Pituitary Disorders and Hypogonadism

From: Dr. Ayman Aref's lectures for 020 batch (1st semester)

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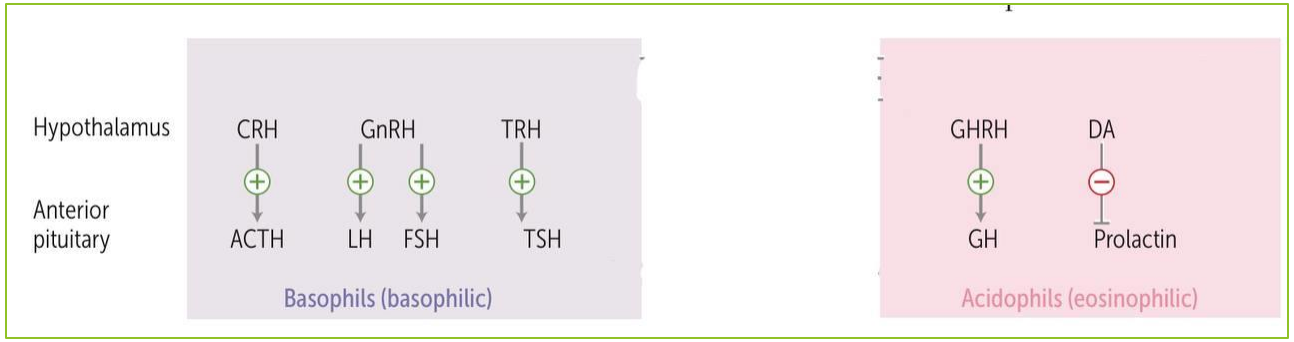
Outline of the Lectures

- Hypothalamic-pituitary axis
- Prolactin disorders
  - Hyperprolactinemia
- Growth hormone disorders
  - Acromegaly
  - Dwarfism
- Hypogonadism
  - Male hypogonadism
  - Female hypogonadism
- Reproductive Endocrinology as a Sub-Specialty

- Slides with a blue background were explained in the lectures.
- Slides with a green background are additional (to help you better understand).
- Slides with a pink background are topics that Dr. Ayman asked us to read about. They are important.

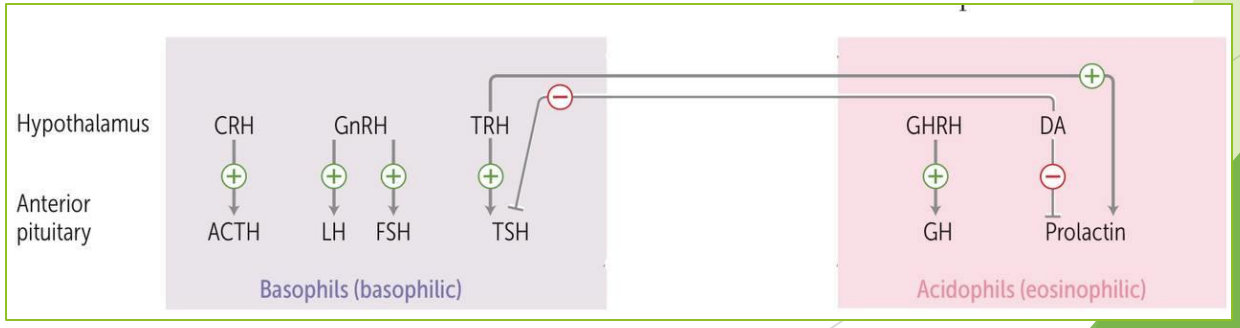
The hypothalamic-pituitary axis

- Let's start with some basic concepts that most of us already know:



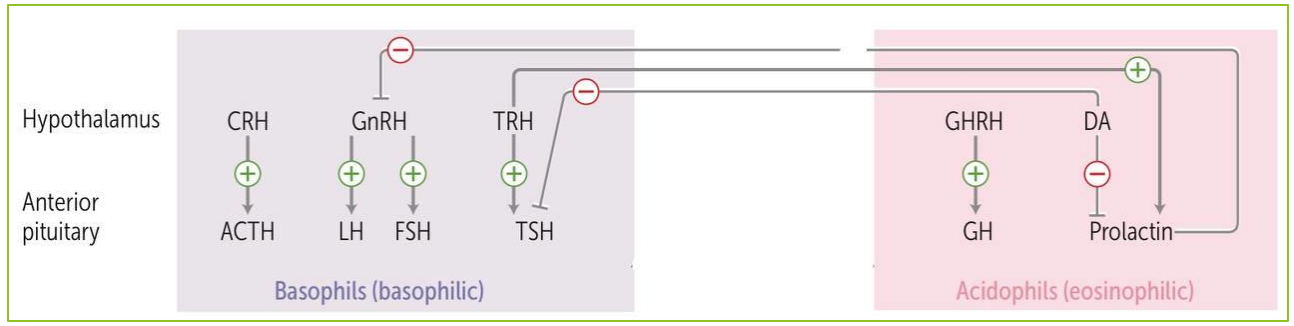
- Notice that on the previous diagram:
  - DA always inhibits prolactin
  - TRH always stimulates TSH.

- So, let's do this:
  - DA inhibits TSH.
  - TRH stimulates prolactin.

