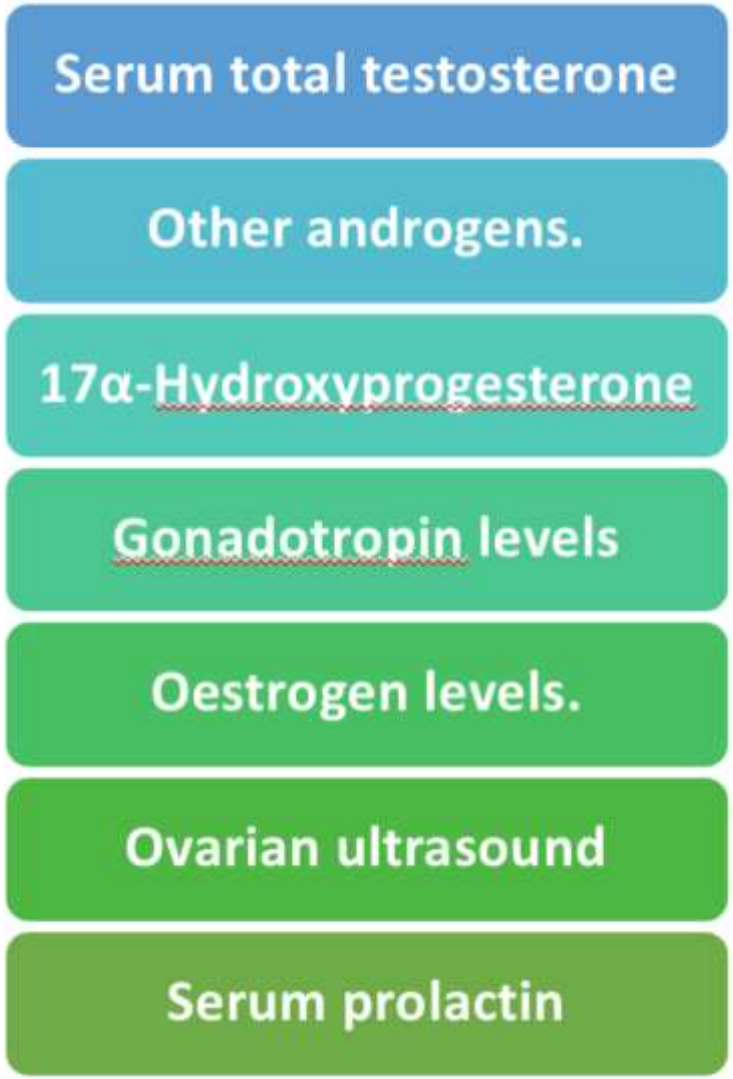
- **conditions that may increase a woman's normally low level of male hormones:**

- **1- Polycystic ovary syndrome , PCOS, (the most common)**
- **2- Congenital adrenal hyperplasia, in turn mostly caused by 21-α hydroxylase deficiency**
- **3- Cushing's disease**
- **4- Growth hormone excess (Acromegaly)**
- **5- Tumors in the ovaries**
- **6- adrenal gland (cancer), Von Hippel-Lindau**
- **7- Insulin resistance/ hyperinsulinemia**
- **8- Stromal Hyperthecosis**
- **9- Obesity**
- **10- Iatrogenic use of drugs like Tetrahydrogestrinone**
- **11- Adverse effect of Phenytoin**
- **12- idiopathic hirsuitism: Hirsutism with no identifiable cause in a women with no other signs of virilization and with normal menstrual cycles, hormone levels and weight.**



- **should be distinguished from hypertrichosis which is generalized excessive terminal hair growth that affect both men and women that doesn’t follow androgen induced pattern**

Investigations



- **Hirsutism may be the initial and possibly only sign of androgen excess, the cutaneous manifestations of which may also include acne and male-pattern balding (androgenetic alopecia).**

