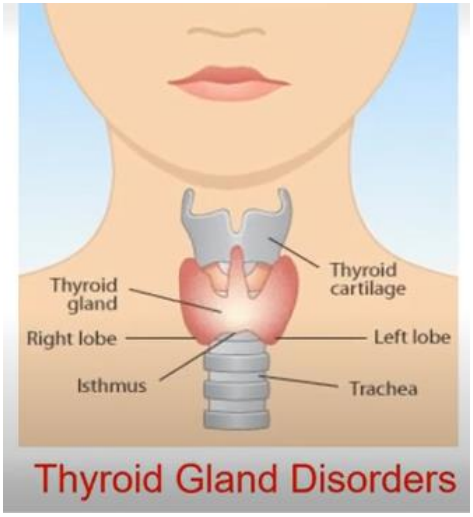
Unit 11 part 2
Clinical Endocrinology

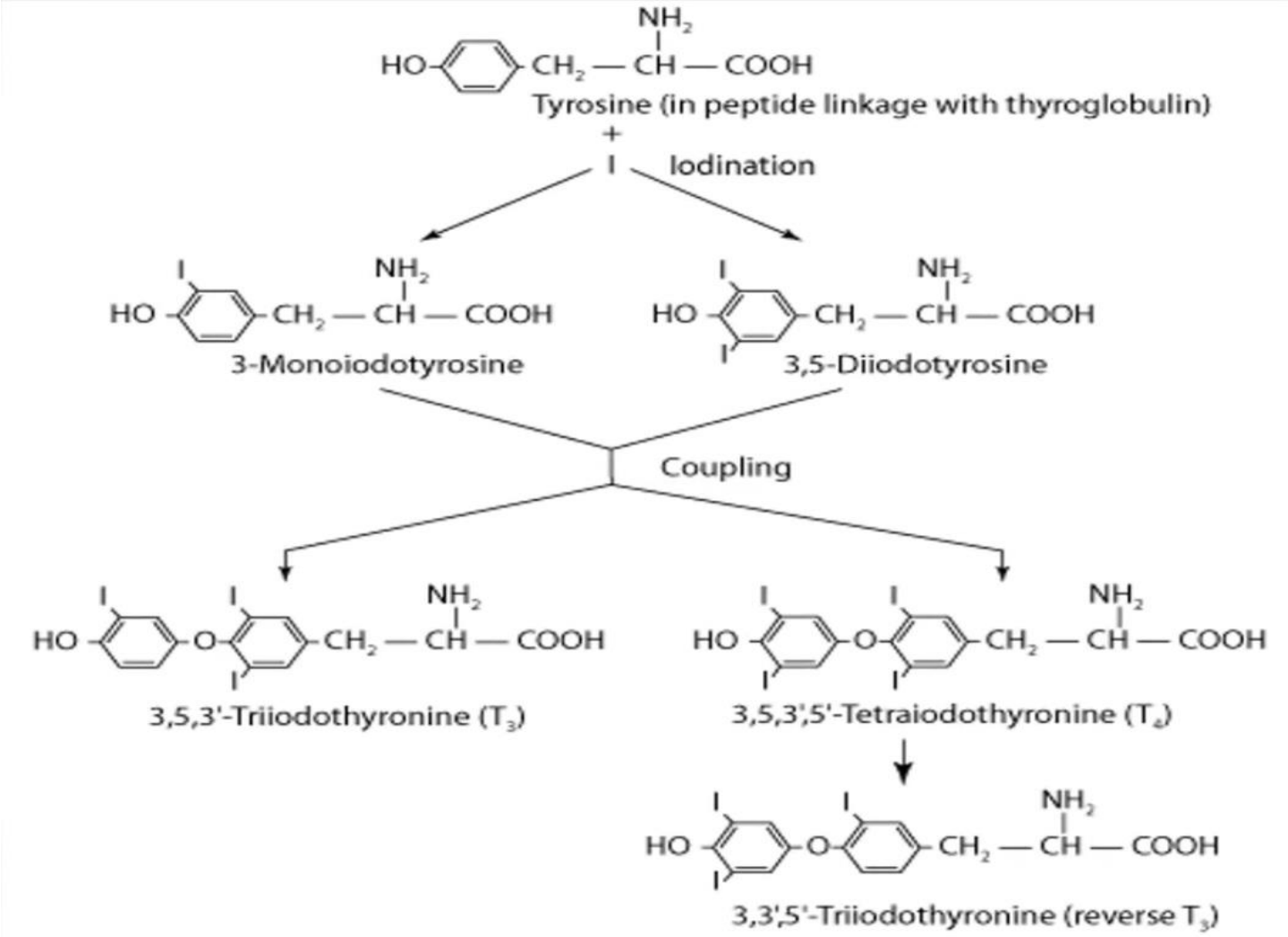
Thyroid gland

Thyroid gland secretes:

1. **Metabolic hormones: tri-iodothyronine (T3),thyroxin (T4).**
2. **Calcitonin (regulates plasma Calcium level)**



- **Both T_3 & T_4 are synthesized from coupling of 2 tyrosine molecules T_4 contains 4 iodine atoms while T_3 contains 3 atoms.**
- **They are synthesized in the thyroid gland as a component of large molecule (Thyroglobin), which upon stimulation of thyroid releases T_3 & T_4.**
- **Thyroid gland secrets mostly T_4 (100 mmol/L) more than T_3 (2 mmol/L) but T_3 is more biologically active.**
- **Peripheral tissues can deiodinate T_4 into T_3 or reverse T_3 (rT_3) which is completely inactive.**
- **By modulating the relative production of T_3 or rT_3 tissues can "fine tune" their local thyroid status.**