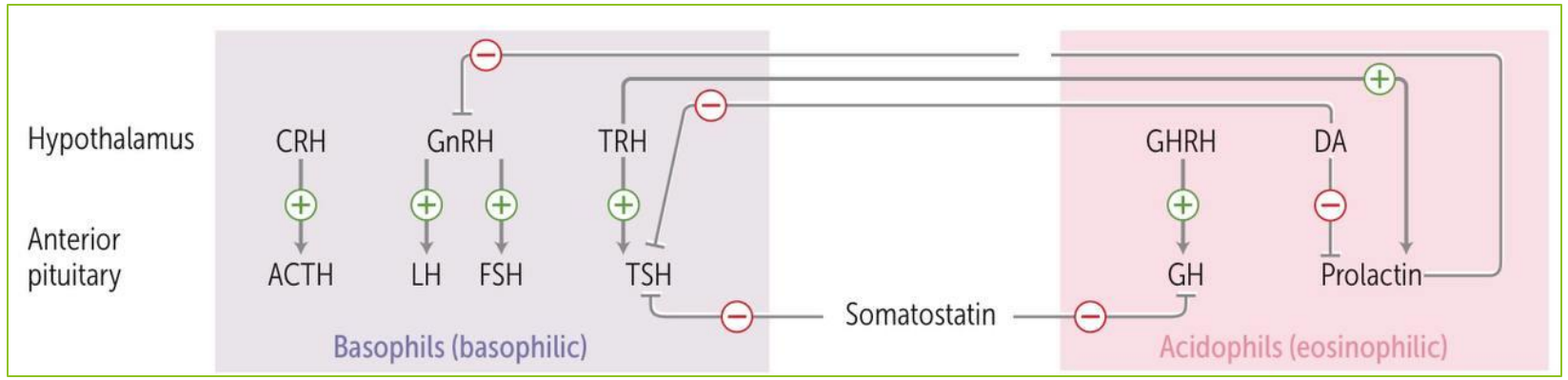


The hypothalamic-pituitary axis

- One last thing: Prolactin can inhibit GnRH:



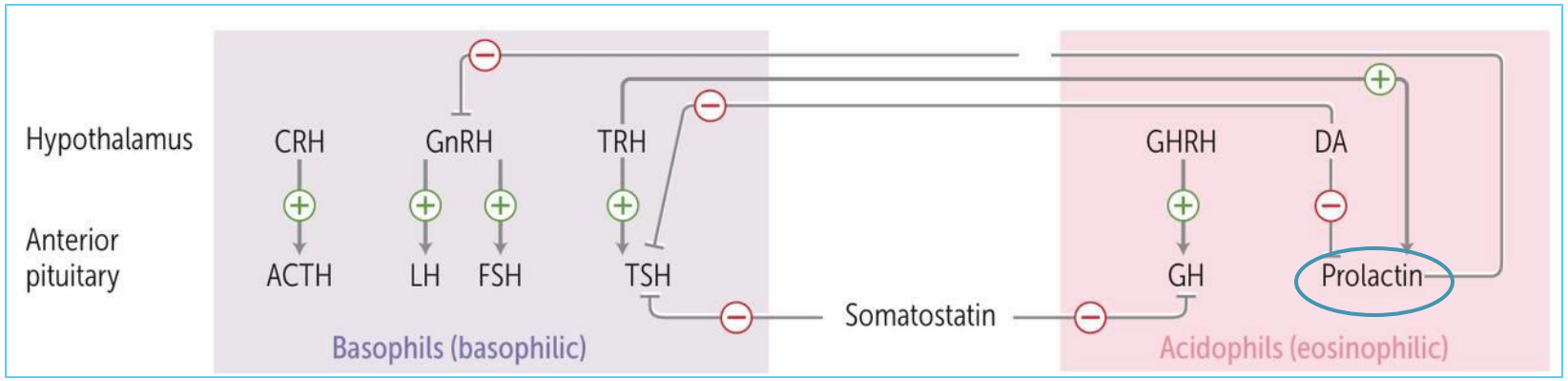
- One really last thing: Somatostatin inhibits GH and TSH:



- **This is the hypothalamic pituitary axis.**

The hypothalamic-pituitary axis

- Dr. Ayman Aref focused on the following:
  - TRH stimulates prolactin, but DA has a stronger inhibitory effect on prolactin.
  - Prolactin inhibits GnRH.



Prolactin Disorders

- Hypoprolactinemia (just mentioned, but not discussed in the lecture).
- Hyperprolactinemia: Increased prolactin levels in the blood.
- بالعربي معروف "بهرمون الحليب"...
- So, this is what happens:
- ↑ Prolactin → ↓ GnRH → ↓ LH and FSH → ↓ Sex hormones (androgens for males / estrogen for females)
- So, symptoms are due to either ↑ Prolactin or ↓ Sex hormones.

Hyperprolactinemia
Clinical Manifestations

	Females	Males
↑ Prolactin	• Galactorrhea	• Galactorrhea (rarely)
↓ Sex hormones	• Menstrual irregularities • Oligomenorrhea or amenorrhea • Infertility • Hirsutism • Osteoporosis • Decreased libido	• Erectile dysfunction • Infertility • Decreased libido • Gynecomastia

Hyperprolactinemia Causes

The causes of hyperprolactinemia could be:

- Physiologic: Such as pregnancy, breastfeeding, and stress.
- Drugs: Such as dopamine antagonists (e.g., antipsychotics, methyldopa), oral contraceptives, cimetidine, metoclopramide.
- Pathologic: Such as hypothyroidism and prolactinoma:
  - Hypothyroidism: ↓ T3, T4 → ↑ TSH, **TRH** → ↑ Prolactin
  - Prolactinoma: A tumor of the lactotroph cells (PL-secreting cells) in the anterior pituitary.