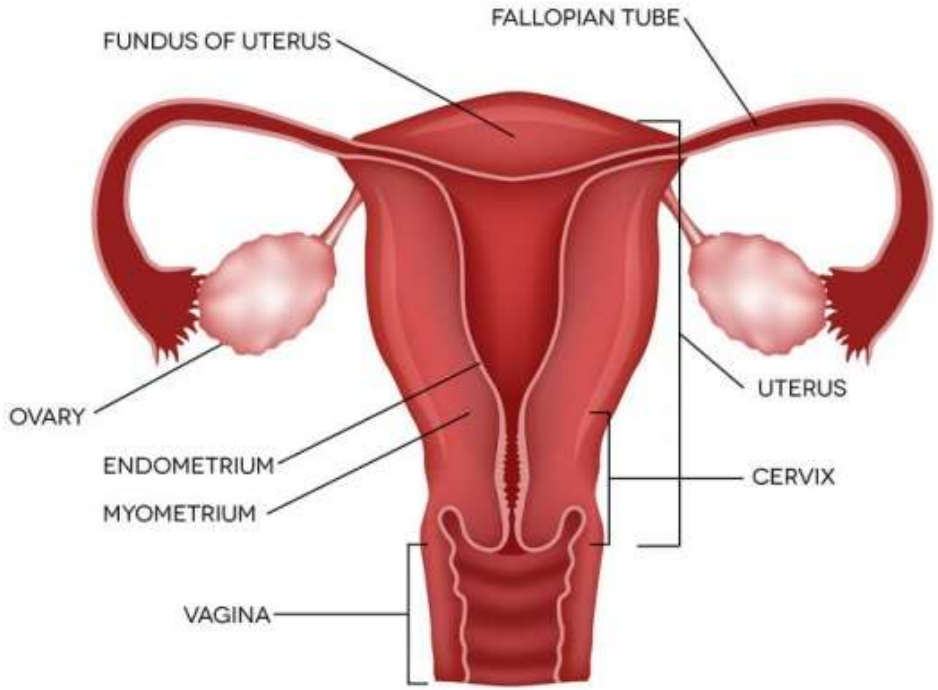
Table 3. Treatment of hirsutism

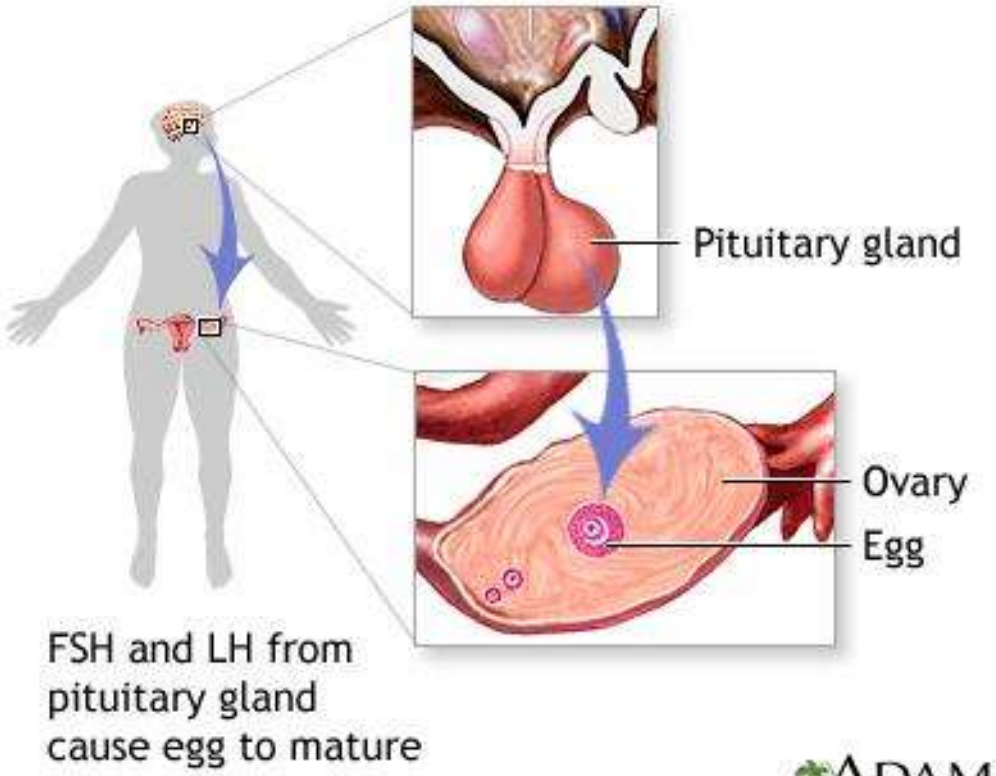
Medications	Cosmetic treatments
Birth control pills	Shaving
Androgen receptor blockers	Eflornithine cream
Spironolactone	Waxing
Flutamide	Bleaching
Glucocorticosteroids	Plucking
Dexamethasone	Depilatory agents
Prednisone	Electrolysis
Methylprednisolone	Laser
Enzyme inhibitors	
Finasteride	
GnRH analogs	

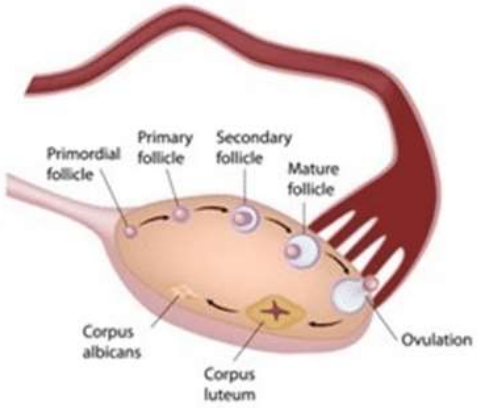
POLYCYSTIC OVARY SYNDROME (PCOS)

|OVERVIEW OF CAUSES, RISK FACTORS, ASSOCIATED CONDITIONS, SIGNS & SYMPTOMS, DIAGNOSTIC METHODS AND TREATMENTS.

