Hyperprolactinemia &Hirsutism

Dr. Zina Abdullah

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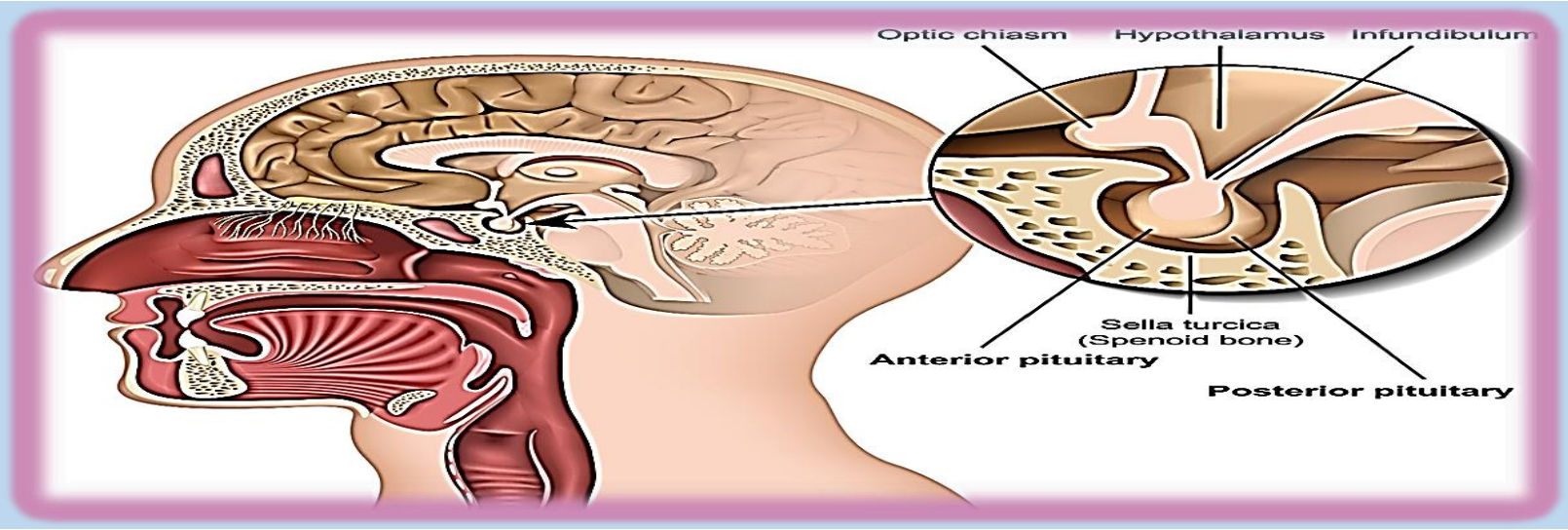
Introduction

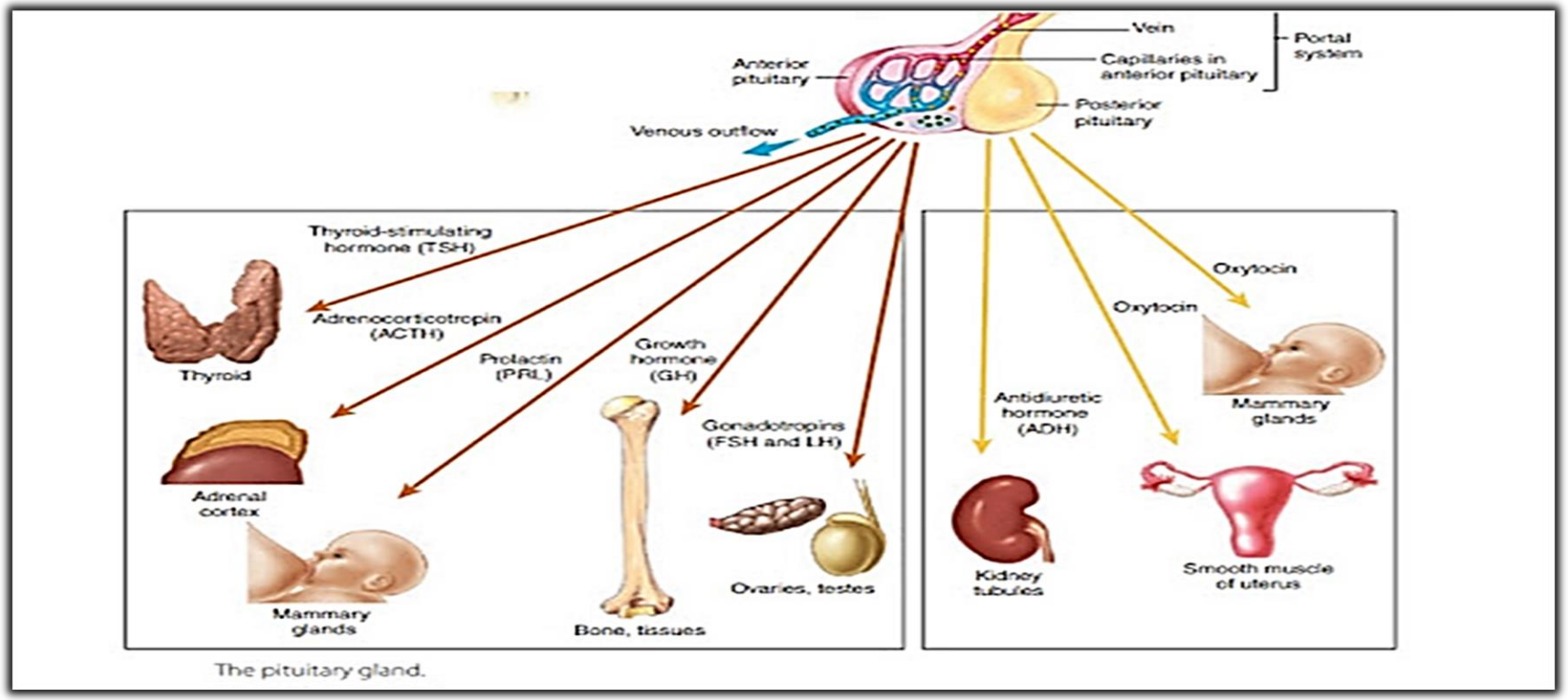
Prolactinomas : Pituitary adenomas may cause hyperprolactinemia, and they make up approximately 10 % of all intracranial tumors their etiology is unknown.it can be divided into two categories: Macroadenomas(>=10mm in diameter)and microadenomas(<10 mm in diameter).