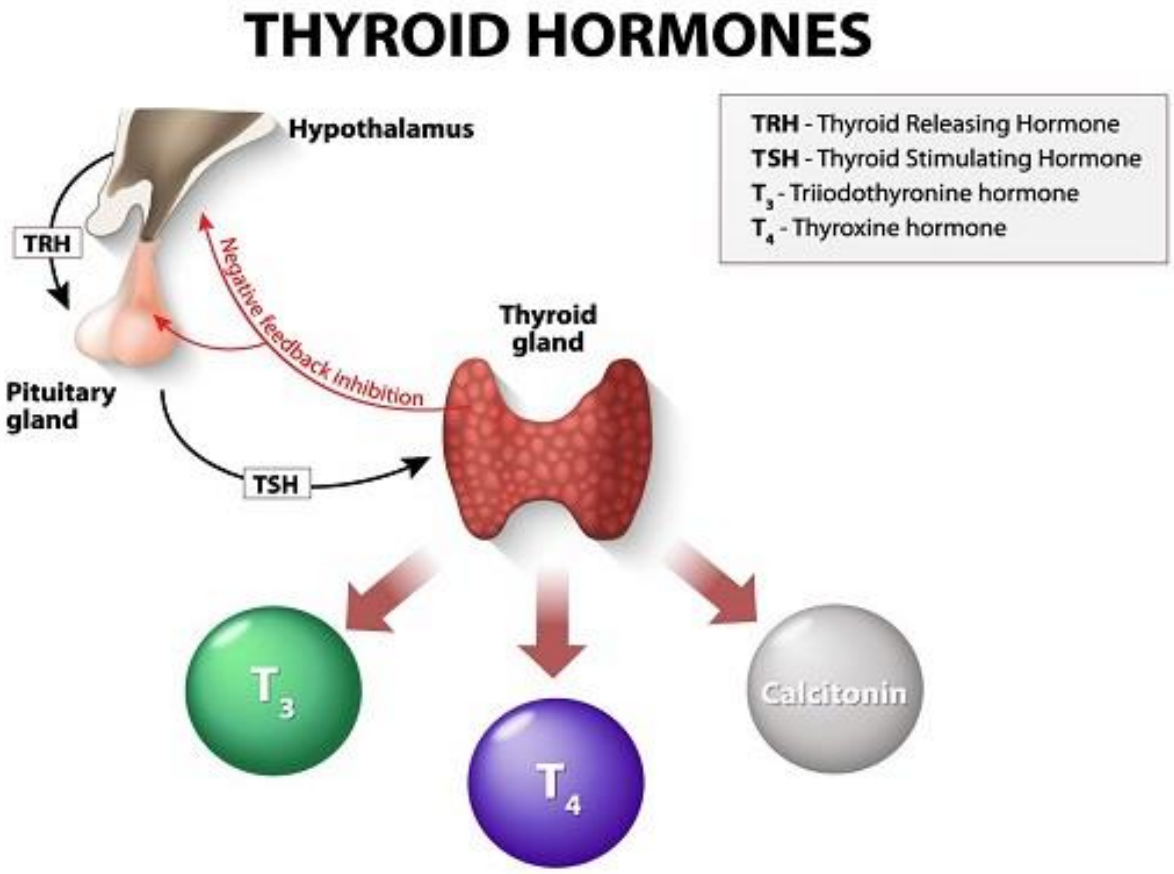


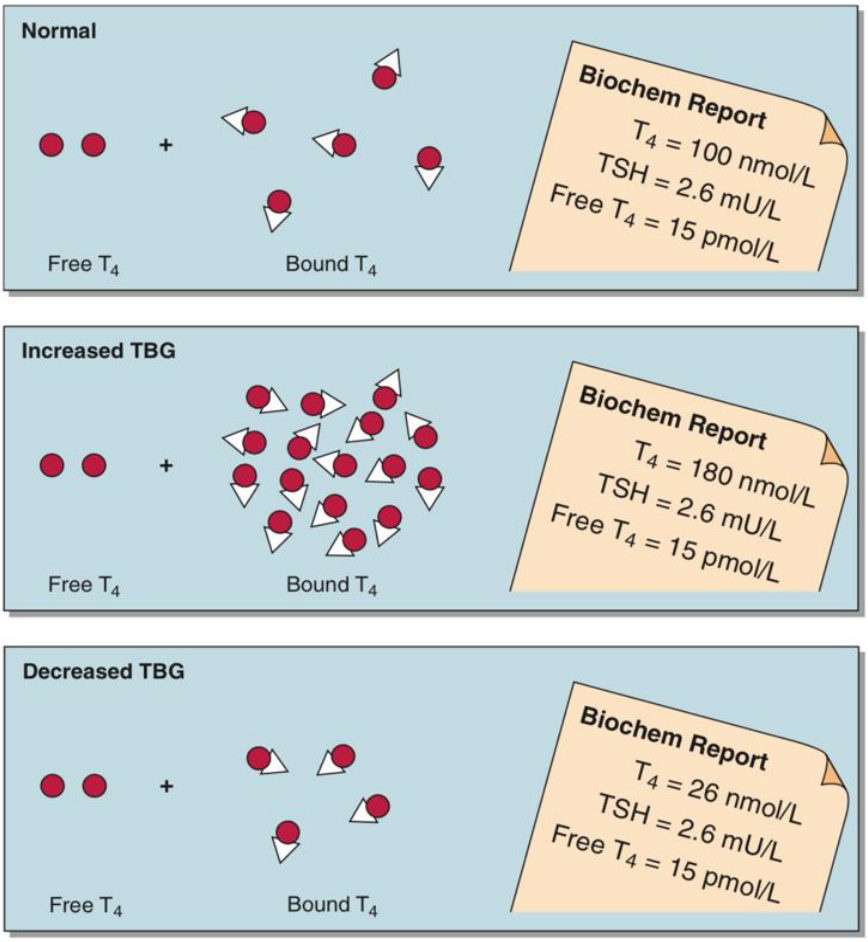
Thyroid Gland

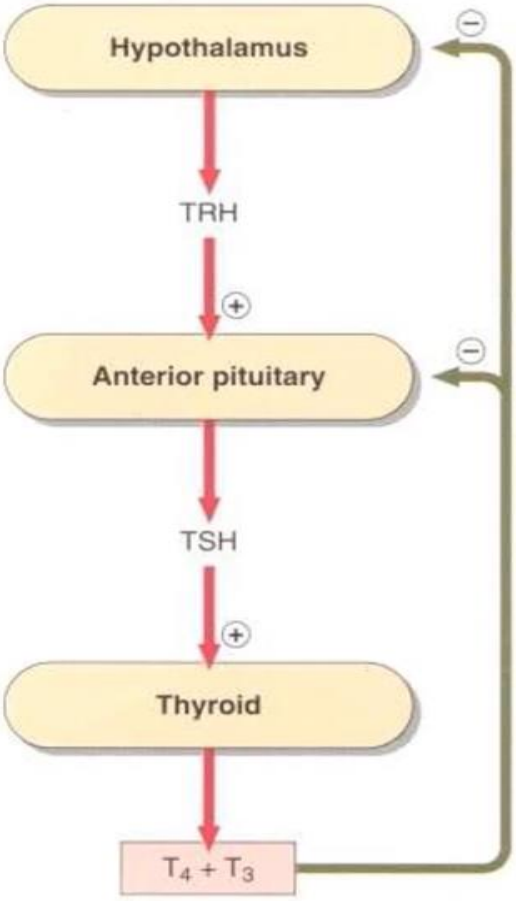
Plasma T_3 & T_4

- About 99.95% of T_4 is bound to plasma proteins and only 0.05% is free, while 99.5% of T_3 is bound to plasma protein and 0.5% is free.
- Only the unbound or free T_3 & T_4 are responsible for biological activities and feedback regulation.
- **Plasma proteins that bound to T3 & T4 are:**
  1. Thyroid-binding globulin (TBG bound to 70%)
  2. Albumin (bound to 25%)
  3. Transthyretin (bound to 5%).
- Changes in the binding protein concentration complicate the interpretation of thyroid hormone results
- **Goiter:** is an enlarged thyroid gland that may be associated with hyper- or hypo- or Euthyroidism.

Hypothalamic pituitary thyroid axis: (regulation of the T3,T4 release)







Thyroid functions

- **They act by entering cells and binding to specific receptors in the nuclei, where they stimulate the synthesis of a variety of species of mRNA, thus stimulating the synthesis of polypeptides, including hormone and enzymes.**

1. **Thyroid hormones are essential for normal growth and development.**
2. **They increase basal metabolic rate (energy).**
3. **They increase heat production and oxygen consumption in most tissues through stimulation of ATPase activity.**
4. **Overall, they increase the catabolism (weight loss and muscle wasting are typical features of excessive secretion of thyroid hormones).**
5. **They increase the sensitivity of the Cardiovascular System (C.V.S) and central nervous system (CNS) to catecholamines, leading to increases in heart rate and cardiac output.**

Thyroid function tests

- **Most laboratories offer a standard 'profile' of thyroid function tests (e.g: TSH and free T4), and perform additional tests only if these results are equivocal or the clinical circumstances require it.**

a) **TSH: it is the first-line thyroid function test.**

Used for screening of congenital hypothyroidism, a condition which, unless treated within 3 months of birth, results in permanent brain damage (cretinism)

Only in hypopituitarism, TSH cannot be used to diagnose primary thyroid diseases.

b) **Total T_4 and T_3 : These tests have the major disadvantage in that it is dependent on binding protein concentration as well as thyroid activity.**

c) **Fee T_4 and T_3 : these tests avoid the problems associated with protein binding.**

d) **Antibodies: the titer of autoantibodies to thyroid tissues may be helpful in the diagnosis and monitoring of autoimmune thyroid diseases.**