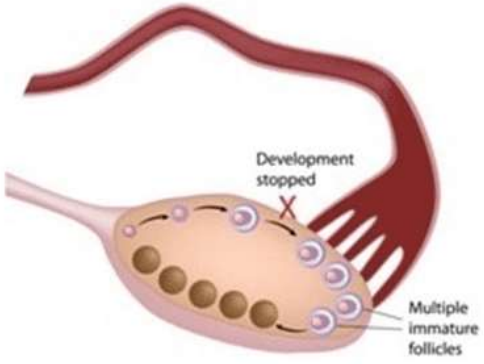
Leen Jalal Damra
Group D33


FUNDUS OF UTERUS
FALLOPIAN TUBE
OVARY
UTERUS
ENDOMETRIUM
MYOMETRIUM
CERVIX
VAGINA

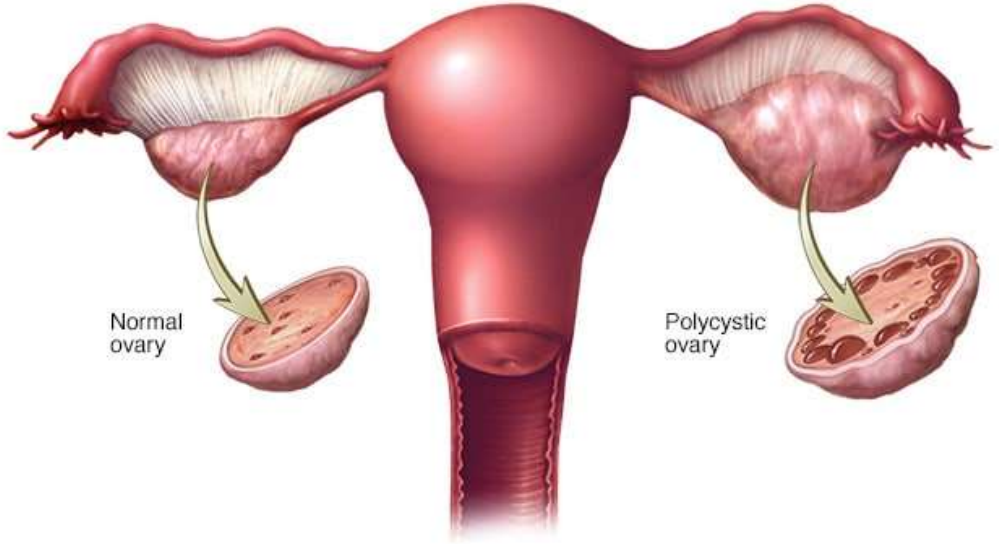

Pituitary gland
Ovary
Egg
FSH and LH from pituitary gland cause egg to mature
A.D.A.M.



Normal Ovary



Polycystic Ovary



PATHOPHYSIOLOGY

In PCOS the ovaries produce too much testosterone "male hormone“, normally the ovaries produce very small amounts, but in PCOS, they make more.

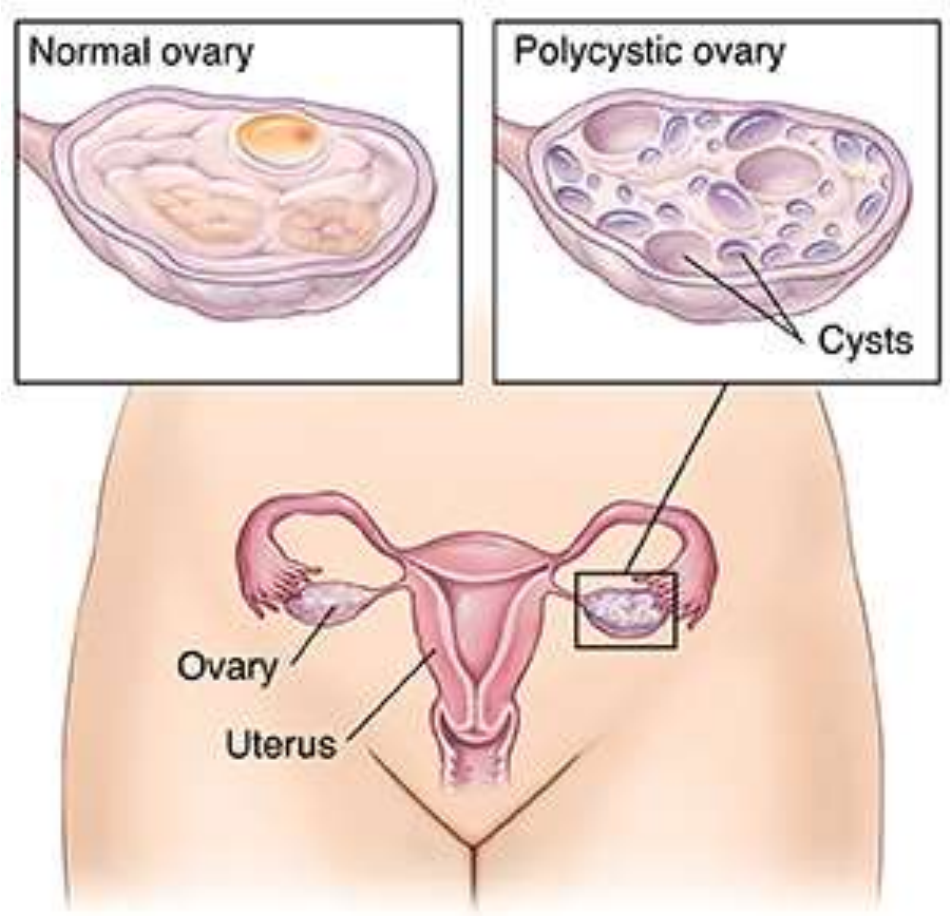
About once a month, a woman's ovaries are supposed to make a "follicle“ As the follicle grows, it makes hormones. Then it releases an egg "ovulation"