- Clinically, symptoms of galactorrhea, menstrual disturbances, or infertility may lead to its diagnosis.
- Most tumors are benign, and only an estimated 0.1 percent of adenomas developed into frank carcinoma with metastasis.
- pituitary adenomas may cause striking abnormalities in both endocrine and nervous system function.

Prolactin hormone

- Made by the pituitary lactotrophs.
- Normal serum level= 10-25 ng/ml, half-life =20 minutes
- Metabolized in the liver and kidney.



The pituitary gland.

Control of prolactin release:

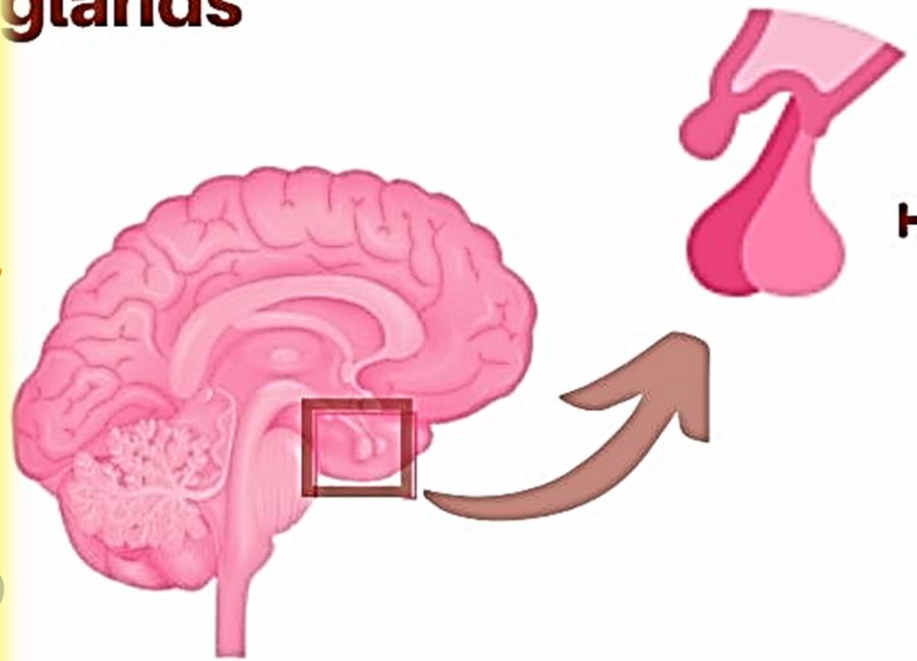
- Prolactin inhibiting factor (dopamine) decrease prolactin.
- Estrogen → ↑prolactin.
- TRH "thyrotropin releasing hormone“ → ↑ prolactin.
- TRH can bind directly to anterior pituitary lactotrophs and stimulate PRL production

How does prolactin act?

