

Hirsutism

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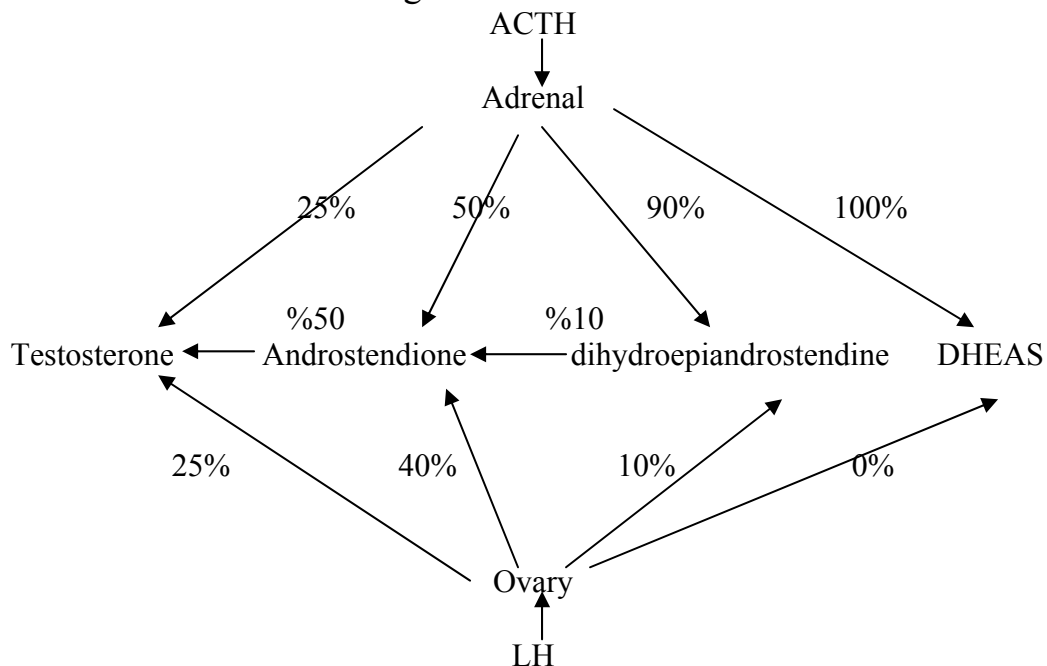
*Introduction...

*Hirsutism is excessive growth of facial & / or body hair in women in a distribution similar to that of a male & may occur in association with an oily skin & acne. Hair are dark, thick, on face , chest, abdomen & back.

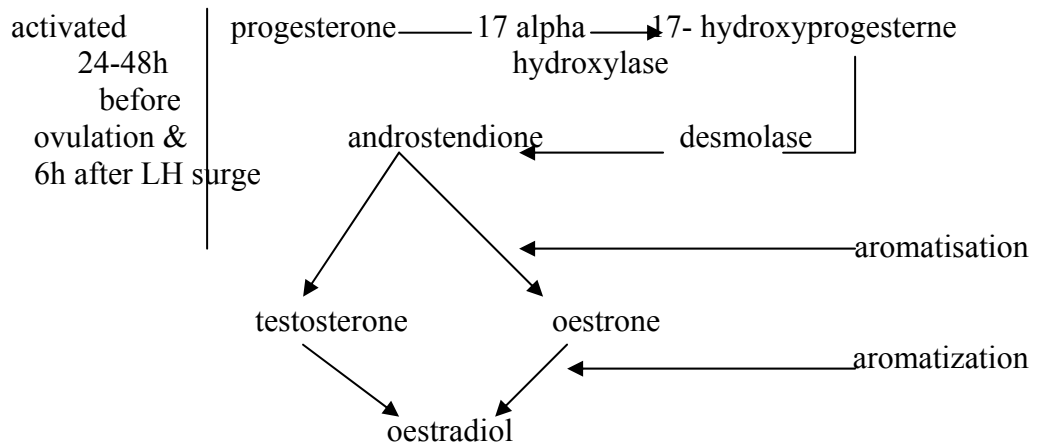
*Hair follicles usually become enlarged & the hairs themselves become larger & darker.