Thyroid dysfunctions

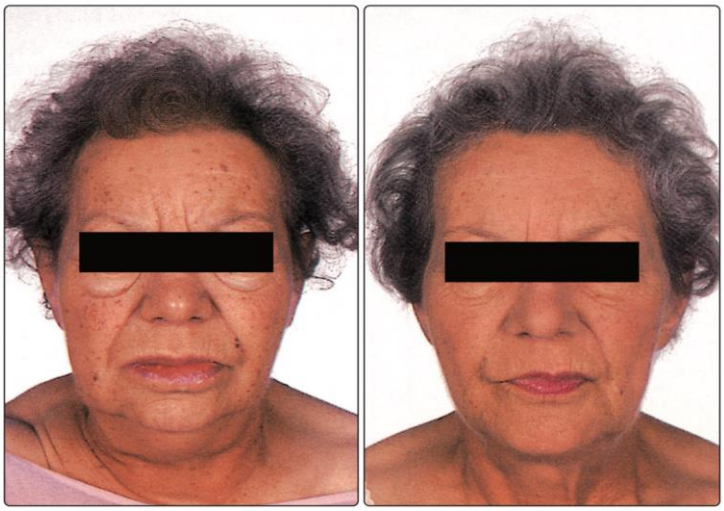
a) **Hypothyroidism: it is under-activity of the thyroid gland that leads to inadequate production of thyroid hormones. Develops slowly**

Cretinism or congenital hypothyroidism occurs in newborn and accompanied by abnormal physical development and mental retardation.

If occurs later (adult) in life it is called myxedema.

- ***Clinical features (symptoms):***

1. **Weight gain**
2. **Lethargy and tiredness**
3. **Cold intolerance**
4. **Dryness and coarsening of skin and hair**

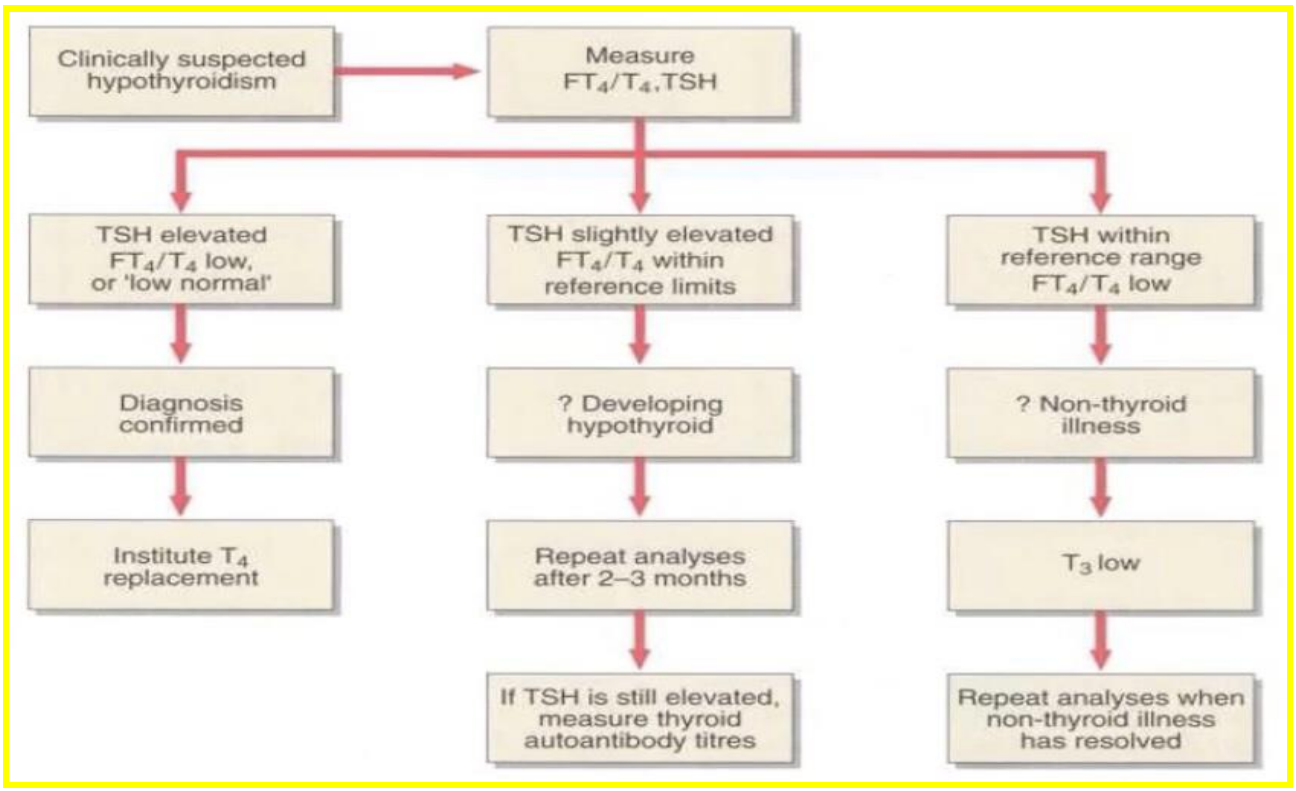


- ***Causes:* most common is**

1. **autoimmune destruction of the thyroid,**
2. **Hashimoto's disease,**
3. **surgical treatment of hyperthyroidism**
4. **or iodine deficiency.**

- ***Lab. Diagnosis (Hypothyroidism) :***

Free T_3 or T_4	TSH	Disorder	Affected gland
↓↓	↑↑	Primary Hypothyroidism	Thyroid gland (common)
↓↓	↓↓	Secondary Hypothyroidism	Pituitary gland (very rare)



Screening of neonatal hypothyroidism (cretinism):

- **Frequency 1/4000 live births**
- **If they are diagnosed at an early age (first 3 months), replacement therapy of T4 is simple and effective, but this must be started as soon after birth as a reliable diagnosis can be made**
- **Untreated, affected children become cretins, with very low intelligence and impaired growth and motor function.**
- **Heal test for TSH, The screening method involves measurement of TSH in a capillary blood spot from the heal (تحليل الكعب) at 6-8 days of age**
- **Elevated TSH in a blood spot is diagnostic of the disease (cretinism)**

b) **Hyperthyroidism: it is the over-activity of thyroid gland.**

- **Thyrotoxicosis occurs when tissues are exposed to high level of thyroid hormone from hyperthyroidism or ingestion of too much T_4**

- ***Clinical features:***

1. **Weight loss despite normal appetite**
2. **Fatigue ,sweating**
3. **Heat intolerance**
4. **Tachycardia**
5. **Goiter**
6. **Hand tremors**

Hyperthyroidism	*Hypothyroidism*
weight loss	weight gain
hot feeling	cold feeling

