Hirsutisim and Hyperprolactinoma

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Hirsutism in the female means an excessive production of hair with a tendency to male distribution. ‘Excessive’ is defined as beyond social acceptability or causing embarrassment to the patient.

Normal pattern hair is of two types:

(i) fine downy, vellus hair which is non-pigmented.

(ii) coarser pigmented terminal hair as in the axilla and pubis.

About one-third of women have some visible pigmented hair on the upper lip, and 5% have it on the chin and sides of the face.

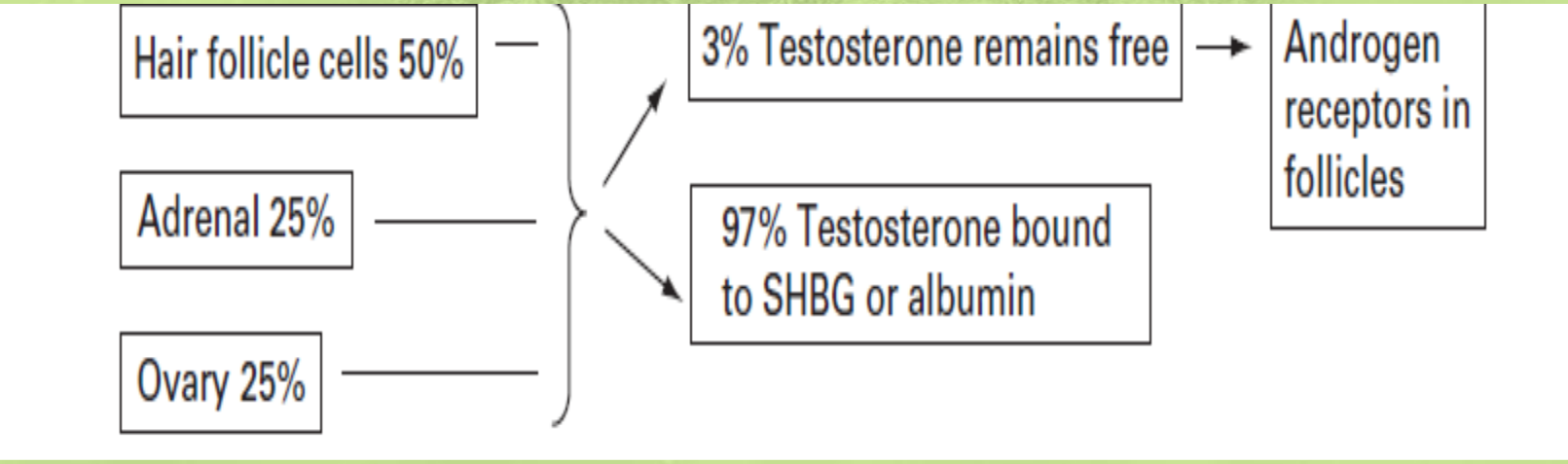
AETIOLOGY

1. Rise in secretion of free androgens.
2. Reduction in SHBG.
3. Increased end organ sensitivity to androgens.

SHBG level falls when testosterone production increases, and probably also in the case of drug induced hirsutism. Oestrogen increases the levels of SHBG and lowers the amount of free androgen.

PHYSIOLOGY OF TESTOSTERONE

- The three principal androgens are dihydrotestosterone, testosterone and androstenedione; the last mentioned is the least potent but is converted to dihydrotestosterone in the follicle cells.



Causes:

1. Idiopathic hirsutism : By far the commonest, it has no apparent androgen increase, and is probably due to increased local testosterone production at the target organ.

2. Polycystic ovary disease

There is usually a higher level of free active testosterone because of reduced SHBG.

3. Androgen-producing tumours These may arise in the ovary or adrenal glands. They should be considered if serum testosterone is greater than 5 nmol/L or if the history is of sudden onset.

4. Congenital adrenal hyperplasia This is an adrenal disease, caused by an enzyme defect (commonly 21- hydroxylase deficiency) resulting in elevated androgens. 17-hydroxyprogesterone is elevated.