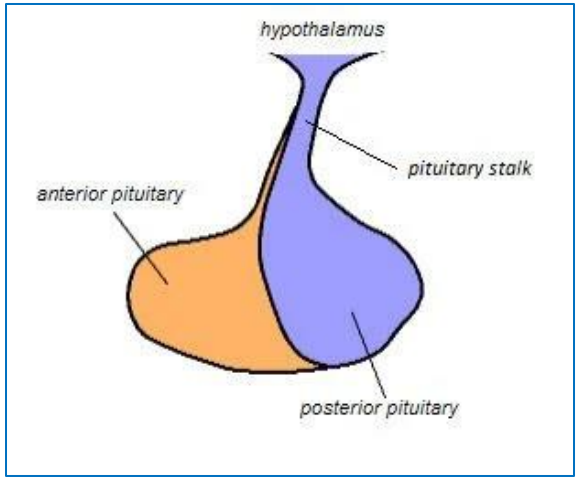
Hyperprolactinemia Causes: Prolactinoma

- Prolactinoma is a rare tumor of the anterior pituitary gland.
- Normal prolactin levels: 3-27 ng/ml in a nonpregnant adult female.
- The size of the tumor correlates with the blood levels of prolactin:
  - Microprolactinoma (<1 cm size) can cuase mild increases in prolactin levels e.g., 100 ng/ml.
  - Macroprolactinoma (>=1 cm size) causes huge increase in prolactin levels e.g., 1000 ng/ml.
    - Macroprolactinoma also manifests with mass effects, such as headache and visual field defects (i.e., bitemporal hemianopia)

Hyperprolactinemia Causes: Prolactinoma

- The following cases are examples of the correlation between tumor size and prolactin levels:
  - A 3 mm tumor in a patient with prolactin levels 100 ng/ml.
  - A 2 cm tumor in a patient with prolactin levels 1000 ng/ml.
- What if a 2 cm tumor was found in a patient whose prolactin levels are 80 ng/ml?
  - In this case, the tumor is definitely not PL-secreting (it could be GH-secreting, TSH-secreting, etc.)
  - But PL levels are still high. Why is that?

Hyperprolactinemia Causes: Stalk Effect

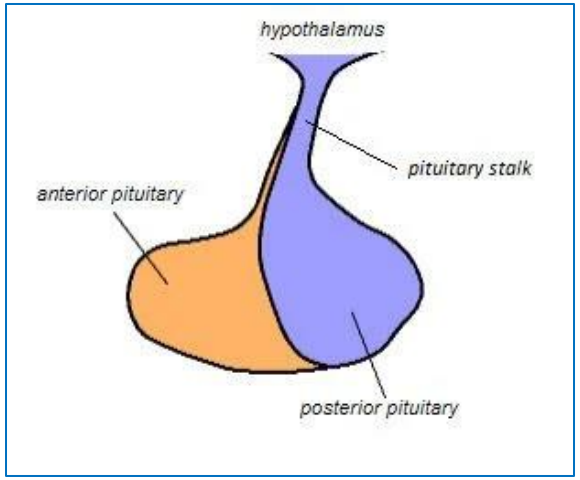


Stalk effect:

- When a pituitary tumor gets too large (e.g., 2 cm), it exerts pressure on the pituitary stalk. This pressure blocks dopamine's movement from the hypothalamus to the anterior pituitary.
- So, ↓ DA → ↑ Prolactin since prolactin is now disinhibited.
- This causes mild hyperprolactinemia (e.g., 80 ng/ml).

- The stalk effect explains how large pituitary tumors (not prolactinomas) cause mild hyperprolactinemia.

Hyperprolactinemia Causes: Prolactinoma



Treatment of prolactinoma:

- The only treatment is dopamine agonists (e.g., Cabergoline 2 times per week, Bromocriptine daily).
- DA agonists can diminish the tumor size.
- Even if the tumor is so large that it compresses the optic chiasm, DA agonists are the treatment.

- If refractory to DA agonists → Try other medical treatments.
- If refractory to all medical treatments → Surgery.

Hyperprolactinemia Physical Examination

Blue = Mentioned by Dr. Ayman in the lecture.

1. General Look: Observe the patient for any signs of systemic illness or distress, including weight changes, pallor, or signs of dehydration. Also, check for abnormal hair distribution.
2. Visual Assessment: Check for visual field defects or signs of cranial nerve involvement, particularly visual disturbances such as bitemporal hemianopsia (loss of peripheral vision).
3. Breast: Evaluate the breasts for abnormal breast size, galactorrhea (abnormal lactation), and any signs of breast masses or tenderness.
4. Thyroid: Palpate the thyroid gland to assess for enlargement or nodules, as thyroid dysfunction can sometimes coexist with hyperprolactinemia.
5. Neurological: Assess neurological function, including cranial nerves, motor strength, reflexes, and coordination.
6. Pelvic: In female patients, perform a pelvic examination to assess for any abnormalities of the ovaries or uterus that may be associated with hyperprolactinemia.
7. Testicular: In male patients, perform a testicular examination to assess for any abnormalities, such as testicular atrophy, which may indicate hypogonadism associated with hyperprolactinemia.
8. Skin: Look for any signs of acanthosis nigricans (dark, velvety skin patches), which may be associated with insulin resistance and underlying endocrine disorders.
9. Vital Signs: Measure blood pressure, heart rate, and temperature to assess for any abnormalities that may be associated with hyperprolactinemia or its underlying causes.
10. Assessment of Other Endocrine Abnormalities: Evaluate for signs of other endocrine disorders that may be associated with hyperprolactinemia, such as Cushing's syndrome or acromegaly.