But in women with PCOS,

1) the ovary makes many small follicles instead of one big one.

2) Hormone levels can get out of balance.

3) ovulation doesn't happen every month the way



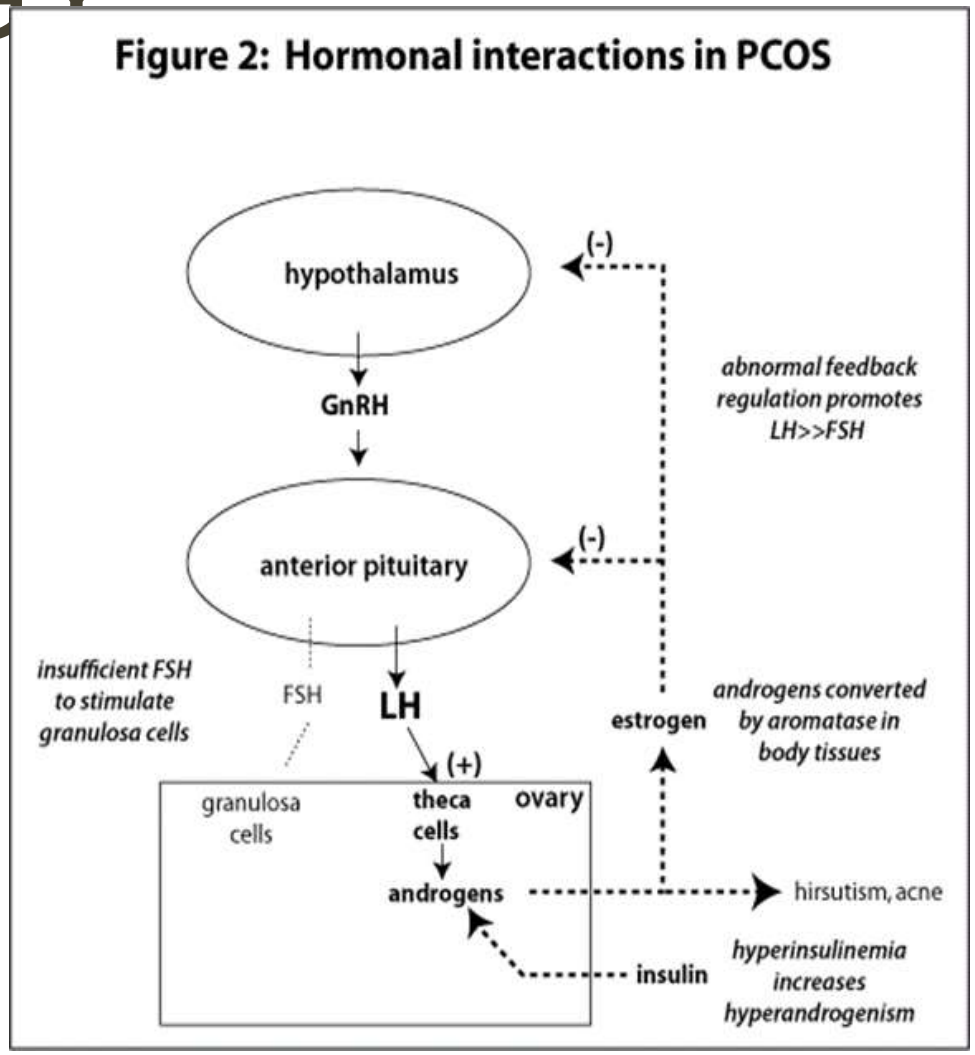
PATHOPHYSIOLOGY

It is important to appreciate that PCOS is a syndrome, not a disease, reflecting multiple potential etiologies.