A. Inhibition of pulsatile GnRH secretion.
B. Decrease ovarian sensitivity to gonadotrophins.
C. Inhibition of FSH-directed ovarian aromatase.
D. Inhibition of progesterone synthesis.

Pituitary Gland

The master of all glands



- TSH → Thyroid
- ADH → Kidney
- Oxyticin & PRL → Breast
- ACTH → Adrenal Gland
- LH → Ovary &Testis
- MSH → Skin
- GH → Muscle & Bone

Healthnise

Causes of hyperprolactinemia:

❑Physiologic conditions

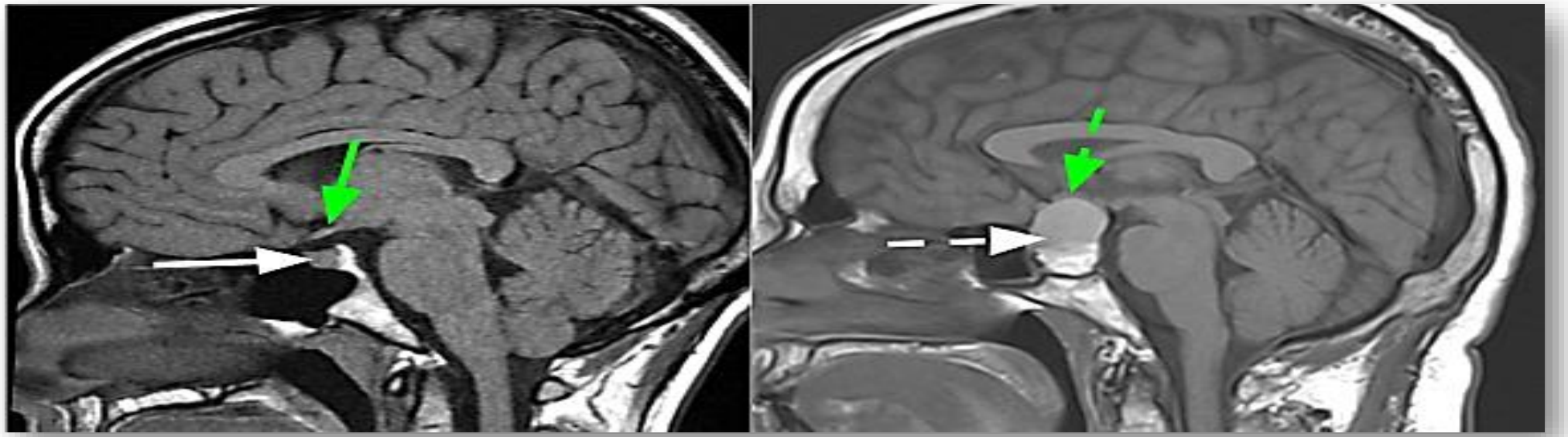
- Sleep.
- Satinity.
- Sex.
- Sucking.
- Second half of menstrual cycle.
- Stress and exercise.
- Pregnancy.

❑Pharmacological

- Estrogen containing drugs/ pills.
- Antidopaminergic drugs --- TCA.
- Antiemetic drugs ---- metoclopramide.
- Antihypertensive drugs ---- methyldopa.
- H2 receptor antagonist.
- Drugs that stimulate serotonin secretion --- hallucinogens.

❑Pathological

- Pituitary---adenoma, GH secreting tumor.
- Hypothalamus—infection, trauma, tumor.
- Thyroid gland---hypothyroidism.



❑Other causes

- Liver cell failure- Chronic renal failure.
- Chest wall disease: burn- scar- Herpes zoster.
- Ectopic secretion: Hypernephroma of kidney.
- Oat cell carcinoma of lung.
- Hyper estrogenic----PCOS.

Clinical Manifestation

- Galactorrhea ---30%.
- Infertility---due to luteal phase anovulation.
- Oligo-hypomenorrhea. The primary mechanism linking hyperprolactinemia and amenorrhea is believed to be a reflex increase in central dopamine levels. Stimulation of the dopaminergic receptors on the GnRH neurons alters GnRH pulsatility, thereby disrupting folliculogenesis.
- Decreased libido.
- Hirsutism—due to decrease in SHBG.

Presenting symptoms of hyperprolactinemia

Adult females	Adult males	Prepubertal children (male and f
Amenorrhea	Decreased in seminal	Delayed puberty
Anovulatory cycle	fluid volume	Galactorrhea
Breast enlargement	Galactorrhea	Gynecomastia
Breast pain	Gynecomastia	Osteopenia or osteoporosis
Galactorrhea	Impotence	Primary amenorrhea (females only)
Hirsutism	Loss of libido	Short stature
Infertility		
Loss of libido		
Oligomenorrhea		

Diagnoses:

- History
- Examination --- eyes, thyroid, breast, chest wall.
- Investigations --- prolactin level

> 100 ng/ ml --- suggestive adenoma.