5. Drugs such as:

- phenytoin
- diazoxide
- minoxidil
- androgen-containing compounds

VIRILISATION

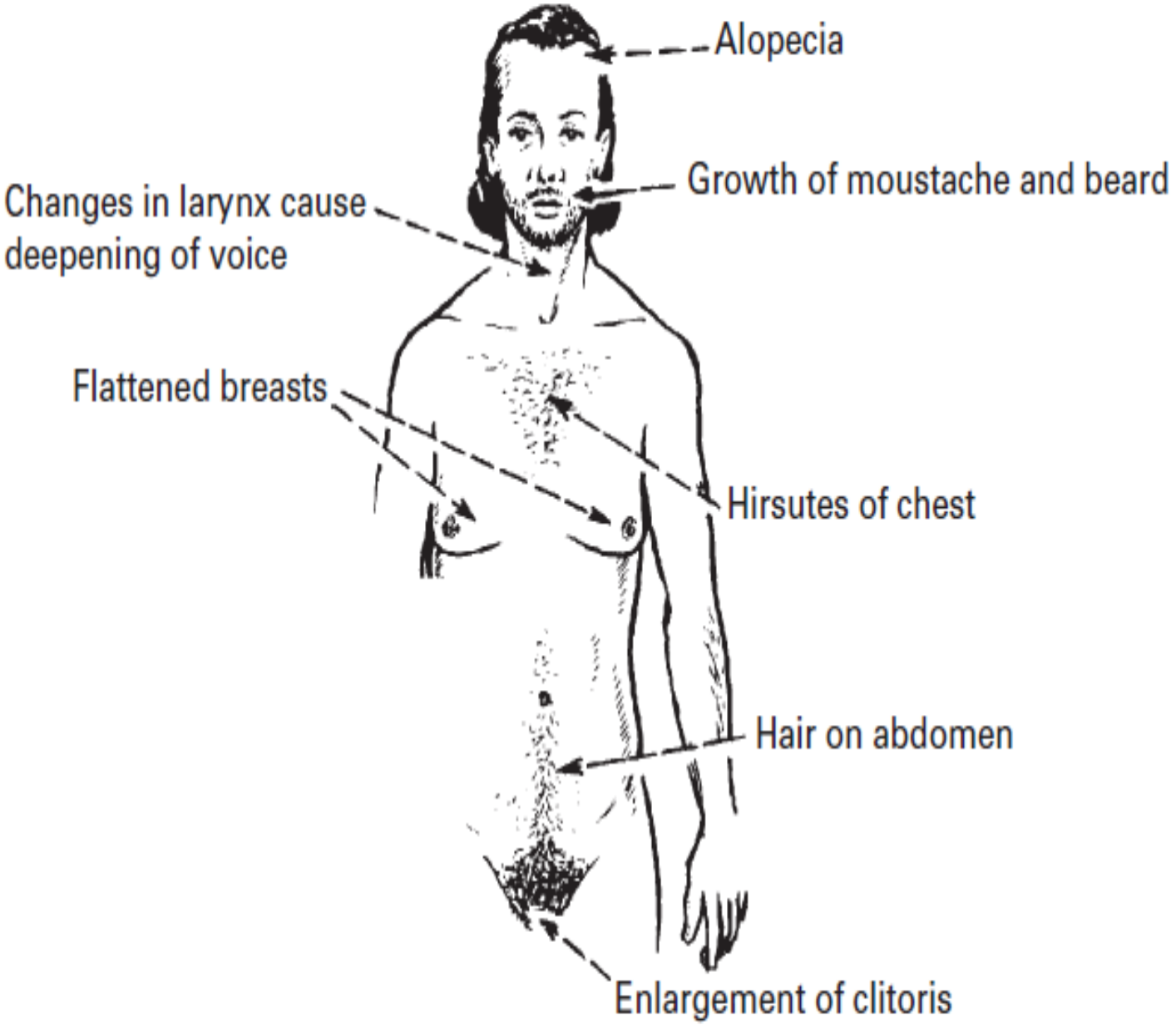
- Masculinisation and virilisation are terms for extreme androgen effects.