Hyperprolactinemia Management

Treat the cause

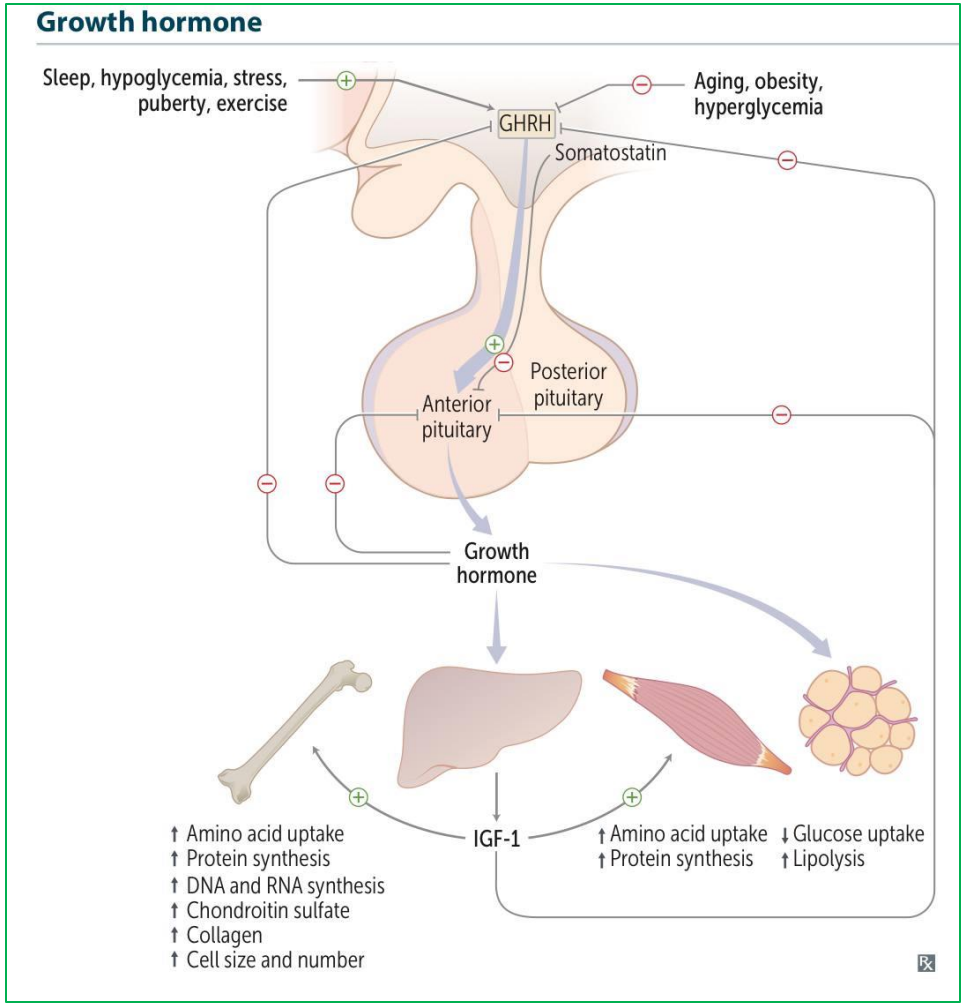
Recap: What is the treatment if the cause is prolactinoma?

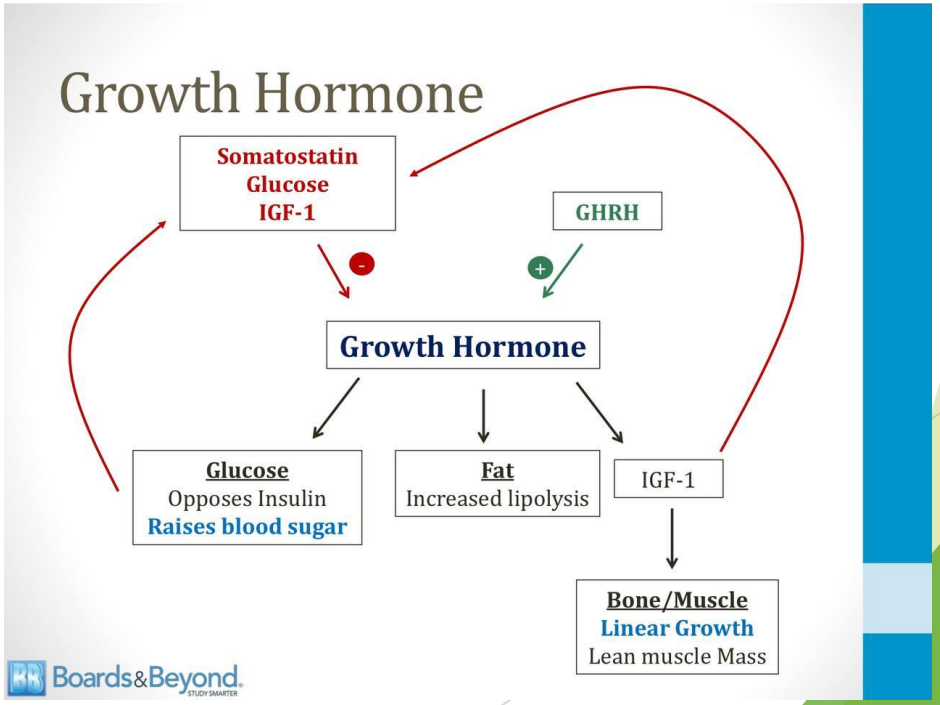
Growth Hormone Disorders

- Over-secretion of GH can cause acromegaly in adults, or gigantism in children.
- Under-secretion of GH in children causes dwarfism.
  - About 5% of school students have short stature due to any cause, including GH deficiency.

Growth Hormone

- Released in pulsatile manner
- Important for linear (height) growth in childhood
- Stimulates the liver to synthesize Insulin-like Growth Factor-1 (IGF-1)
- Has an anti-insulin effect
  - It raises blood sugar levels ("diabetogenic")





Growth Hormone

Blue = Mentioned by Dr. Ayman in the lecture.

- IGF-1 is a better indicator of GH function than GH itself, because it is not affected by circadian rhythm, sleep, etc. (unlike GH).
- IGF Binding Protein-3 (IGFBP-3) test is requested if patient has dwarfism. When there is a deficiency of growth hormone, either due to decreased production or impaired action, it leads to reduced stimulation of the liver to produce IGF-1. Consequently, decreased levels of IGF-1 result in lower levels of IGFBP-3, as there is less IGF-1 available for binding. This reduction in IGFBP-3 levels contributes to the impaired growth observed in individuals with dwarfism.

Growth Hormone Disorders Approach

- Screening tests: Request if you suspect a GH disorder in your patient.
  - Blood IGF-1 levels: Increased in acromegaly patients.
  - Blood IGFBP-3 levels: Decreased in dwarfism patients.

- Definitive dx tests: Request if you want to confirm the GH disorder.
  - Oral glucose tolerance test: Failure to suppress GH in acromegaly patients.
  - GH stimulation test (usually by injecting insulin to induce hypoglycemia in the patient): Failure to stimulate GH in dwarfism patients.