> 300 ng/ ml --- diagnostic adenoma.

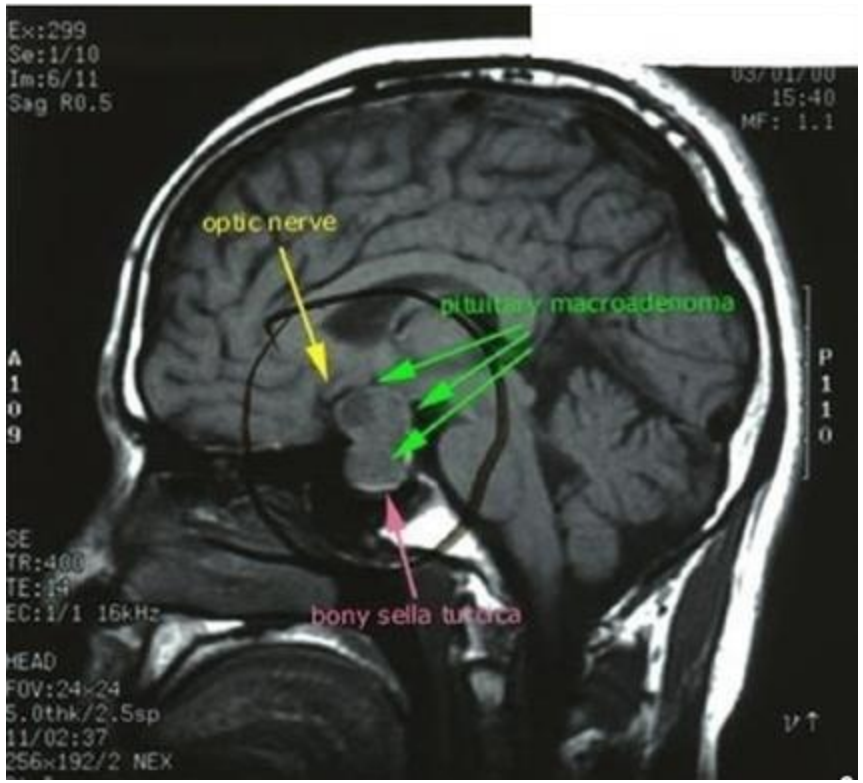
> 2000 ng/ ml --- cavernous sinus.

- ➢ Thyroid function test.
- ➢ Liver function test.
- ➢ Kidney function test.

Brain MRI

macroadenoma (> 1cm).

microadenoma (<1cm).



Treatment Of Galactorrhea And Hyperprolactinemia

Observation: as long as galactorrhea is not socially embarrassing and the patient has regular menses, there is no need to institute treatment. Because the growth rate of microadenomas is slow, an annual measurement of serum prolactin is appropriate in patients with normal estrogen level Thus, asymptomatic patients with a microprolactinoma may be managed conservatively with serial MR imaging and serum PRL levels every 1 to 2 years as the risk of progression to a macroadenoma is < 10 percent.

Macroadenoma require further evaluation by periodic pituitary scanning and possible Treatment.

- When tumors of any size are associated with amenorrhea or galactorrhea, therapy is considered .

- Neurosurgical evaluation is mandatory when visual field defects or severe headaches are present.

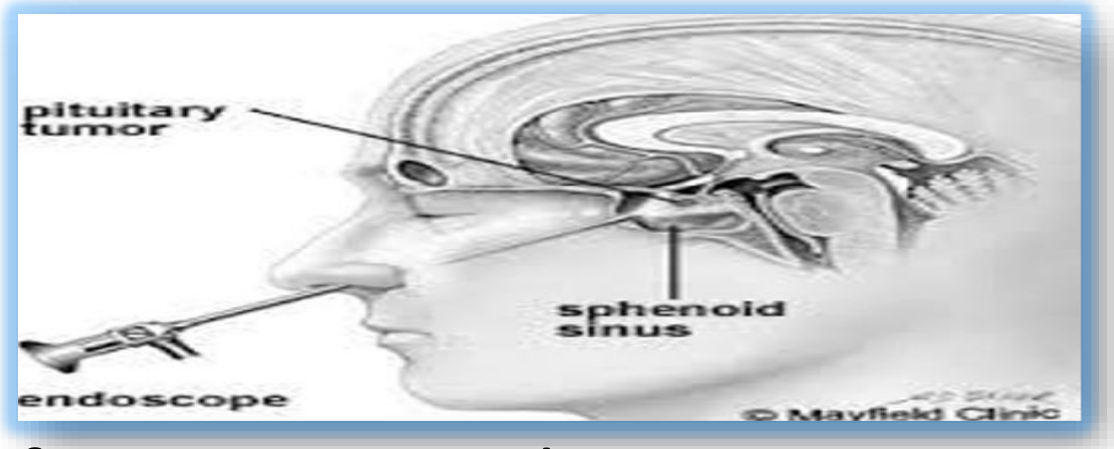
Treatment:

- **Medical therapy:** bromocriptine and cabergoline act as dopamine agonists to reduce prolactin secretion and allow for the restoration of cyclic, physiologic estrogen secretion.
  - Bromocriptine normalizes the secretion of prolactin in about 80% of women microadenomas, and it restores menses and fertility in over 90%
- Started at a low dose. tab or 0.125 mg—each night to minimize associated nausea and dizziness. This dose can be slowly increased to three times daily as tolerated

- Lisuride (dopergine):
  - More potent: Lisuride acts as a mixed agonist and antagonist of dopamine, serotonin, and adrenergic receptors
  - Less side effects
- Cabergoline (dostinex)
  - Longer half-life. Less side effect
  - Better tolerated by patient
  - Initial cabergoline dosages are 0.25 mg orally twice weekly.

- Quinagolide (Norprolac):
  - non-ergot preparation
  - Less side effect.

Surgery:

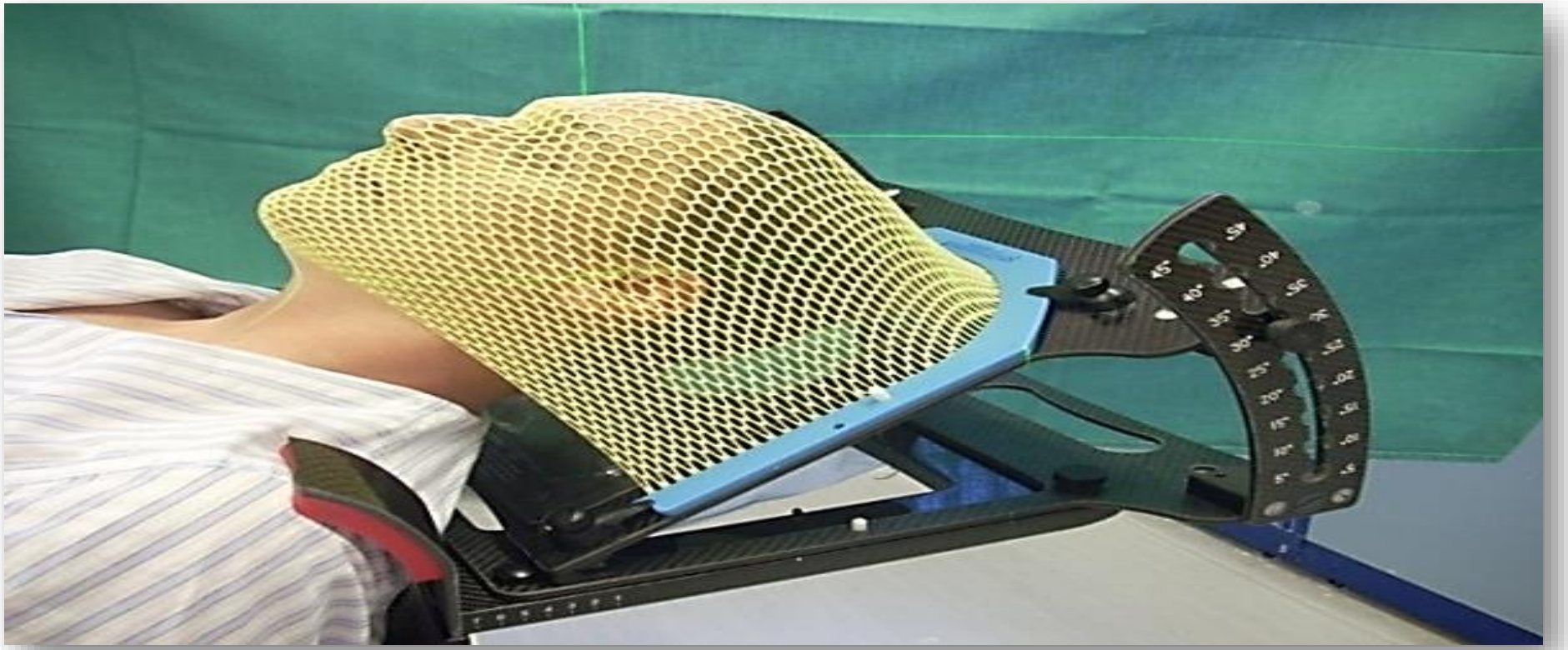


Trans sphenoidal resection

- **Surgery** should be performed for patients with significant visual field defects or symptoms that cannot be relieved by medical therapy.
- **Surgery** :reserved for cases with expansion outside the Sella turcica or for compressive symptoms, such as visual field defects. Women who do not tolerate pharmacologic therapy may need surgery.