CLINICAL FEATURES

The symptoms and signs include the following:

- male pattern balding
- cliteromegaly
- deepening of the voice
- increased muscle mass
- male body habitus.

These symptoms are more likely to represent an androgen secreting tumour, but mild symptoms such as male pattern balding can occur with PCOS.


Alopecia
Growth of moustache and beard
Changes in larynx cause deepening of voice
Flattened breasts
Hirsutes of chest
Hair on abdomen
Enlargement of clitoris

INVESTIGATION

- serum testosterone
- serum dehydroepiandrosterone sulphate (DHAS) (elevated in adrenal disease)
- 17-hydroxyprogesterone (17-OHP) (elevated in congenital adrenal hyperplasia)
- 24 h urinary free cortisol if Cushing's syndrome is suspected.

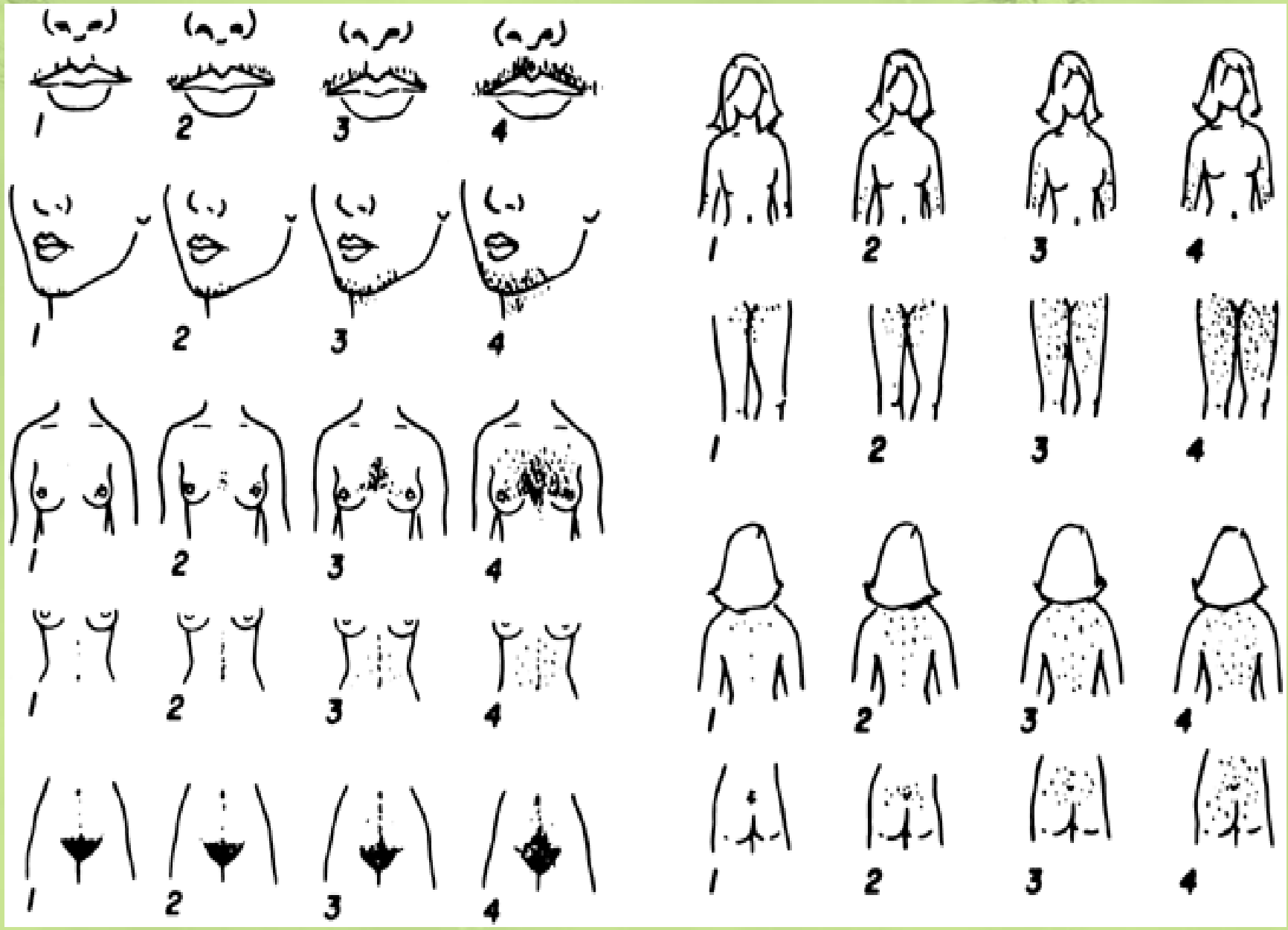
If the testosterone levels are significantly elevated, an androgen secreting tumour of the ovary or adrenal gland is likely. Ultrasound, CT scanning and perhaps even laparoscopy may be required to make the diagnosis.