*Hypertrichosis is an increase in hair growth all over the body ,but this is usually fine, resembling lanugo, & again it dose not have pathological implications .

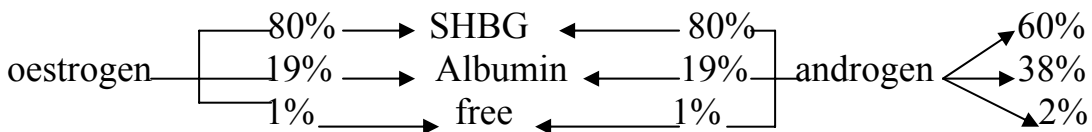
*Source of female androgen:



*Theca cells under the influence of LH secret androgenic precursors by the 5-pathway:

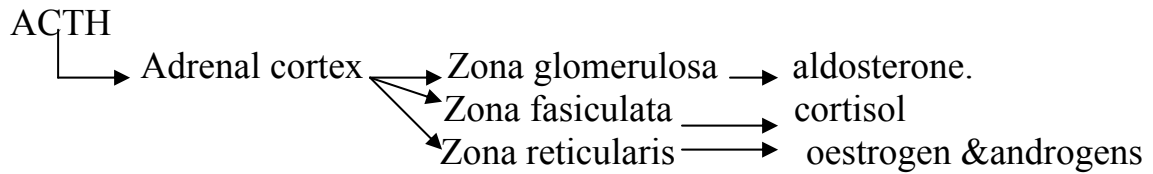


*After ovulation → small luteal cells (corresponding to theca) → LH → androgen
 → large luteal cell (corresponding to granulosa) → FSH → oestrogen.



*Testosterone itself binds very weakly to the receptors & must first be converted to dihydrotestosterone by the enzymes 5-alpha reductase, (100 time potent). This conversion is essential in hair follicles.

*SHBG → levels → depressed by testosterone.
 → increased by estradiol.
 → synthesis → stimulated by oestrogen & thyroxin.
 → inhibited by insulin, growth hormone, androgenic drugs & progestogens .



*Androgens are partly metabolized to Androsteron & aetiocholanolone prior to excretion in urine as the water-soluble sulphate or glucuronide.

*Dihydrotestosterone is excreted as 3-alpha- & 3-beta-androstenediols.

*Classification, etiology & pathophysiology:

* The old classif:

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graph LR
  Old_classif[The old classif] --> Androgen_induced[Androgen-induced hirsutism (hyperandrogensim).]
  Old_classif --> Non_androgen_induced[Non-androgen-induced hirsutism (familial , idiopathic).]
  Old_classif --> Drug_induced[Drug-induced hirsutism.]
  
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* The new classif:

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graph LR
  New_classif[The new classif] --> Idiopathic[Idiopathic hirsutism... is probably hereditary , women have normal menstrual cycles & no evidence of any underlying pathology.]
  New_classif --> Secondary[Secondary hirsutism... is most often associated with :]
  Secondary --> Ovarian[Ovarian conditions..as PCOD , tumors.]
  Secondary --> Malfunctions[Malfunctions of the pituitary or adrenal glands.]
  Secondary --> Tumors[Adrenal or pituitary tumors.]
  Secondary --> Drugs[Use of drugs that induce hirsutism.]
  
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* 95% of cases... no pathology → 90% constitutional.
 5% associated with obesity, menarche, menopause, liver disease or drugs.

*5% of cases... with pathology → ovarian.. adrenal.. pituitary.

- N.B.** -when hirsutism is associated with obesity & menstrual abnormalities, the source of androgen excess is often ovarian , typically polycystic ovary syndrome.
- when it is associated with average weight & normal menses ,the source is often adrenal & rarely pituitary.