Radiation therapy:

- May be used for patients with surgically nonresectable, persistent, or aggressive tumors.



HIRSUTISM

Hirsutism:

Excessive growth of androgen dependent hair in an abnormal sites of female body (beard, nostrils, upper lip, chest, abdomen, extensors of arms & back of the trunk) associated with loss of cyclic menstrual pattern.

- Testosterone (T): a measure of ovarian adrenal activity.
- DHEA-S- measure of adrenal activity.
- DHT is the intracellular active form of T and it is twice potent as T and produced from testes under the effect of 5 alpha reductase enzyme.

Etiology Of Hirsutism

❖Physiological : 3p

A. PUBERTY: due to increased adrenal androgens before ovarian estrogens.

B. PREGNANCY: unexplained.

C. POSTMENOPAUSE: due to relative increase of androgen from the adrenal and ovary.

Idiopathic Hirsutism

- Women exhibit mild to moderate hirsutism
- with normal ovulatory function and circulating androgen levels, a condition referred to as IH

Idiopathic Hirsutism

- The commonest type! More in Mediterranean women due to increased activity of 5a- reductase enzyme.
- To consider the case as idiopathic there must be:

1. Normal menstrual pattern.
2. Normal or slightly increased androgens especially 3 a ag.(androstanediol glucuronide)

❖Ovarian causes:

A. Hyperthecosis of the ovaries: is hyperplasia of the theca interna of the ovary. Hyperthecosis occurs when an area of luteinization occurs along with stromal hyperplasia. The luteinized cells produce androgens, which may lead to hirsutism and virilization in affected women
B. Polycystic ovary syndrome (PCOS).
C. Androgen secreting ovarian tumors.
D. luteoma of pregnancy.

The condition is diagnosed as ovarian neoplasm if:

1. serum testosterone is > 2ng/ml or.
2. serum testosterone is > 2.5-fold the normal.

Androgen Producing Ovarian Tumors

1. Sertoli-Lyedig cell tumor.
2. Hilus-cell tumor.
3. Lipoid cell tumor.
4. OTHERS:
    a) Malignant cystadenocarcinoma.
    b) Brenner's tumor.
    c) Krukenberg's tumor.

❖Adrenal causes:

A. Congenital adrenal hyperplasia (CAH): 3 forms / presentations:
   1. infantile CAH= female pseudohermaphrodite.
   2. pre-pubertal = precocious puberty.
   3. adult type= virilism.

B. Cushing's syndrome: overproduction of cortisol by adrenal cortex due to:

a) overproduction of ACTH by pituitary (Cushing's disease).

b) Ectopic ACTH by non-pituitary tumor.

c) Autonomous secretion of cortisol by adrenal or ovarian tumors.

d) Ectopic corticotropin-releasing hormone production.

C.Adrenal tumors : DHEA-S > 8pg/ml (normal 1-4 μg/ml)

❖Other causes:

A. Iatrogenic (drugs): androgens, norgestrel, danazole, diazoxide, dilantin.

B. Incomplete testicular feminization syndrome: (Reifenstien's syndrome) Reifenstein syndrome is a term comprising a heterogeneous group of androgen deficiency syndromes due to X-linked recessive androgen receptor defect in 46, XY men with normal androgen secretion. Females are clinically not affected.