What stimulates the ovaries to produce excessive amounts of male hormones (androgens), particularly testosterone, either one or a combination of the following :

1) Luteinizing hormone (LH) by the anterior pituitary gland through high levels of insulin in the blood (hyperinsulinemia) in women whose ovaries are sensitive to this stimulus

2) Alternatively or as well, reduced levels of sex-hormone binding globulin can result in increased free androgens.



CLINICAL FEATURES?

Polycystic ovarian syndrome is a condition that can cause women have:

- menstrual irregularity (Delayed menarche, Oligomenorrhea, Amenorrhea).

- Hyperandrogenism (Acne, Hirsutism, Hair loss).

- Polycystic ovaries

The condition can also make it hard to get pregnant without medical help, **it's the most common cause of infertility**, due to anovulatory cycles.

INCIDENCE

-Most common endocrinological disorder in reproductive-age women worldwide.

Prevalence estimated to be anywhere between 5-15%

CAUSE

Considerable evidence suggests that it arises as a complex trait with contributions from both heritable and uninheritable intrauterine and extrauterine factors, among which insulin resistance and obesity are most common

This ovarian dysfunction is unique: it appears to be intrinsic and is characterized by abnormal ovarian steroidogenesis and folliculogenesis that are manifested clinically by androgen excess and anovulation.

RISK / ASSOCIATED FACTORS

1) Genetics

- Monozygous twins with PCOS
- First-degree relatives with PCOS

2) Environmental influences

3) Obesity

- Pre-pubertal

4) Early-onset menarche

5) Large/small for gestational age

6) Valproic acid use

7) Fetal androgen exposure (**?**)