MANAGEMENT OF HIRSUTISM

- If the woman is untroubled by her symptoms, no treatment is needed. Women who are overweight should be advised to lose weight.
- LOCAL TREATMENT

Ferriman Galwey Charts

These charts provide a semi-objective scoring system for hirsutism. If they are completed at each patient visit, the change in symptoms may be assessed.


1
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3
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- Shaving This method has to be repeated frequently.
- Electrolysis Decomposition of the hair follicle by the passage of an electric current. Low galvanic current is used through a fine electrode. The hair is electrolysed after about 10 s and plucked out painlessly.
- Diathermy The follicle is coagulated instantly and the hair pulled out. Electrical destruction of individual hairs is permanent, but prolonged treatment is tedious and expensive and may cause scarring.

Depilatory Creams These are alkaline solutions, which dissolve the hairs and allow them to be wiped away. They will injure the skin if left on too long.

- Depilatory Waxes The wax is melted and spread on to the skin. When it sets, it is pulled off, plucking the hairs with it. This is painful and leaves the skin tender and reddened.

DRUG TREATMENT

- 1. Combined oral contraceptive pill (COCP) These drugs act firstly by suppressing LH production and thereby attenuating ovarian androgen synthesis.
- Secondly, the oestrogens stimulate SHBG production by the liver. The effect of the progestogen component can vary as some such as norethisterone and levonorgestrel have an androgenic derivation. Some of the available preparations contain antiandrogenic progestogens, these include Cyproterone Acetate and Drospirenone.
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- 2. Antiandrogens
- cyproterone is a progesterone, which inhibits LH production. It also binds to the androgen receptor and therefore acts as an antiandrogen. It can either be administered as with ethinyloestradiol (the contraceptive pill ‘Dianette’) or daily from days 5–14, with ethinyloestradiol on days 5–25 (the ‘reverse sequential’ regimen).
- Other antiandrogens include flutamide, a non-steroidal, and finasteride, a 5a reductase inhibitor. Finasteride inhibits the conversion of testosterone to dihydrotestosterone

- 3. Insulin sensitising agents

Metformin will improve insulin sensitivity and reduces free androgens in women with PCOS.

- 4. Dexamethasone

Dexamethasone inhibits adrenal androgen production, and is useful in hirsutism caused

by adrenal disease.