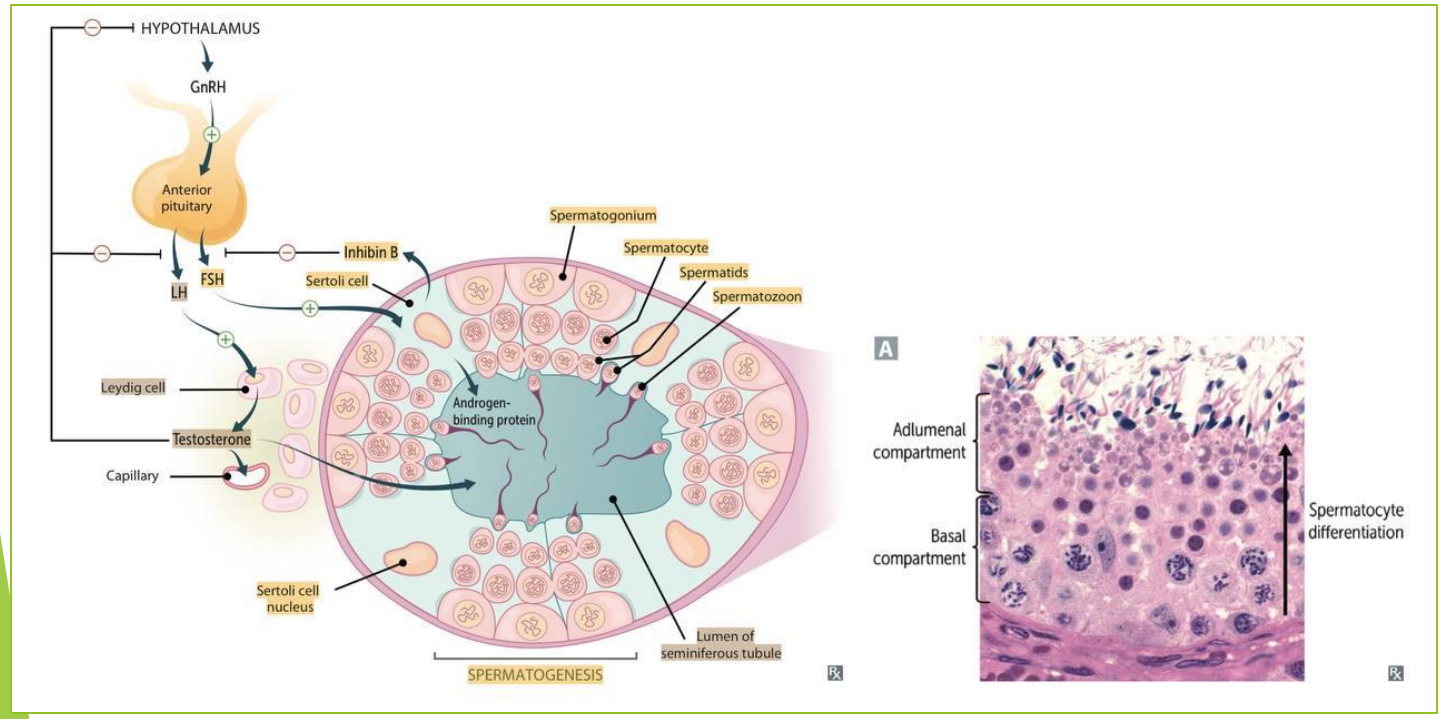
Gonadotropins

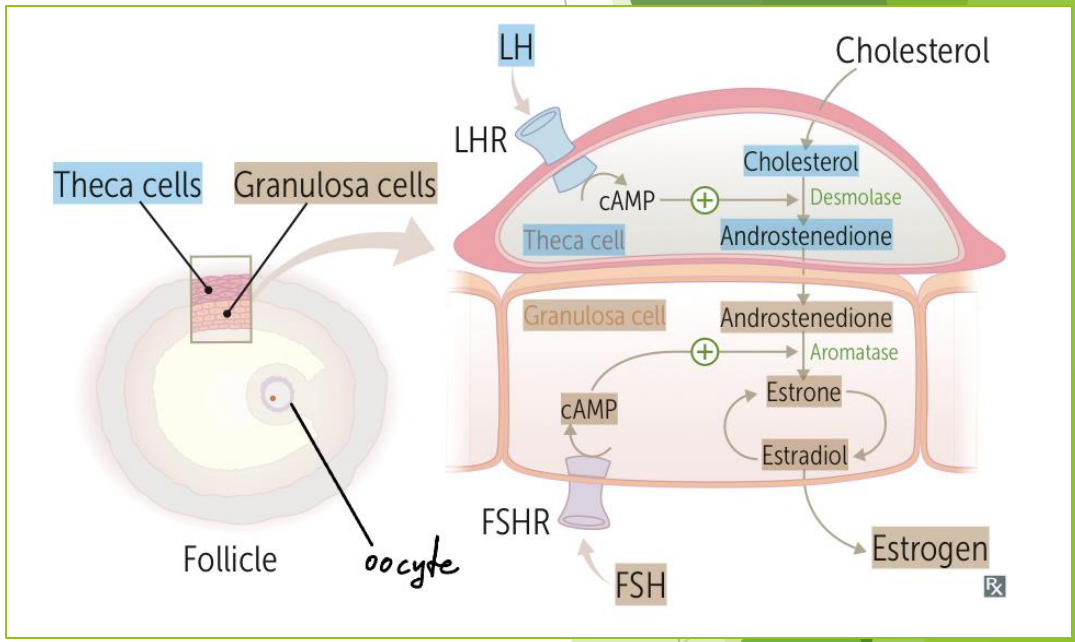
- The gonadotropins are anterior pituitary hormones that stimulate the gonads to function:

Gonaotropin	Males		Females	
	Gonadal hormone stimulated:	Effect exerted:	Gonadal hormone stimulated:	Effect exerted:
LH	Testosterone			Development of genitalia and breasts
FSH		Spermatogenesis	Estrogen	Follicle stimulation Ovulation

- Keep in mind: When suspecting hypogonadism (↓ Testosterone or estrogen), we check LH for males, and FSH for females.