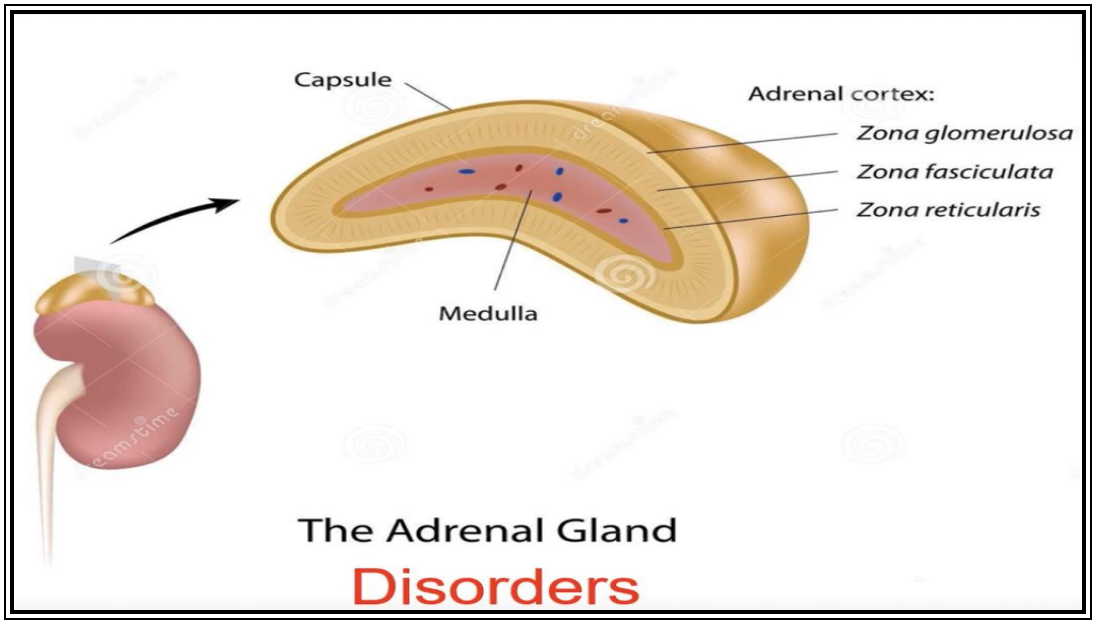
- ***Causes:***

1) **Graves' disease, an autoimmune disorder ultimately caused by auto-antibodies stimulating thyroid growth and function through their interaction with the TSH receptor on thyroid follicular, is the most common cause of hyperthyroidism**
2) **Multinodular goiter**
3) **Thyroiditis**
4) **Excessive T_4 ingestion**
5) **Exogenous iodine-containing drugs**

- ***Lab. Diagnosis:***

- **Total T_4 in the serum does not always reflect metabolic status**
- **Example as in pregnancy, the total T_4 will be above the normal although free T_4 will be normal due to increased synthesis of TBG under the effect of high level of estrogen**
- **Congenital TBG deficiency can also cause confusion**
- **So, it is preferable to measure free T4 than total**
- **Suppressed TSH and elevated free T4 is diagnostic**

Free T_3 or T_4	TSH	Disorder	Affected gland
↑↑	↓↓	Primary Hyperthyroidism	Thyroid gland
↑↑	↑↑	Secondary Hyperthyroidism	Pituitary gland



Site		Hormones	Regulation
Adrenal Cortex	Zona Fasiculata	Glucocorticoids (Cortisol)	Stimulated by ACTH
	Zona Glomerulosa	Mineralocorticoids (Aldosterone)	Stimulated by: a. Renin-angiotensin. b. ↑ K & ↓ Na. c. ACTH (minimal role)
	Zona Reticularis	Adrenal androgens	Stimulated by ACTH
Adrenal Medulla		Adrenaline	Stimulated by: a. Hypoglycemia b. Hypotension c. Pain, anger, fear

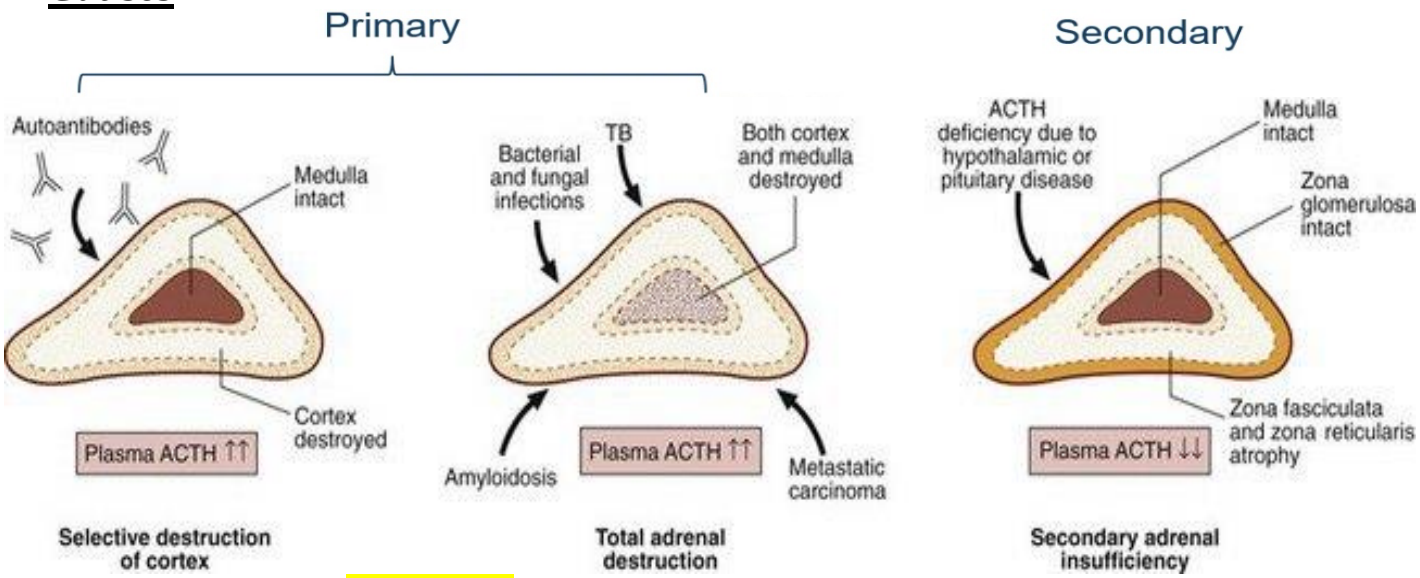
Hormones	Metabolic effects
Glucocorticoids Cortisol	a. ↑ lipolysis b. Promote protein breakdown in muscles c. ↑ gluconeogenesis in liver (↑ BGL) d. Suppress immune & inflammatory responses
Mineralocorticoids (Aldosteron)	a. Na and H_2O retention b. Secretion of K, H and ammonium.
Adrenal androgens	They are androstenedione and dehydroepiandrosterone (DHEA) They are converted to **testosterone** in the peripheral tissues
Adrenaline	a. Neurotransmitter b. Regulation of metabolism c. Increase cardiac output & blood pressure d. Relaxation of smooth muscle of bronchi and intestine

Adrenal gland dysfunctions

a) **Adrenal insufficiency (Addison's): It is a rare condition that if unrecognized is potentially fatal. It is relatively simple to treat once it is diagnosed.**

It is characterized by decrease in glucocorticoids, mineralocorticoids and androgens leading to hypoglycaemia, hyperkalaemia, hyponatraemia, postural hypotension, decreased androgen and hyper-pigmentation (due to ↑ ACTH).

- ***Causes***



- ***Lab. Diagnosis (Addison's): :***

1) **Hyponatraemia: ↓in aldosterone ⟶ increased Na and H_2O loss⟶ hypovolaemia and hypotension ⟶ stimulation of ADH ⟶ H_2O retention**
2) **Hyperkalaemia**
3) **Elevated serum urea**
4) **Hyperpigmentation: In primary hypo function, ACTH increased due to feedback stimulation of anterior pituitary. ACTH has melanocyte-stimulating activity**
5) **Serum cortisol and ACTH levels**

Plasma cortisol	Plasma ACTH	Disorder	Affected gland
↓↓	↑↑	Primary Addison	Adrenal gland
↓↓	↓↓	Secondary Addison	Pituitary gland