- 5. GnRH analogues with addback hormone replacement therapy (HRT)

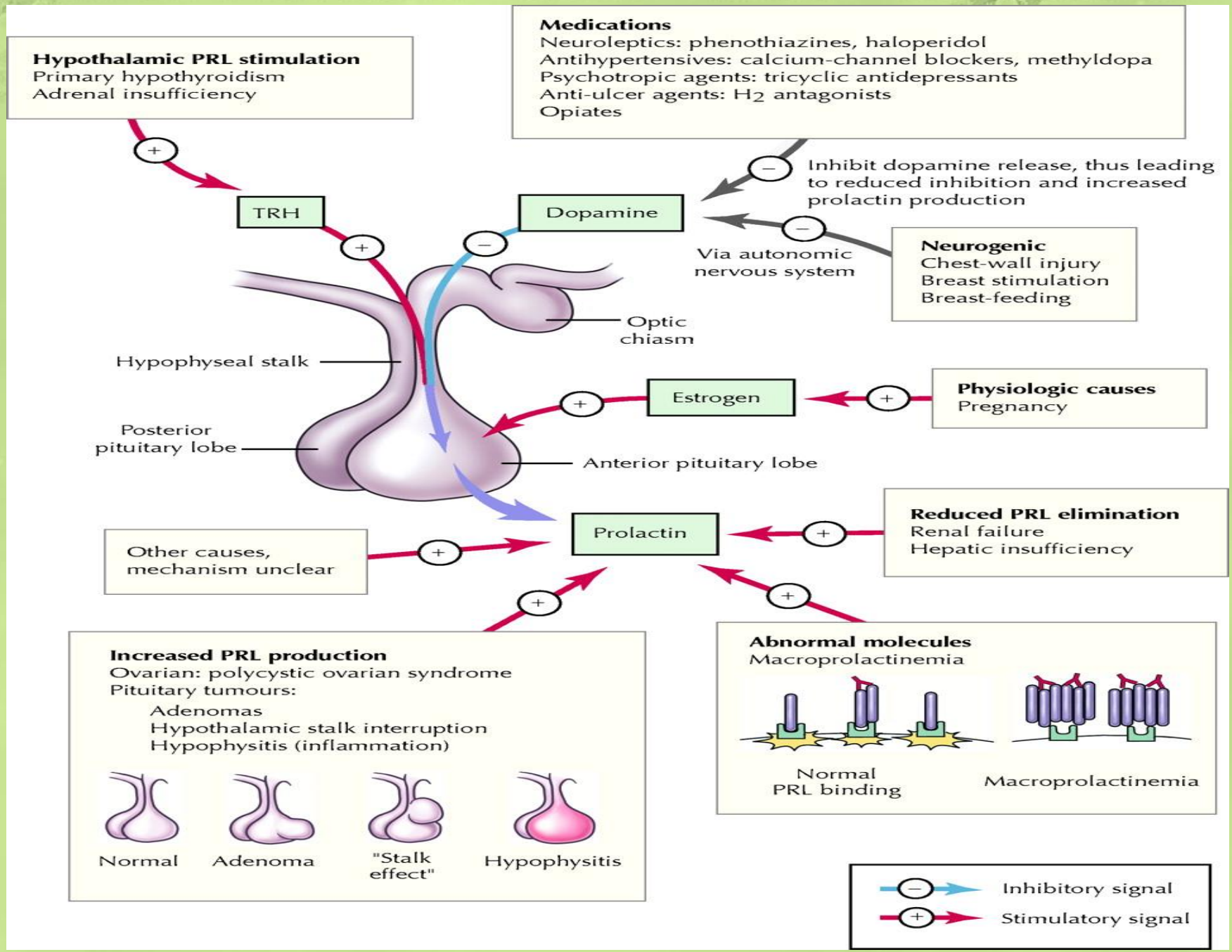
This treatment is expensive, but has been shown to be effective in clinical trials.

- 6. Eflornithine cream locally slows hair growth by inhibiting the enzyme orthinine decarboxylase.

- With all of the above, it may be 3 months or more before an improvement in symptoms
- can be expected, and the patient should be counselled regarding this.