Gonadotropins





Hypogonadism

- Usually refers to ↓ Sex hormones (Testosterone in males / Estrogen in females)
- This disorder has different manifestations based on the patient's sex and age.
- In this lecture, we will focus on **adult-onset hypogonadism** for both sexes.

Hypogonadism in Adult Males

Testosterone deficiency in males can lead to:

- Mild-moderate disease (most common): Fatigue, generalized weakness, depression, mood swings, daytime sleepiness, reduced self-confidence and self-esteem, decreased libido, mild erectile dysfunction.
- Advanced disease: Loss of facial hair and muscle mass, gynecomastia.
- Very severe cases: Infertility

Hypogonadism in Adult Males

Physical Examination should include:

- Hair distribution (loss of normal male hair distribution)
- Breast size (gynecomastia)
- Genitalia examination (testicular atrophy)

Investigations:

- Blood free testosterone levels (reduced in primary hypogonadism)
  - Must be done carefully: In the morning, while patient is fasting, and ideally 3 samples, each is 1 hour apart from the next one.
- Blood GnRH, LH/FSH levels (reduced in central hypogonadism)

Klinefelter's Syndrome

Blue = Mentioned by Dr. Ayman in the lecture.

- Klinefelter syndrome is a chromosomal disorder that occurs in males and is typically characterized by the presence of an extra X chromosome, resulting in a karyotype of 47,XXY instead of the usual 46,XY. This additional X chromosome leads to various physical, developmental, and hormonal differences compared to males with a typical chromosome configuration. In Klinefelter syndrome:
  - Testicular Abnormalities: Individuals typically have small, firm testes and reduced testosterone production, which can result in infertility and impaired spermatogenesis.
  - Hormonal Imbalance: There is often a relative increase in estrogen levels compared to testosterone due to impaired testicular function, leading to features such as gynecomastia (enlarged breast tissue), reduced facial and body hair, and decreased muscle mass.
  - Tall Stature: Some individuals with Klinefelter syndrome may be taller than average due to delayed closure of the epiphyseal plates. They also have disproportionately longer upper/lower limbs relative to their height.
  - Learning and Developmental Differences: There may be difficulties with learning, language development, and social interaction, although intelligence is typically within the normal range.
  - Other Features: Additional features may include decreased bone density, increased risk of autoimmune disorders, and a higher incidence of certain medical conditions such as type 2 diabetes and breast cancer.

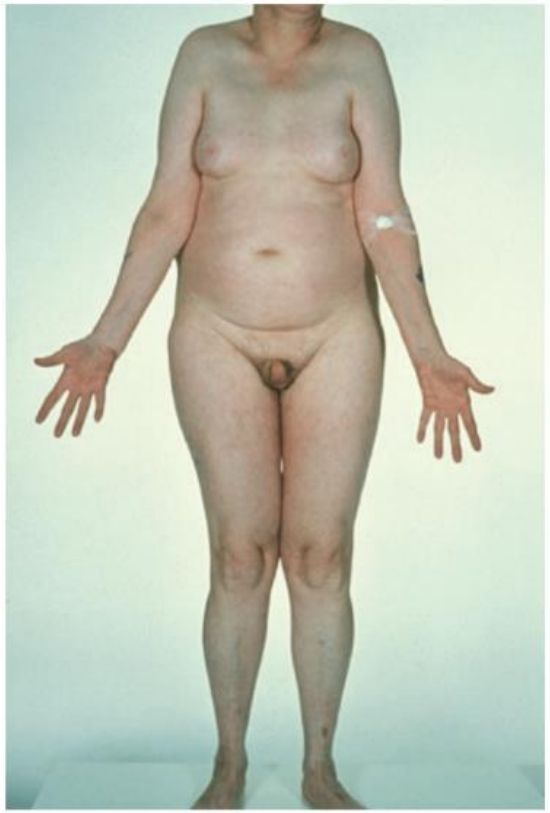


Fig. 10.13 Klinefelter's syndrome. Tall stature, gynaecomastia, reduced pubic hair and small testes.

Other Causes of Primary Hypogonadism

- Viral infection of the testicles
- Radiation exposure
- Chemotherapy
- Infiltrative disease (e.g., hemochromatosis)

- **Kallman syndrome** is characterized by infertility + anosmia. It is a cause of central hypogonadism.

Primary vs Central Hypogonadism

	Primary Hypogonadism	Central Hypogonadism
Sex hormones	↓	↓
LH/FSH	↑	↓ or normal

Test

- A 25-year-old male patient presented with decreased libido, fatigue, and depression. His testosterone levels are low, and LH levels are normal. What is the most appropriate next step?

A. Start testosterone therapy
B. Pituitary MRI
C. Testicular ultrasound
D. Chromosomal analysis
E. Observation

Answer: B

Test

- An 18-year-old male patient was referred to the endocrinology clinic because he was found to have low testosterone and very high LH/FSH levels. What is the most appropriate next step?

A. Pituitary MRI
B. Start testosterone therapy
C. Observation
D. Chromosomal analysis
E. Repeat testosterone test in 6 months, and if still abnormal, do testicular ultrasound.

Answer: D

Hypogonadism in Adult Females

- Remember: Estrogen levels in women fall after menopause. **Postmenopausal hypogonadism in females is normal.**
- Thus, in postmenopausal females, we usually find ↓ Estrogen and ↑ FSH.
- Menopause at an early age in females is an indicator of premature ovarian failure.

- The approach to primary and secondary hypogonadism in females is the same as the approach to males. (previously discussed)

- Turner's syndrome is a cause of primary female hypogonadism.
- Kallman's syndrome is a cause of secondary female hypogonadism.