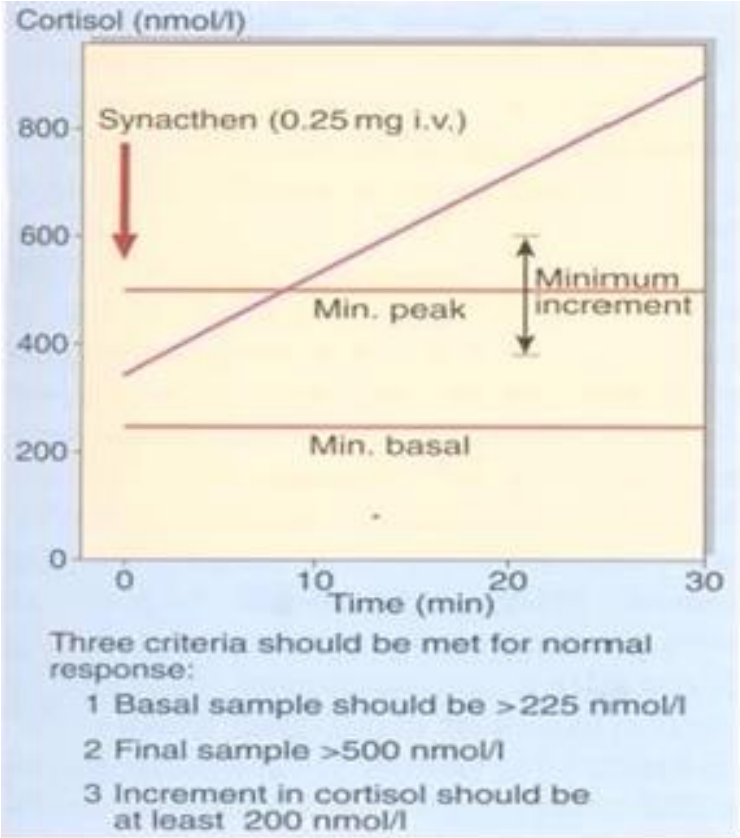
6) Synacthen stimulation tests:

Synacthen is a synthetic analogue of ACTH

a) Short Synacthen test (SST): IV administration of 25 ug of Synacthen, cortisol is measured at 0, 30, and 60'

b) Long Synacthen test (LST): equivocal response to SST may require LST.

IM 1 mg of depot Synacthen is administered daily for 3 days



a) Hyper function: increased levels of cortisol, adrenal androgens, aldosterone

- **Cortisol excess (Cushing's Syndrome):**

  Prolonged exposure of the body tissues to cortisol or other glucocorticoids leads to clinical feature known as Cushing's syndrome

- ***Causes :***

  1. **Excessive production of ACT from pituitary tumour (secondary).**
  2. **Adrenal gland tumour (primary).**
  3. **Exogenous administration of glucocorticoids or ACTH (iatrogenic).**
  4. **Ectopic ACTH-secreting tumour.**

- ***Symptoms*: Moon face, truncal obesity with a buffalo hump, hirsutism, acne Hypertension, menstrual disturbance, osteoporosis, emotional disorders muscle weakness and capillary fragility.**

- **Lab. *Diagnosis*:**

1. Urinary free cortisol:

- **The excess amounts of cortisol will exceed the available capacity of plasma binding protein and the free cortisol is filtered readily into the urine.**
- **Free cortisol is measured in 24-hrs urine sample or assessed as cortisol : creatinine ratio in an early morning urine sample.**

- **Cortisol: creatinine ratio can be made on a small aliquot of urine, if the test is negative on three occasions, Cushing's syndrome may be excluded.**

2. Serum cortisol level:

- **Cortisol is measured at 8.00 and 22.00 (morning sample having higher value than the evening). This difference is not apparent (morning sample equal evening). in Cushing's syndrome**

3. Dexamethasone suppression test

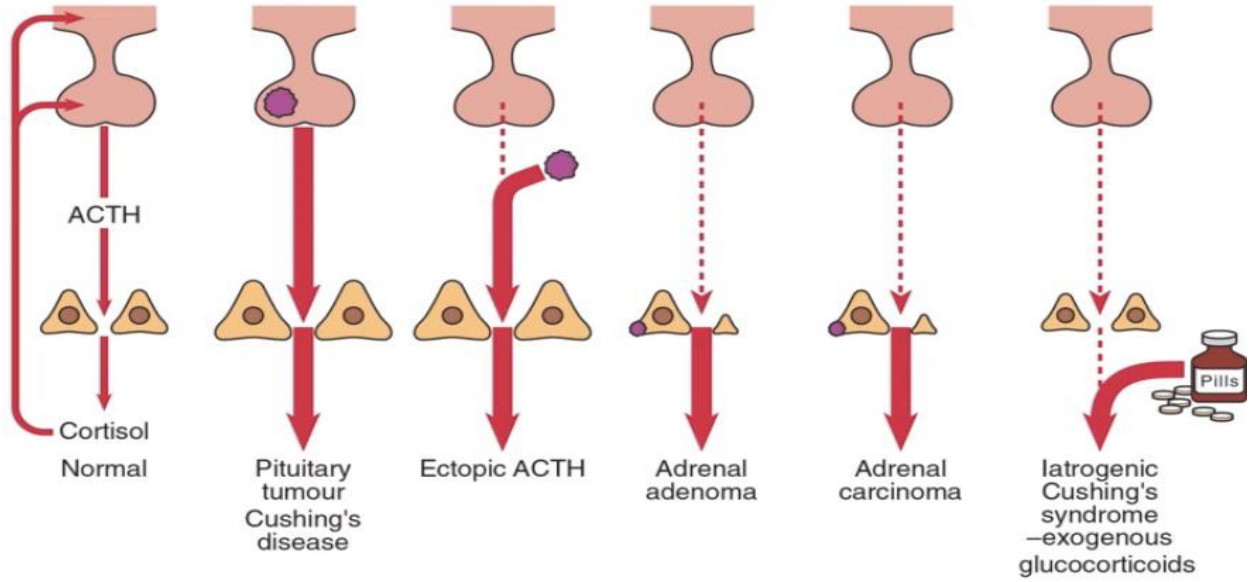
- **Low dose DSI: (1 mg Dexamethason orally at 23.00 and cortisol measured at 9:00, if < 50 nmol/L ⟶ normal**
- **High dose DSI: (8 mg of Dexamethason is used if failure to response to Low dose DST due to overproduction of ACTH (Cushing or ectopic malignant or adrenal production of cortisol)**

4. Insulin-induced hypoglycemia: ****

- **In normal, a hypoglycaemia (<2.2 mmol/L) leads to rise in serum cortisol more than 200 mmol/L**
- **Failure of the serum cortisol to rise after insulin-induced hypoglycaemia is diagnostic for Cushing's syndrome**

5. Differential diagnosis:

Cortisol	ACTH	Disorder	Affected gland
↑↑	↓↓	Primary Cushing	Adrenal gland
↑↑	↑↑ or normal	Secondary Cushing	Pituitary gland
↑↑	Very ↑↑	Ectopic ACTH production	Ectopic foci



Aldosterone excess:

- **Primary hyperaldosteronism (Conn's Syndrome) is rare disease, in most causes is due to a single adrenocortical adenoma.**
- **Secondary hyperaldosteronism is common and associated with renal, heart or liver diseases**

- ***Symptoms:*** **polydipsia and polyuria, tetany , hypertension.**
- ***Lab. Diagnosis:*** **Hypernatremia, hypokalaemia with increased urinary potassium**
  - **Plasma levels of aldosterone and renin**
  - **Hypokalaemia with increased aldosterone level is diagnostic to Conn's Syndrome**
  - **Adrenal androgens excess: adrenal carcinomas may produce excess androstenedione and DHEA causing hirsutism and virilization in females**