Hyperprolactinemia

- Prolactin is secreted from the anterior pituitary.
- Normal blood level is between 150 and 600 mU/L depending on the laboratory.
- During pregnancy, there is a 10-fold increase in serum prolactin levels.
- Non-physiological hyperprolactinaemia can cause amenorrhoea or galactorrhoea (inappropriate lactation) or both.
- Hyperprolactinaemia is the principal cause of amenorrhoea in around 20% of women with this condition.


Hypothalamic PRL stimulation
Primary hypothyroidism
Adrenal insufficiency
Medications
Neuroleptics: phenothiazines, haloperidol
Antihypertensives: calcium-channel blockers, methyldopa
Psychotropic agents: tricyclic antidepressants
Anti-ulcer agents: H2 antagonists
Opiates
Inhibit dopamine release, thus leading to reduced inhibition and increased prolactin production
TRH
Dopamine
Via autonomic nervous system
Neurogenic
Chest-wall injury
Breast stimulation
Breast-feeding
Optic chiasm
Hypophyseal stalk
Estrogen
Physiologic causes
Pregnancy
Posterior pituitary lobe
Anterior pituitary lobe
Prolactin
Reduced PRL elimination
Renal failure
Hepatic insufficiency
Other causes, mechanism unclear
Increased PRL production
Ovarian: polycystic ovarian syndrome
Pituitary tumours:
Adenomas
Hypothalamic stalk interruption
Hypophysitis (inflammation)
Normal
Adenoma
"Stalk effect"
Hypophysitis
Abnormal molecules
Macroprolactinemia
Normal PRL binding
Macroprolactinemia
Inhibitory signal
Stimulatory signal

Diagnosis of Hyperprolactinemia

Measurement of serum prolactin levels and must depend on the following criteria to measure PRL that includes:

- PRL levels are drawn in the morning.
- Prior to testing, breast examination is avoided to prevent false-positive results.
- If a mildly elevated PRL level is found, sampling should be repeated because PRL levels vary throughout the day.
- Moreover, many factors including the stress of venipuncture may produce false elevations.