Turner's Syndrome

Blue = Mentioned by Dr. Ayman in the lecture.

- Turner syndrome is a genetic disorder that affects females, typically resulting from a complete or partial absence of one of the X chromosomes, thus having a karyotype of 45, XO. It is characterized by various physical features and medical conditions, including:
  - Short Stature: Individuals with Turner syndrome often have a shorter-than-average height, typically due to impaired growth during childhood and adolescence.
  - Gonadal Dysgenesis: Most individuals with Turner syndrome have underdeveloped (streaks of ovarian tissue) or completely absent ovaries, leading to infertility and absence of menstruation (amenorrhea).
  - Physical Features: Common physical features may include a webbed neck, low hairline at the back of the neck, low-set ears, drooping eyelids, and a broad chest with widely spaced nipples.
  - Lymphedema: Some individuals with Turner syndrome may develop swelling of the hands and feet (lymphedema) during infancy or early childhood.
  - Heart and Kidney Abnormalities: Turner syndrome can be associated with congenital heart defects, such as aortic coarctation, and kidney abnormalities.
  - Hearing Loss: Sensorineural hearing loss is more common in individuals with Turner syndrome compared to the general population.
  - Learning and Developmental Differences: Some individuals with Turner syndrome may experience learning difficulties, particularly in areas such as mathematics and spatial reasoning.

Reproductive Endocrinology as a Sub-Specialty

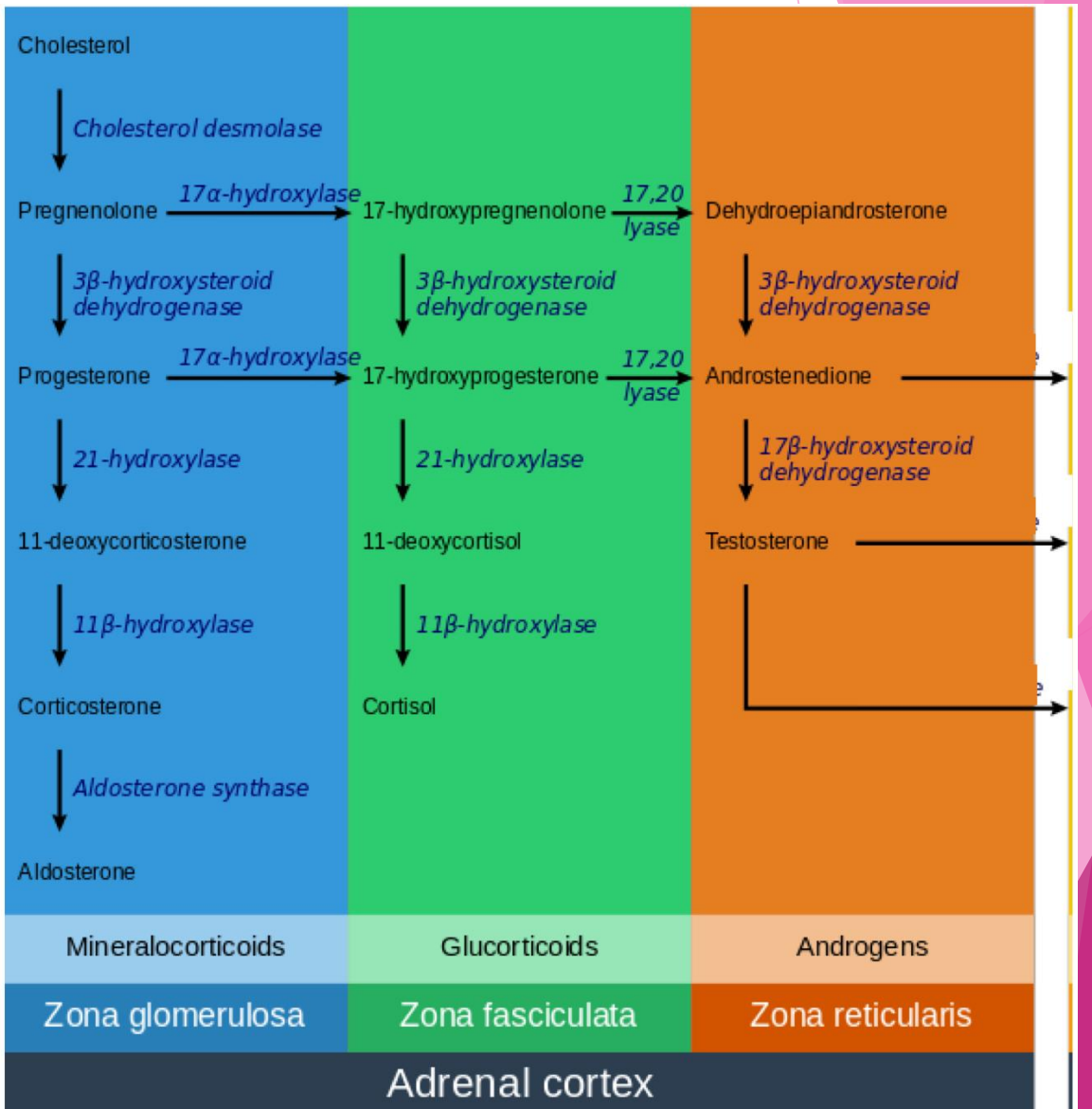
Reproductive endocrinology is a sub-specialty on its own in medicine. It is wide with many details and features that the patient can present with. Some the most common presentations are:

- Gynecomastia in males
  - Usually bilateral (in both breasts) but could be unilateral.
  - Indicates reduced testosterone levels relative to estrogen. (Estrogen > Testosterone).
  - Or the hormone levels could be normal, but their receptors are thus affected.
  - 40% of the causes are idiopathic.
  - 60% are due to various causes.
- Hirsutism in females
  - This presentation has wide list of differential diagnoses.
  - Examples include: Hypothalamic disorders, Congenital adrenal hyperplasia (21-hydroxylase deficiency), Gonadal dysfunction, Polycystic ovarian syndrome (associated with insulin resistance).