Gonadal Disorders

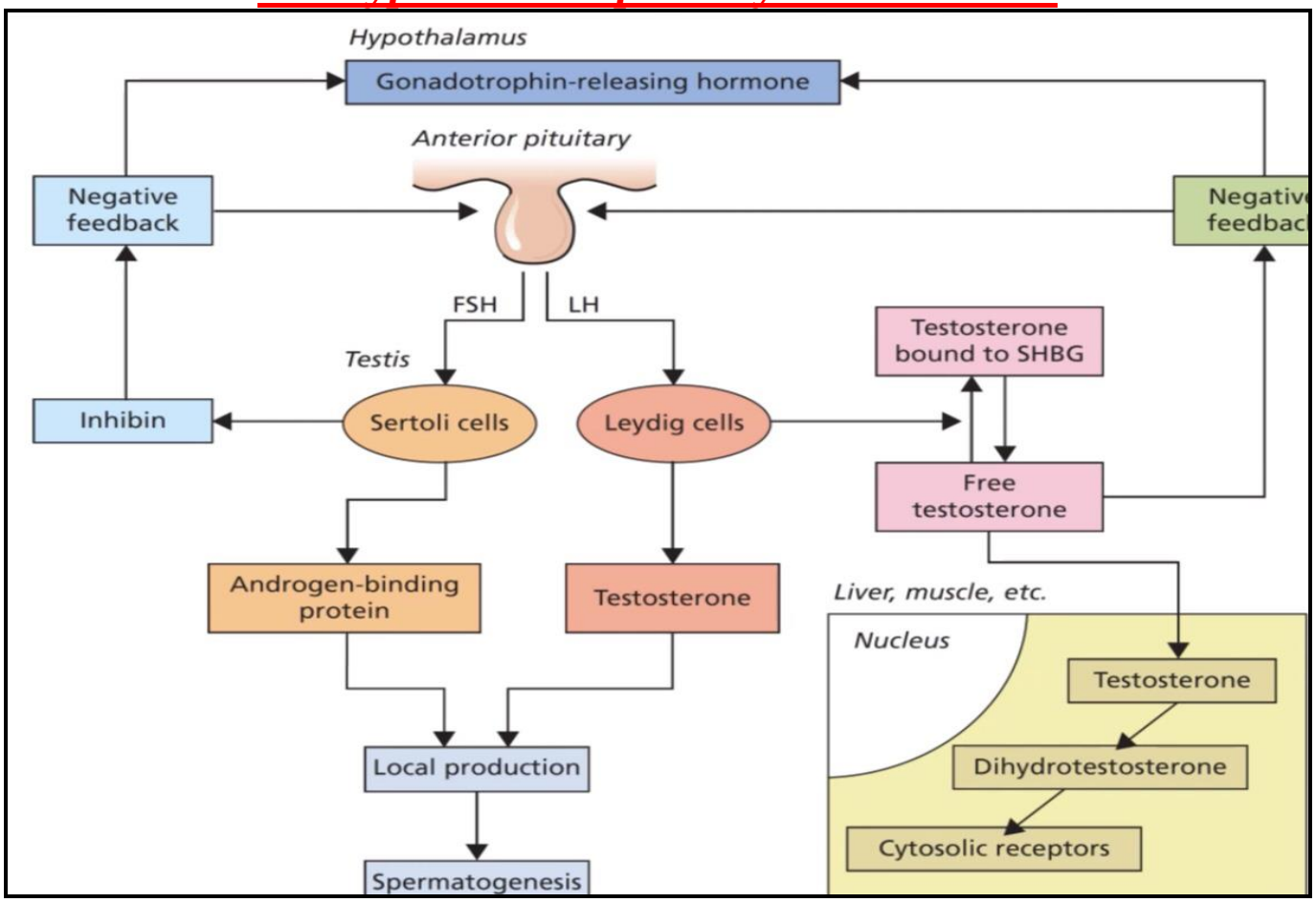
Male sex hormone

1) **Testosterone is the principal androgen and is synthesized by the testes. It is most important androgen, both in terms of potency and the amount secrete.**
2) **Androstenedione and DHEA: these are weaker androgens that secrete by testes .Also secrete by the adrenal glands but adrenal androgen secretion does not appear to be physiologically important in the male.**
3) **Estradiol: very little amounts are present due to the peripheral conversion of testosterone and androstenedione in the liver and adipose tissue by the action of aromatase enzyme**

Plasma androgens:

- **Testosterone in the plasma is very low before puberty, but then rise rapidly to reach normal adult values**
- **In the circulation, 98% of testosterone is protein bound, 60% to Sex Hormone Binding Globulin (SHBG) and 38% to albumin. So, factors that alter the concentration or affinity of SHBG will have a significant effect on the circulating total testosterone.**
- **It was believed that only the free testosterone could enter cells and exert a biological effect. However, some consider that both the "free' and 'albumin-bound fraction" of testosterone may be able to enter cells and thus be the 'bioavailable testosterone' fraction.**
- **Few laboratories measure the "free' testosterone or bioavailable testosterone'. Most laboratories will offer a 'free androgen index (FAI) which requires the measurement of [SHBG] and [total testosterone] and applying these in the formulae. (Total testosterone/SHBG)X 100 .**

The hypothalamic-pituitary-testicular axis



➢ Androgens Functions

- **Testosterone: Testosterone is a powerful anabolic hormone It is essential both to the development of secondary sexual characteristics in the male and for spermatogenesis.**
- **The biological activity of testosterone is mainly due to 5α- dihydrotestosterone (5α-DHT). This is formed from testosterone target tissues by 5α-reductase.**
- **In a rare condition in which there is deficiency of this enzyme, 5α-DHT cannot be formed; male internal genitalia develop normally (Wolffian duct development in the fetus is testosterone dependent) but masculinization, which requires 5α- DHT, is incomplete**
- **In states of androgen insensitivity, defects of the receptors for either testosterone or 5α-DHT or both can cause a spectrum of clinical abnormalities ranging from gynecomastia to disorders of sex development.**

➢ Disorders of male gonadal function

- **Hypogonadism (infertility): The term hypogonadism implies defective spermatogenesis or testosterone production or both It can be primary (i.e. due to testicular disease) or occur secondarily to pituitary or hypothalamic disease.**

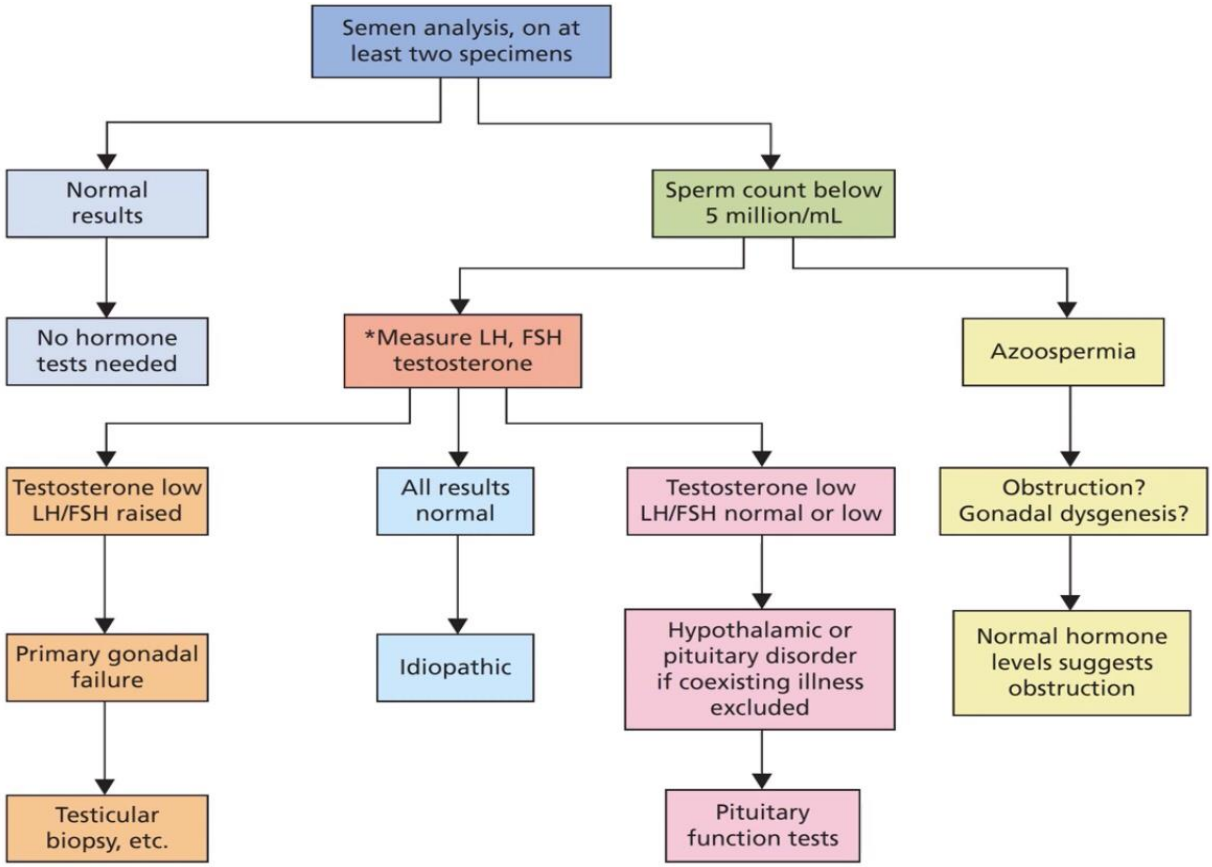
- **Semen analysis is the primary test for assessment of male infertility.**
- **If on two occasions the sperm count is less than 20 X 10^6/ml and/or motility is poor in more than 50% of the sperm, measurements of serum LH, FSH, PRL and testosterone should be made to determine whether hypogonadism is caused by a primary defect in the testes or in the hypothalamic-pituitary region.**
- **Primary hypogonadism is sometimes referred to as 'hypergonadotrophic hypogonadism' and secondary hypogonadism as 'hypogonadotrophic hypogonadism**