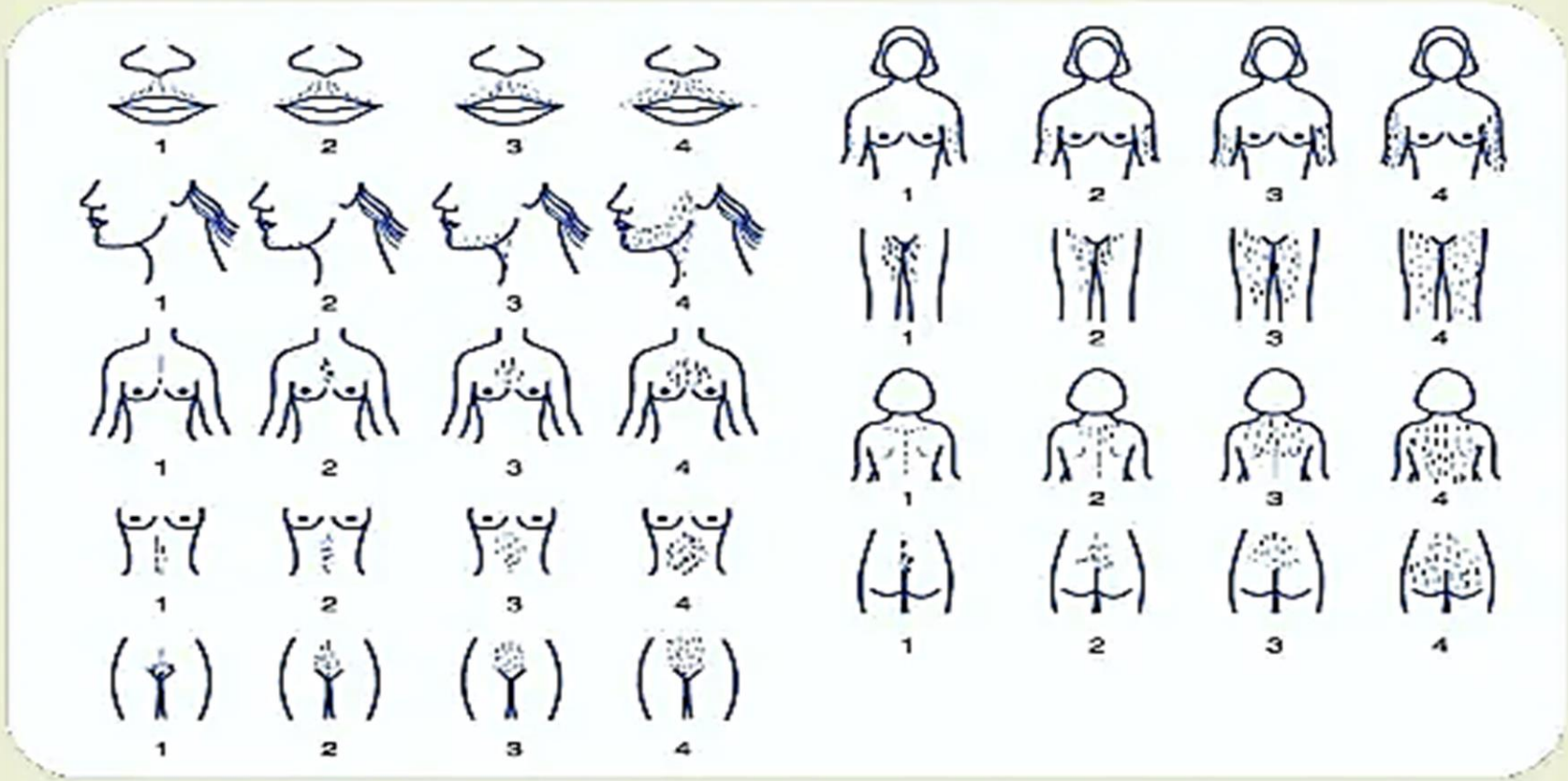
C. RARE TYPES :

- Acromegaly.
- Porpheria.
- DES- exposed female infant.

Evaluation of hirsutism

- History :PCOS or late-onset CAH often initially appears during puberty and tends to progress slowly throughout adolescence into adulthood. In contrast, neoplastic processes can occur at any time .
- Examination:
  - ➢ Distribution of excess hair growth
  - ➢ Body built
  - ➢ Signs of virilization
  - ➢ Abdominal examination

Ferriman- Gallwey Scale



Modified Ferriman–Gallwey (F–G) hirsutism scoring system. Each of the nine body areas is rated from 0 (absence of terminal hairs) to 4 (extensive terminal hair growth), and the numbers in each area are added for a total score. A modified F–G score ≥ 6 generally defines hirsutism

- Investigations:

1.Serum testosterone is a marker of ovarian and adrenal activity.

➢Total testosterone levels greater than 200 ng/dL suggest an androgen-producing tumor. Imaging is warranted.

➢Pelvic ultrasound is best to provide an image of the ovaries.

➢Computed tomography or magnetic resonance imaging views the adrenal glands.

➢Elevated total testosterone levels but less than 200 ng/dL associated with anovulation and hirsutism suggest PCOS.