1) Constitutional cases.... 90%

- The extent of normal hair growth varies between individuals, families & races, being more extensive in the Mediterranean & some Asian peoples.
- The condition usually develop during puberty & becomes more pronounced as they years go by.

2)Drug induced hirsutism...

-Many drugs can induce hirsutism ,both generalized & localized.

*Commonly used drugs that have androgenic activity are :

-Testosterone (sustanon, testoviron), DHEA-S, danazol (danol) ,corticotropin, high dose corticosteroids, anabolic steroids, acetazolamide (diamox=carbonic anhydrase inhibitors ,diuretic &used to decrease elevated intraocular pressure).

-Non-androgenic drugs that can cause hirsutism includes: cyclosporine (consupren = immunosuppressive agent): used to prevent rejection of implanted tissues, it increase hair growth.

Phenytoin (anticonvulsant) , penicillamine : used in treatment of Wilson disease.

3)Androgen-excess hirsutism...

-Androgen receptors are found in the active phase in follicles ,dermal papillae & associated sebaceous gland. Circulating androgen arriving at

the dermal papillae receptors, enter the cell & are metabolized to the final most potent androgen (dihydrotestosterone) → Hirsutism .

-Persistent androgen excess has a high association with endometrial cancer, osteopenia & osteoporosis.

***Poly cystic ovary syndrome..**

-It is the most common cause of hirsutism .Rosenfield loosely defines PCO as unexplained hyper-androgenism with variable degrees of cutaneous symptoms, anovulatory symptoms & obesity

***Other ovarian disorders..**

-Ovarian hyperthecosis ,elevated level of androgen & all the risks of polycystic ovary syndrome have been reported in postmenopausal women with recent onset of hirsutism.

-Another recently described ovarian androgen disorder is transient hyper-androgenism which occurs either in the early follicular phase in ovulatory cycles or in the second phase in delayed or anovulatory cycles.

-Musculinising ovarian or adrenal tumors are rare but should be considered in sudden onset of severe hirsutism.

***Adrenal disorders..**

-Adrenal androgens are elevated in late onset adrenal hyperplasia, congenital adrenal hyperplasia, Cushing's syndrome, pituitary adenomas that produce excess corticotrophin or prolactin & acromegaly .

N.B. -CAH is a group of autosomal recessive syndrome resulting from defects in the enzymes steps of adrenal steroidogenesis → stimulates ACTH& MSH → increase androgens.

-The specific adrenal androgen – excess marker is DHEA-S.

-Less common abnormalities :

As..*21-hydroxylase deficiency → elevated 17-alpha-hydroxyprogesterone → severe hirsutism & oligomenorrhea.

*3- beta ,11-hydroxysteroid dehydrogenase deficiency → early or late onset congenital adrenal hyperplasia.

***Diagnosis.**

1)History..

-Extensive clinical history taking is essential including: personal history of menstrual period, pregnancy, infertility, birth control methods & menopausal symptoms & signs.

-Drug history & question regarding family history of androgen excess, thyroid disorders, diabetes, hyperlipidemia are also important.

2)Physical examination:

-Include: Bl.Pr., weight, skin examination with specific observation of hirsutism, acne, seborrhea, obesity & acanthosis nigricans.

-With androgen excess more widespread stigmata of the male are present like: receding hairline, deepened voice, increased male-type muscle mass & distribution, clitoromegaly & atrophy of the breasts.

3)Investigations..

-Laboratory testing may be divided into:

1-Simple evaluation..includes:

-testosterone level, total & free.... increase with virilizing tumors, may be elevated in PCOS normal (low levels of SHBG).

-other androgens: androstendione & DHEA-S are elevated in CAH & virilizing tumors.