Diagnosis of Hyperprolactinaemia

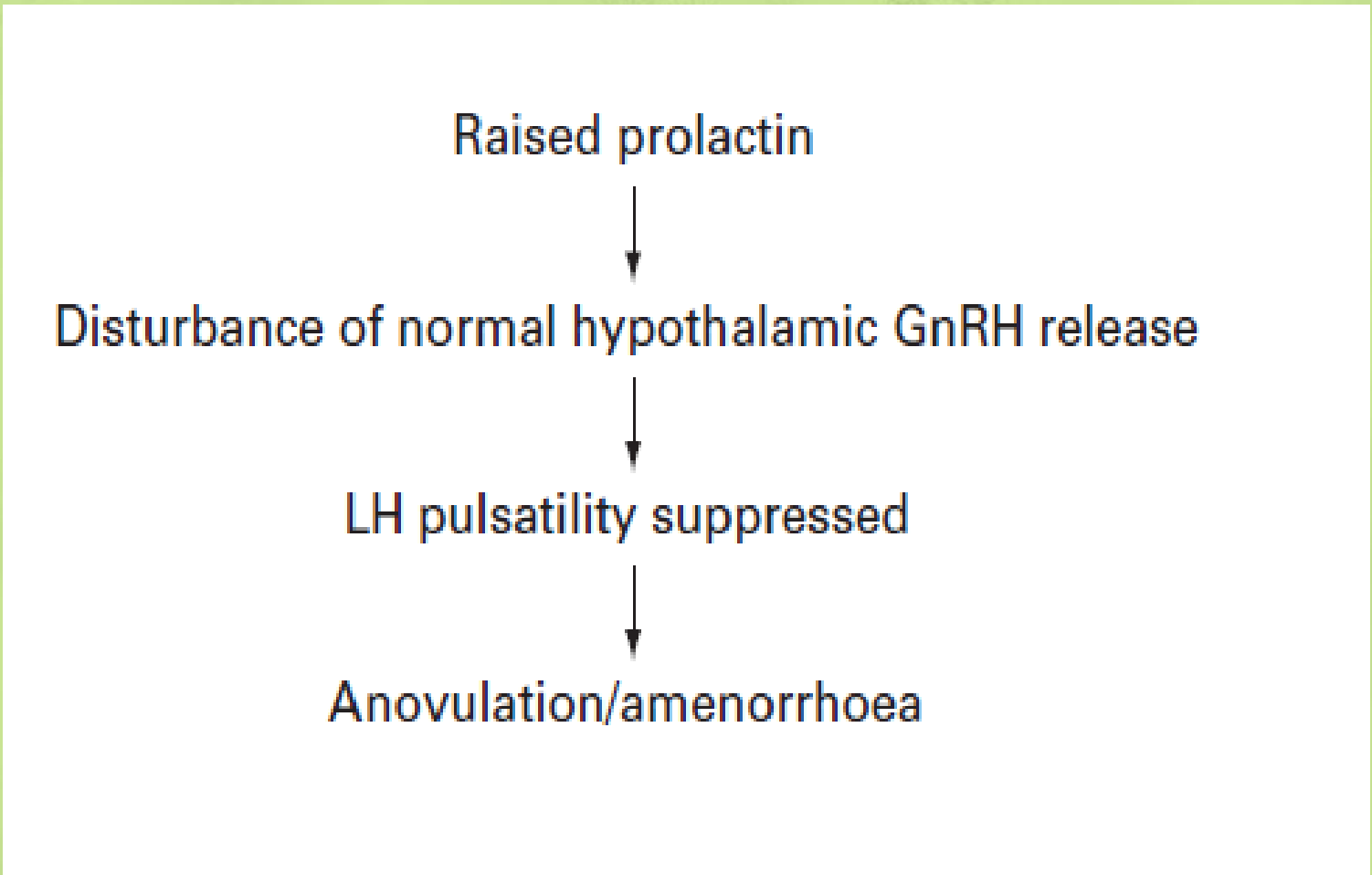
- The diagnosis of hyperprolactinaemia can be made on a single serum measurement. In the presence of oligo- or amenorrhoea, a serum prolactin of 800 mU/L or greater is likely to be of pathological significance.

- In the absence of an obvious alternative cause, radiological examination such as (CT) scanning or (MRI) should be performed to exclude a pituitary tumour.

Levels of prolactin

<1000 m U/L	<5000 m U/L ≤ 10 mm diameter	➢ 10,000 m U/L ➢ ≥ 10 mm diameter
stress	Micro-prolactinoma	Macroprolactinoma
hypothyroidism	Pituitary stalk disconnection	
PCOS		

Mechanism of Amenorrhoea in woman with hyperprolactinaemia



Treatment

- Medication

Dopamine is the prolactin release inhibiting factor produced by the hypothalamus, and medical treatment for hyperprolactinaemia is based around dopaminergic stimulation.

Bromocriptine	Cabergoline	Quinagolide
1st dopamine agonist since early 1970	New, high affinity for lactotroph dopamine receptors	
2-3 x/day 5-30mg/day (7.5mg/d)	1-2x/week 0.5-2 mg/wk	Once daily 0.05-0.25 mg
Nausea, postural hypotension, dizziness, headache, depression	Improved efficacy and few side effects *NEJM 94; 331: 904-909*	May be better tolerated than bromocriptine
Start with low dose and increase dosage gradually. Start 0.625 mg Nocte Duration 2-6 years?	Most effective in reducing tumor size *JCEM 2000 85 2247-2252*	

Surgery Transnasal
Trans-sphenoidal surgery can be used to resect both micro- and macroadenomas. Symptoms of hypopituitarism, particularly diabetes insipidus, may be a long-term consequence of surgery. The results of treatment vary greatly between centres. Knowledge of local data can be used to determine whether surgery or medical treatment is most appropriate for each patient .

Radiation therapy may be used for patients with surgically nonresectable or persistent tumors.

Gene therapy has been proposed as a treatment for pituitary tumors

Thank you