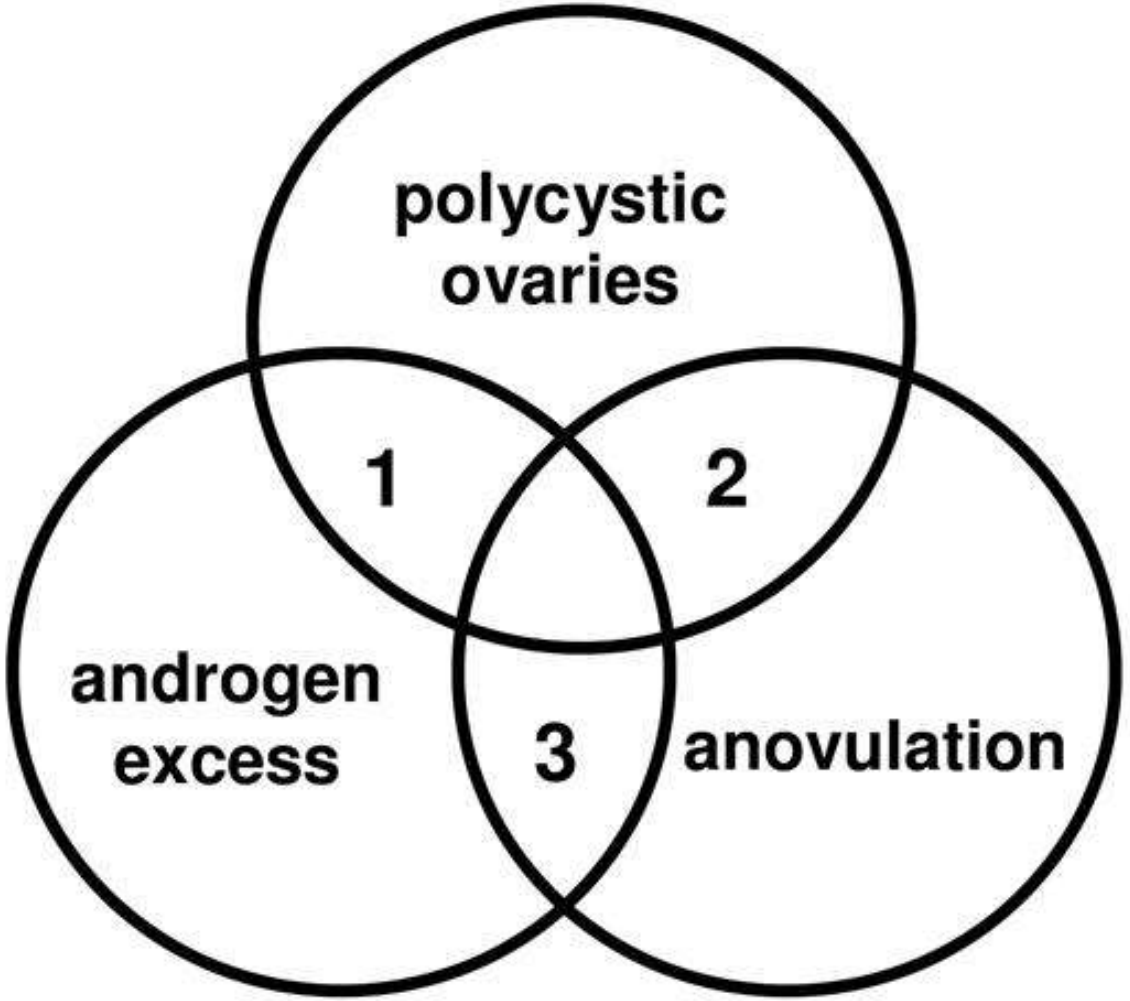
PCOS ASSOCIATED CO-MORBIDITIES

- Obesity and metabolic syndrome
- Impaired glucose tolerance & Type-2 Diabetes
- Endometrial cancer
- Infertility (anovulation)
- Obstructive Sleep Apnea
- Depression & Anxiety
- Cardiovascular Disease
- Non-alcoholic fatty liver disease (NAFLD)

DIAGNOSIS

All conditions that mimic polycystic ovarian syndrome (PCOS) should be ruled out before a diagnosis of PCOS is confirmed.

Over the past 25 years, internationally accepted diagnostic criteria have been developed for adults based on various combinations of otherwise unexplained hyperandrogenism, anovulation, and a polycystic ovary. To diagnose PCOS you must have 2 out of 3 "Rotterdam criteria".



TESTS SHOULD BE DONE

Tests are based on age, symptoms, and individual situation.

Possible tests include:

serum total testosterone, other androgens (androstenedione and dehydroepiandrosterone sulphate). SHBG levels are often low (due to high insulin levels), leading to high free androgen levels.

17 a-hydroxyprogesterone

Gonadotropin levels

Estrogen levels

Serum prolactin

Insulin and glucose levels

A pregnancy test if there is missed period.

Pelvic ultrasound – uterus and ovaries.

SCREENING AND INVESTIGATIONS

The Royal College of Obstetricians and Gynecologists (RCOG) recommends the following baseline screening tests for women with (PCOS):

1-Thyroid function tests, to exclude Hypothyroidism

2-Serum prolactin levels, to exclude hyperprolactinemia

3-Free androgen index (defined as total testosterone divided by sex hormone binding globulin [SHBG] × 100, to give a calculated free testosterone level)

4-Any cause of “adrenal hyper-functioning“ test for Cushing syndrome, adrenal hyperplasia, serum 17-hydroxyprogesterone levels.

IMAGING

The syndrome acquired its most widely used name due to the common sign on ultrasound examination of multiple (poly) ovarian cysts.

These "cysts" are actually immature follicles, not cysts.

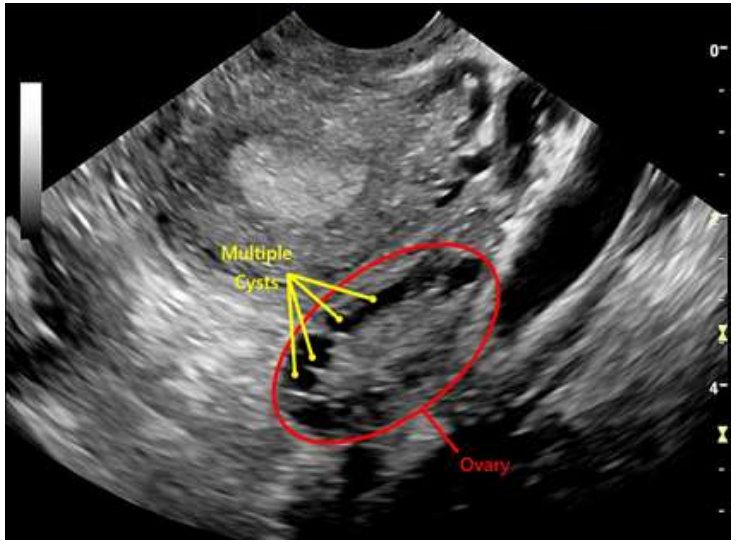
The follicles have developed from primordial follicles, but the development has stopped (“arrested”) at an early antral stage due to the disturbed ovarian function.

The follicles may be oriented along the ovarian periphery, appearing **as a ‘string of pearls’ on ultrasound examination.**

If the patient tests revealed high testosterone level + rule out other causes of amenorrhea, Hirsutism, infertility …. Etc.

Ultrasound (transabdominal and/or transvaginal ultrasonography): bilateral enlarged ovaries, multiple small follicles and increased stromal echogenicity.

If you suspected a tumor then use CT or MRI.