2-Extensive evaluation..includes:

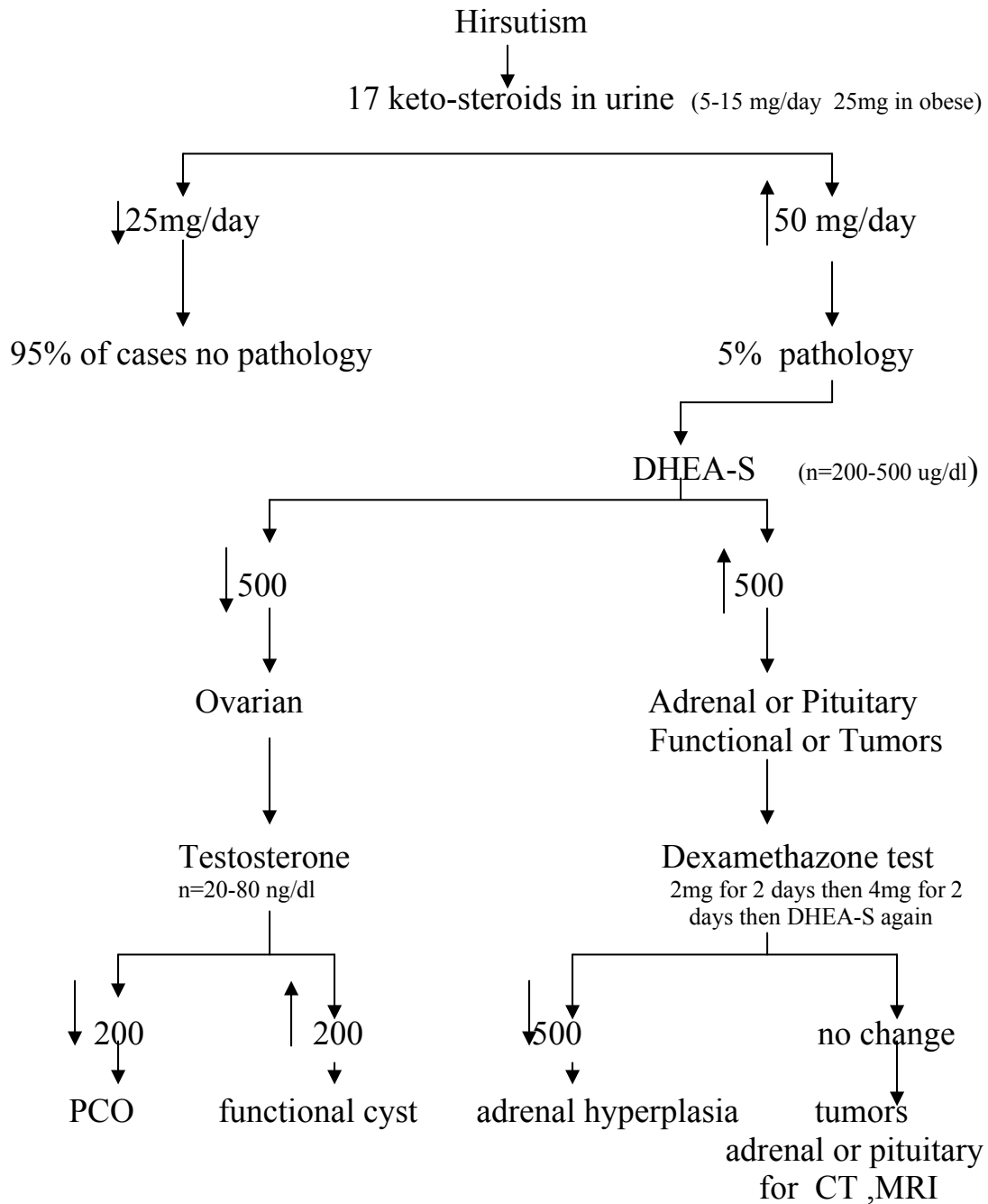
-gonadotrophin levels, LH hypersecretion is a consistent feature of PCODS.

-17-x-hydroxyprogesterone is elevated in classical CAH.

-oestrogen levels: oestradiol is usually normal in PCO, but oestrone may be elevated due to peripheral conversion.

-prolactin mild hyperprolactinaemia is common in PCO but rarely exceeds 1500ul.