Congenital Adrenal Hyperplasia

- CAH is an enzyme deficiency syndrome in which one of the enzymes involved in the process of adrenal steroidogenesis is lost:

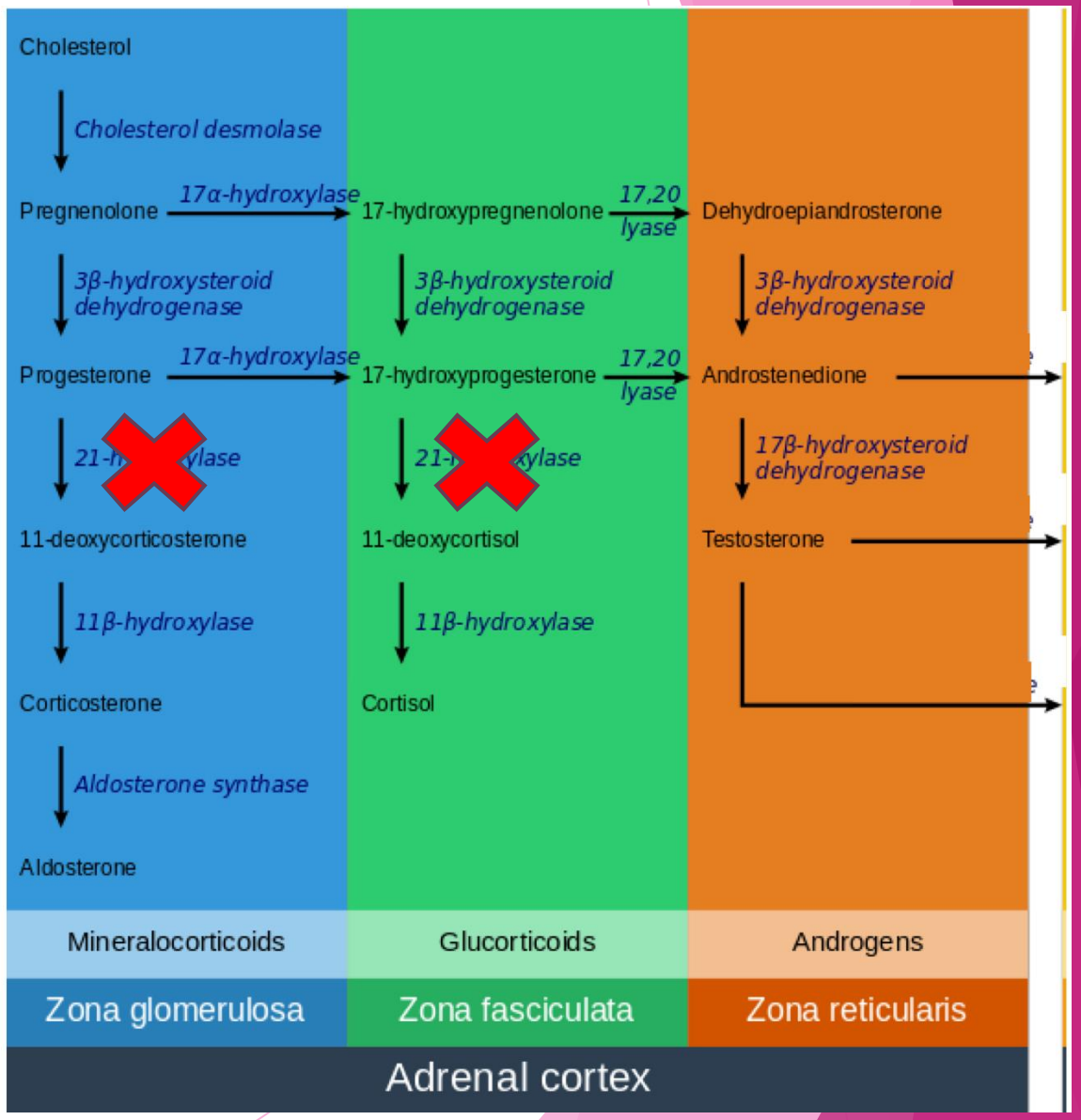
1. 21-hydroxylase deficiency **(most common)**
2. 11ß-hydroxylase deficiency
3. 17α-hydroxylase deficiency
4. 3ß-hydroxysteroid dehydrogenase deficiency



21-hydroxylase Deficiency

Symptoms are based on the abnormal levels of each of the affected hormones:

- Low aldosterone:
  - Loss of water and dehydration
  - Hypovolemia (shock)
  - Hyperkalemia
  - ↑ Renin
- Low cortisol:
  - Hypoglycemia
  - Nausea and vomiting
- Excess androgens:
  - Ambiguous genitalia in females
  - Precocious puberty in males
- Excess ACTH:
  - Skin hyperpigmentation



Polycystic Ovarian Syndrome

Blue = Mentioned by Dr. Ayman in the lecture.

- The name of this disease is actually a misnomer. Patients with PCOS do not necessarily present with cysts in the ovaries.
- Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response → ↑ LH:FSH ratio, ↑ androgens (eg, testosterone) from theca interna cells, ↓ rate of follicular maturation → unruptured follicles (cysts) + anovulation. Common cause of ↓ fertility in females.
- Diagnosed based on ≥ 2 of the following: cystic/enlarged ovaries on ultrasound, oligo-/anovulation, hyperandrogenism (eg, hirsutism, acne). Associated with obesity, acanthosis nigricans. ↑ risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.
- Treatment: cycle regulation via weight reduction (↓ peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene (ovulation induction); spironolactone, finasteride, flutamide to treat hirsutism.

References

- Dr. Ayman Aref's lectures for 020 batch (1st semester)
- First Aid
- Boards and Beyond
- Macleod's Medical Examination (14th edition)
- ChatGPT