- Serum DHEAS is almost exclusively produced by the adrenal glands and reflects adrenal androgen activity.
  - Levels greater than 700 ng/dL suggest an adrenal tumor.
  - Moderately elevated DHEAS levels may occur with anovulation, PCOS, or adrenal hyperplasia.
  - Normal DHEAS levels indicate that adrenal disease is less probable and that ovarian androgen production is more likely.
- Elevated levels of serum androstenedione suggest ovarian disease, but this test is rarely recommended
- Serum 17-OHP
  - 17-OHP is elevated in 21-hydroxylase deficiency,

- Gonadotropins may be useful. An elevated LH-to-follicle-stimulating hormone (FSH) ratio (3:1) suggests PCOS.
- However, this finding is not present in approximately 40% of patients with PCOS and is not considered diagnostic.
- T3,T4,TSH
- Sr.prolactine

Management Of Hirsutism

- **General measures.**
- **Antiandrogens:**

1. **cyproterone acetate (CPA).** block the binding of androgens to their receptor
2. **Spironolactone (Aldactone).** Spironolactone (Aldactone), 100 mg to 200 mg daily, has antiandrogenic effects that may enhance treatment of androgen-excess syndromes, particularly severe hirsutism. Combination therapy with an oral contraceptive or with dexamethasone appears to have a beneficial effect
3. **Flutamide**. block the binding of androgens to their receptor.
4. **Ketoconazole**.
5. **Eflornithine hydrochloride cream** ,an irreversible inhibitor of epidermal androgenic activity, can be applied topically to treat facial hirsutism.

- **Ovarian suppression.**

1. **COCs.**
2. **GnRHa.**

➢ Adrenal suppression:

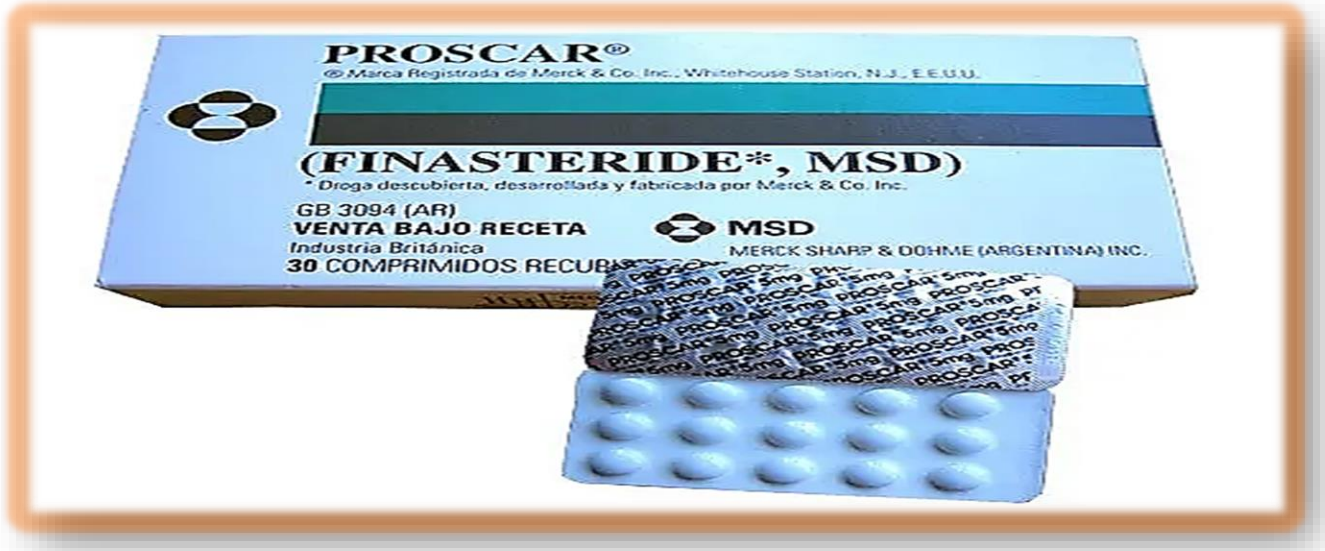
- ➢ Dexamethasone (0.25-0.5 mg) taken at night suppress ACTH morning surge & adrenal production of androgens.
- ➢ In some cases, insulin - sensitizing agents such as metformin may be used to reduce insulin resistance and anovulation.

Patients with adrenal hyperandrogenism, including late-onset CAH, can be treated with glucocorticoids.

➢Finasteride (Proscar)

5 a reductase inhibitor used in cases of idiopathic hirsutism - it is non steroidal compound exerting specific competitive inhibition with 5 a reductase thus decreases the conversion of testosterone into intracellular active DHT, decreasing hirsutism

Dose: 5mg /day



➢Surgical procedures:

1. ovarian wedge resection (old fashion treatment replaced by laparoscopic ovarian drilling).
2. bilateral oophorectomy.
3. surgical treatment of the cause (if indicated).

In the rare instance of an ovarian or adrenal neoplasm, surgical removal of the tumor is indicated.

In Cushing ,treatment is surgical removal of the source of excessive cortisol or ACTH (adrenal or pituitary tumor).

VIRILIZATION

is more severe condition of androgen excess in female; it includes combination of hirsutism and masculinity, clitoromegaly, deepening of voice, balding, and changes of body habitus (e.g.: increase muscle mass, decreased breast size).


THANK YOU