Primary (FSH and LH are high)	Secondary (FSH and LH are low)
Congenital: Testicular agenesis 5α-reductase deficiency Klinefelter's syndrome **Acquired:** Testicular torsion Cytotoxic drugs Irradiation Mumps infection	Pituitary tumor specially if causing hyperprolactinemia Hypothalamic disorders such as Kallman's syndrome

Table 10.3 Symptoms and signs associated with male hypogonadism.

Physical	Psychological	Sexual
Decreased muscle mass and strength	Depression	Decreased sex drive (libido)
Decreased bone mineral density or osteoporosis	Lack of energy	Decreased sexual thoughts
Gynaecomastia	Fatigue	Erectile dysfunction
Reduced body hair		Infertility
Hot flush		
Sweating		

Disorders of male gonadal function



2) **Gynecomastia: Breast development in males may be caused by:**

a) **Physiological: imbalance between estrogens to androgens**

1) **Neonatal: as a result of exposure to maternal estrogens.**
2) **Pubertal, approximately 50% of normal boys develop gynecomastia owing to temporarily increased secretion of estrogens relative to androgens. In both instances, the gynecomastia resolves spontaneously**
3) **Elderly, as a result of a decrease in testosterone secretion.**

b) **Pathological: increased estrogens, decreased androgens or androgens insensitivity**

c) **Pharmacological: estrogens, digoxin (binds to estrogen receptors), anti- androgen drugs, or cytotoxic drugs (testicular damage)**

3) Erectile dysfunction (ED):

- **It is most commonly caused by diabetes , neurological disorders, cardiovascular disease , medication such as beta blockers, alcohol abuse, thyroid disease, liver and renal disease and psychological problems.**
- **Androgen deficiency and Hyperprolactinemia are uncommon causes of erectile dysfunction and such patients often complain of loss of libido in addition to their ED.**

Female sex hormone

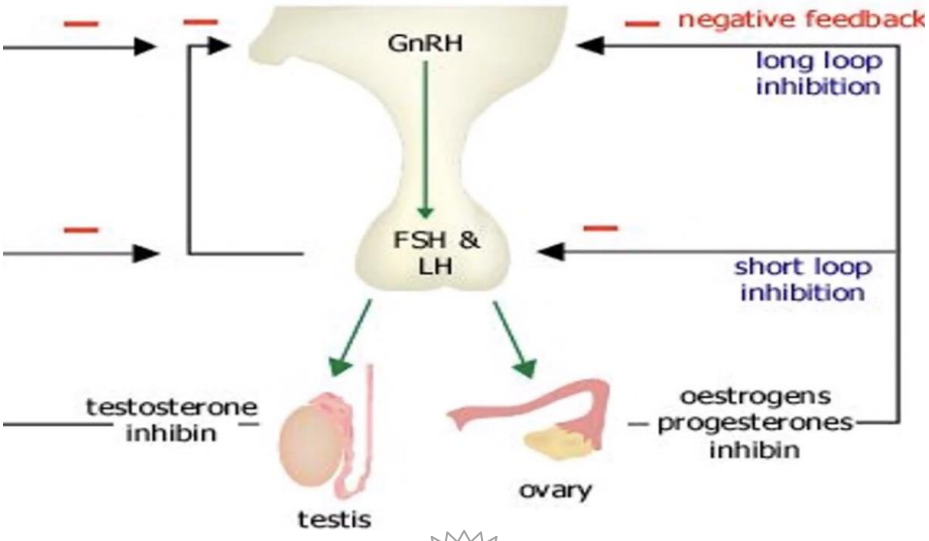
1) **Estradiol: secrete by ovaries and widely varied in plasma throughout the female menstrual cycle.**
2) **Progesterone: secrete by ovaries and corpus luteum after ovulation**
3) **Testosterone: very little amounts, about half of which comes from ovaries and half from peripheral conversion of androstenedione and DHEA**

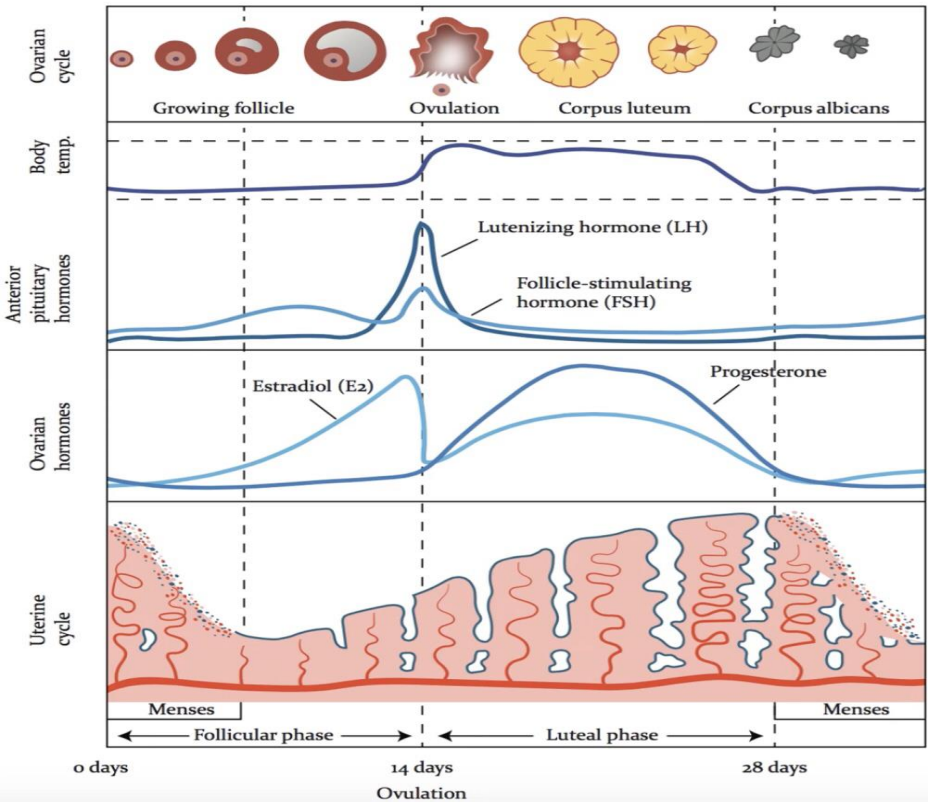
- **Plasma estradiol:**
- **Plasma estrogens are low before puberty. During puberty, estrogen synthesis increases and cyclical changes until the menopause. After the menopause, the sole source of estrogens is from the metabolism of adrenal androgens, plasma concentrations fall to very low values.**
- **in the plasma estrogens are transported bound to protein; 60% to albumin and the remainder to SHBG.**