TREATMENT GOALS

The overall goals of therapy of women with PCOS include:

Amelioration of hyperandrogenic features (hirsutism, acne, scalp hair loss)

Management of underlying metabolic abnormalities and reduction of risk factors for type 2 diabetes and cardiovascular disease

Prevention of endometrial hyperplasia and carcinoma, which may occur as a result of chronic anovulation

Contraception for those not pursuing pregnancy, as women with Oligomenorrhea ovulate intermittently and unwanted pregnancy may occur.

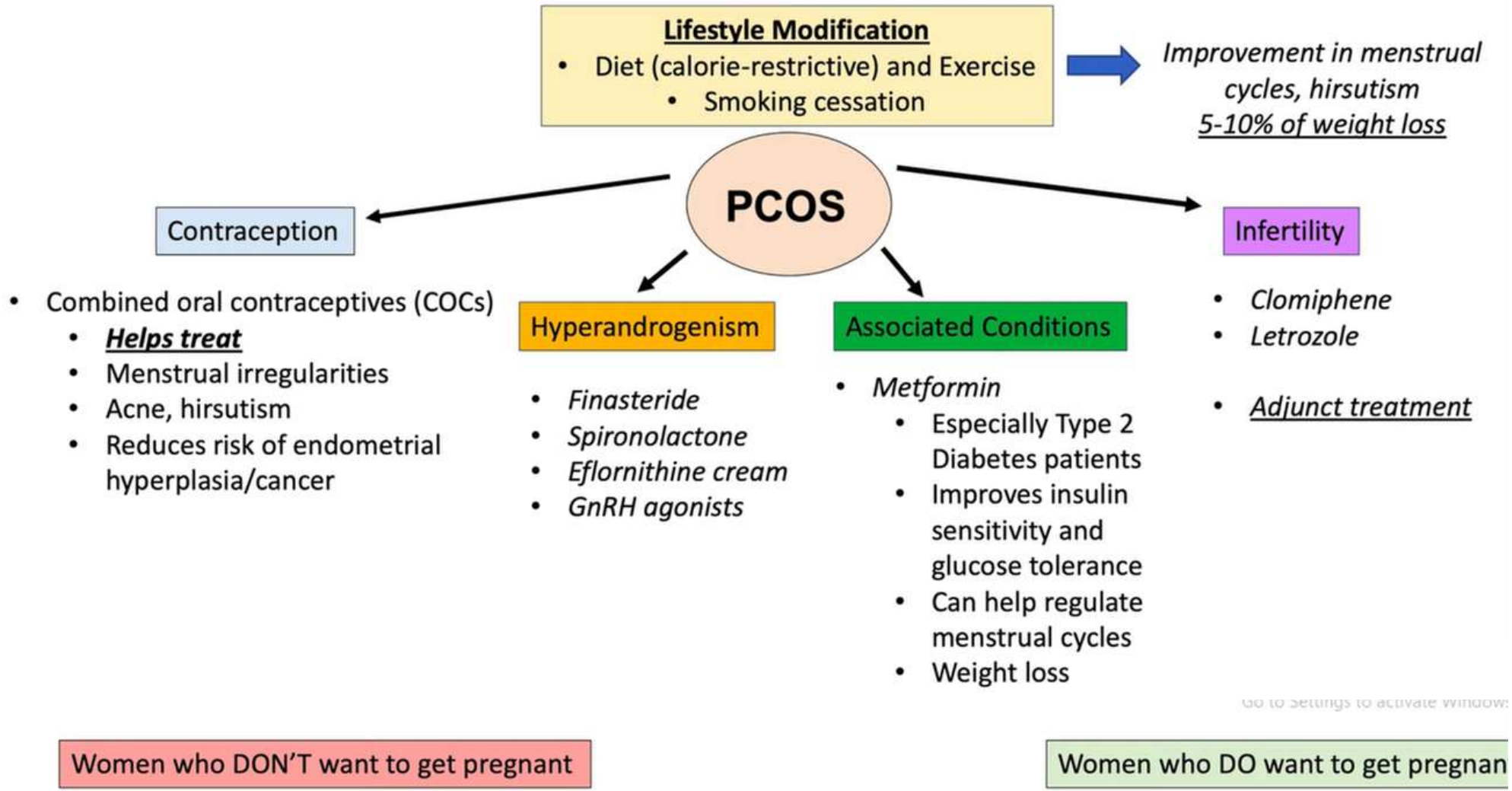
Ovulation induction for those pursuing pregnancy.

LIFESTYLE CHANGES

Diet and exercise for weight reduction are the first step for overweight and obese women with PCOS. For improving insulin resistance and hyperandrogenism.

In addition, there appear to be reproductive benefits as well.

TREATMENT METHODS



TREATMENTS CON.

Birth control pills – the main treatment for PCOS. The pills don't cure the condition. But they can improve many of its symptoms, like irregular periods, acne, and facial hair. It also protect women from cancer of the uterus.