- sex hormone-binding globulin level.



Treatment:

*Treatment of hirsutism involves: understanding & consideration of the cause & available cosmetic & antiandrogen approaches.

*Sources of androgen excess can rarely be permanently removed, so treatment is long term & either continuous or intermittent.

*Discontinuation of antiandrogen therapy has results in recurrence of hirsutism within 6 months.

1) Cosmetic approaches..

*Standard treatment of hirsutism are camouflaging with :
-Heavy makeup -Bleaching -Removal with:

1-physical methods as: rubbing ,cutting ,shaving (safest & easiest but skin may become irritant ,use 1% hydrocortisone cream) , plucking & waxing (not recommended as can cause irritation & make the hair grow faster by increasing the blood supply to the follicle).

2-chemical depilatories as calcium thioglycolates (used on specific body location) .

*Most physical & chemical methods are temporary with effect lasting hours to days.

*Thermo-destruction of hair follicle: electrolysis (delivering a small electrical current through a needle placed into the hair follicle).
——>retards re-growth for days to weeks & when repeated can permanently remove hair , expensive & time consuming.

*Photo-thermo-destruction with laser ..very expensive, prevent hair from growing back.

*All of these methods can induce skin irritation, folliculitis, pigment abnormalities & ,rarely scarring.

2)Weight loss..

*Obese women with PCO & hirsutism can benefit from weight loss. Obesity is associated with excess levels of insulin, androgen & testosterone .

3)Anti-androgen agents..

*Includes: - drugs that block androgen cytochrome p-450 receptors resulting in decreased testosterone, DHEA & DHEA-S levels.
- drugs that inhibit 5-alpha reductase which hinder conversion of testosterone to dihydrotestosterone & results in increased testosterone & estradiol levels.

1-Oral contraceptives: Compete for the androgen receptor ,(progestogenic components is a competitive inhibitor of androgens at the hair follicle level). With it, suppression is greater for ovarian than for adrenal androgens. Estrogen increase SHBG which bind androgen. Agent containing androgenic progestin as norgestrel should be avoided.

2-Hormone replacement: In peri-menopausal & menopausal women with hirsutism.

3-Cyproterone acetate: It is the most popular therapeutic agent worldwide for androgen excess, PCO & hirsutism. It is an effective antiandrogen & is often combined with oral contraceptive component ethinyl estradiol.

4-Glucocorticoid agent : specific for adrenal androgen excess, either late-onset or congenital types. Low dose dexamethasone (0.125 to 5 mg/day) or prednisolone (2.5 to 5mg/day) given at night reduce androgen excess without impairing immune function, mineral levels ,the hypothalamus-pituitary-adrenal axis ,or adrenal function.

5-GnRH agonist: Low-dose monthly reduces LH, which down-regulates ovarian testosterone & androstendione but not effective over adrenal one (high cost).

6-Spirolactone: *It is the most popular antiandrogen agent for hirsutism in USA. Spirolacton blocks the androgen cytochrome-p-450 receptor, reducing testosterone metabolism.

*Dose rang from 100-300 mg/day.

*Side effect: abnormal menstrual periods, tender & enlarged breast (temporary loss of sodium & retention of potassium). Recent studies indicate that spironolactone with an oral contraceptive agent produces enhanced benefit.

7-Flutamide (Eulexin): An anti-androgen that blocks the androgen receptor. It is effective at low dose (125 to 250 mg/day) .Liver toxicity reported with higher doses. Combination with OCS enhances effectiveness.

8-Finasteride (Proscar): Anti-androgen agent inhibits 5-alpha-reductase type2 which reduce dihydrotestosterone & increase testosterone, estradiol levels. Dose: 5mg/day, combination with OCS enhance effectiveness & prolonged remissions.

9-ketoconazole (Nizoral): Has anti-androgen activity with dose 400 mg/day, (has liver toxic effect).

10-Cimetidine: Weak anti-androgen activity & block androgen receptors at doses of 800-1600mg/day .

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