➢ Oestrogens Functions

- **Estrogens are responsible for the development of many female secondary sexual characteristics.**
- **They also stimulate the growth of ovarian follicles and the proliferation of uterine endometrium.**
- **Progesterone has many important effects on the uterus, including preparation of the endometrium for implantation of the conceptus. It is pyrogenic and mediates the increase in basal body temperature that occurs with ovulation.**
- **SHBG binds both testosterone and estradiol in the plasma, although it has greater affinity for testosterone. The plasma concentration of SHBG in males is about (half that in females).**
- **If SHBG concentration decreases, the ratio of free testosterone to free estradiol increases, although there is an absolute increase in the concentrations of both hormones. If SHBG concentration increases, the ratio decreases.**

The hypothalamic-pituitarygonadal axis

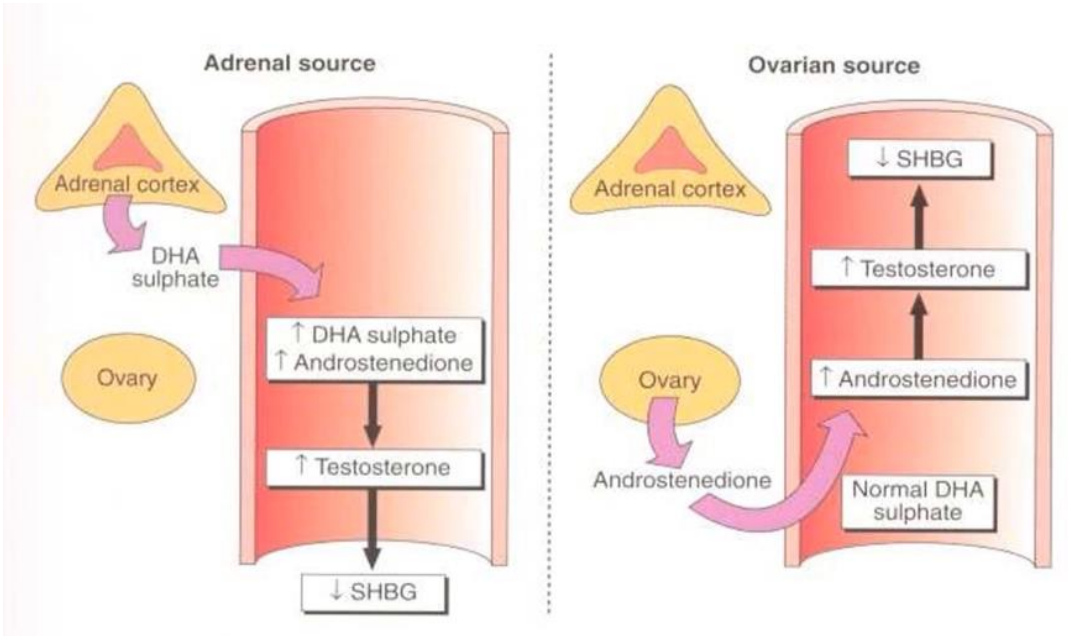


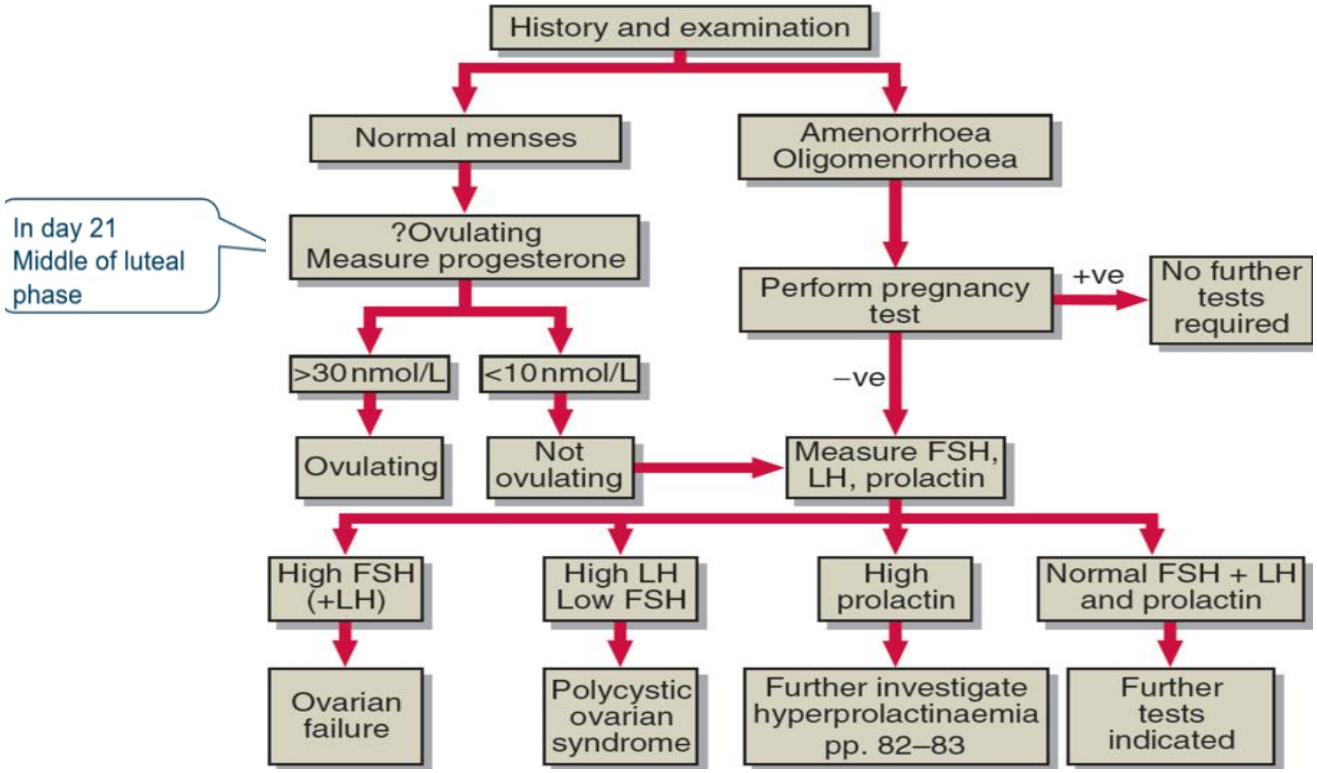


➢ *Disorders of female gonadal function*

1) **Hypogonadism: Girls with delayed puberty usually present because of absence of breast development or amenorrhoea (see below). Girls with no breast development by the age of 13 or with primary amenorrhoea after the age of 15 should be investigated further**
2) **Hirsutism is an increase in body hair with male pattern distribution: It may be idiopathic but the commonest pathological cause is obesity**
3) **Virilism: it is uncommon but serious disease. Characterized by marked elevation in testosterone leading to clitoromegaly, male-pattern hair growth, deepening of the voice frontal balding and breast atrophy.**

- **The androgens screen in females:**
- **A decreased SHBG in women is evidence of elevated androgen, as the synthesis of the SHBG in the liver is depressed by testosterone.**


Adrenal source
Adrenal cortex
DHA sulphate
Ovary
↑ DHA sulphate
↑ Androstenedione
↑ Testosterone
↓ SHBG
Ovarian source
Adrenal cortex
Ovary
Androstenedione
↓ SHBG
↑ Testosterone
↑ Androstenedione
Normal DHA sulphate


History and examination
Normal menses
Amenorrhoea Oligomenorrhoea
In day 21 Middle of luteal phase
?Ovulating Measure progesterone
Perform pregnancy test
+ve
No further tests required
>30 nmol/L
<10 nmol/L
–ve
Ovulating
Not ovulating
Measure FSH, LH, prolactin
High FSH (+LH)
High LH Low FSH
High prolactin
Normal FSH + LH and prolactin
Ovarian failure
Polycystic ovarian syndrome
Further investigate hyperprolactinaemia pp. 82–83
Further tests indicated