Anti-androgens – These medicines block hormones that cause some PCOS symptoms like acne and facial hair growth. Spironolactone (Aldactone) anti-androgen.

Progestin –hormone to make periods regular, only if taken every month. It also lowers the risk of cancer of the uterus. Medroxyprogesterone (Provera) or natural progesterone (Prometrium).

Metformin (Glucophage) – This help to make periods more regular. But it works only in about half of the women who try it. In women with diabetes, helps keep blood sugar levels normal.

Medicated skin lotion or antibiotics to treat acne.

Laser therapy or electrolysis to remove extra hair

TREATMENT FOR WOMEN NOT PURSUING PREGNANCY

Menstrual dysfunction: Endometrial protection — The chronic anovulation seen in PCOS is associated with an increased risk of endometrial hyperplasia and possibly endometrial cancer.

Combined estrogen-progestin oral contraceptives (COCs) as first-line therapy for menstrual dysfunction and endometrial protection.

Androgen excess :

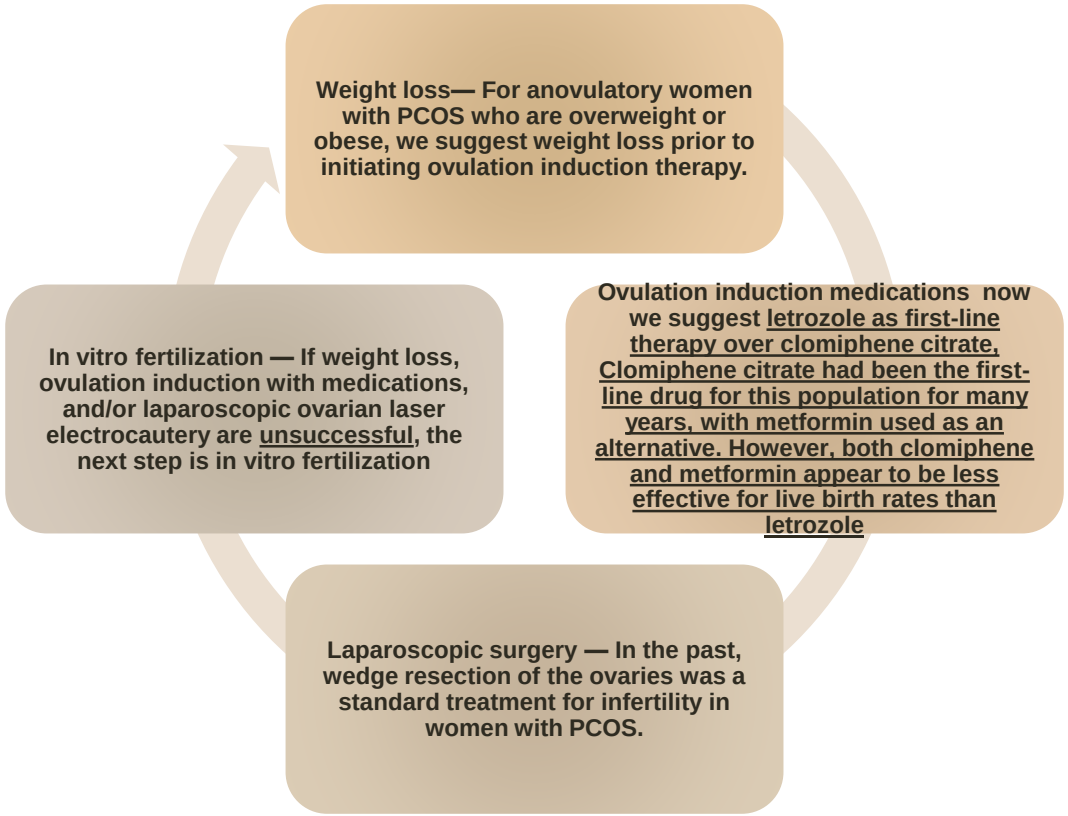
1) Hirsutism, 2) Choice of oral contraceptive, 3)Antiandrogens — After six months, if the patient is not satisfied with the clinical response to COC monotherapy (for hyperandrogenic symptoms), 4) Acne and androgenetic alopecia.

Metabolic abnormalities:

Obesity — Weight loss, which can restore ovulatory cycles and improve metabolic risk, is the first-line intervention for most women. Weight reduction/Bariatric surgery

Insulin resistance/type 2 diabetes — Several drugs, including biguanides (metformin) and thiazolidinediones (pioglitazone, rosiglitazone), can reduce insulin levels in women with PCOS.

TREATMENT FOR WOMEN PURSUING PREGNANCY



Resources

Davidson’s Principles and Practice of Medicine
Kumar and Clark’s Clinical Medicine
Costanzo Physiology
UpToDate

THANK YOU