Androgen Excess In Female (HIRSUTISM)

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- Biology of hair growth
- Androgens in females
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DEFINITION

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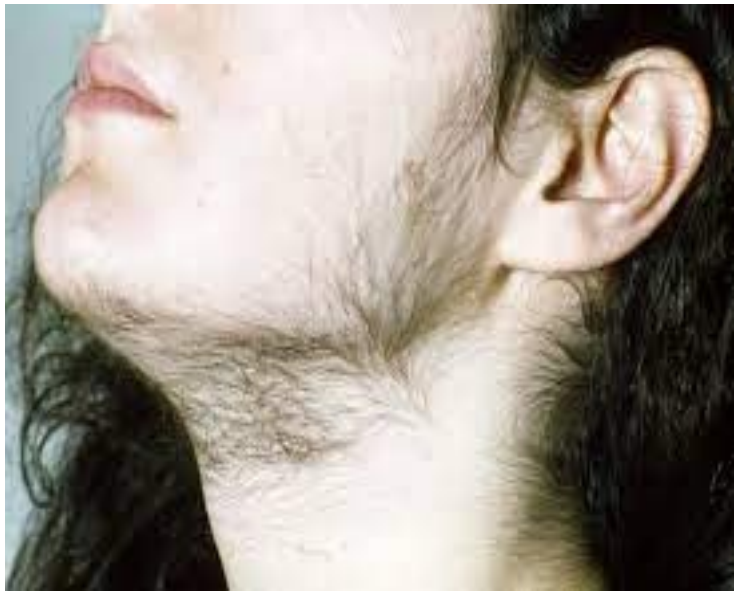
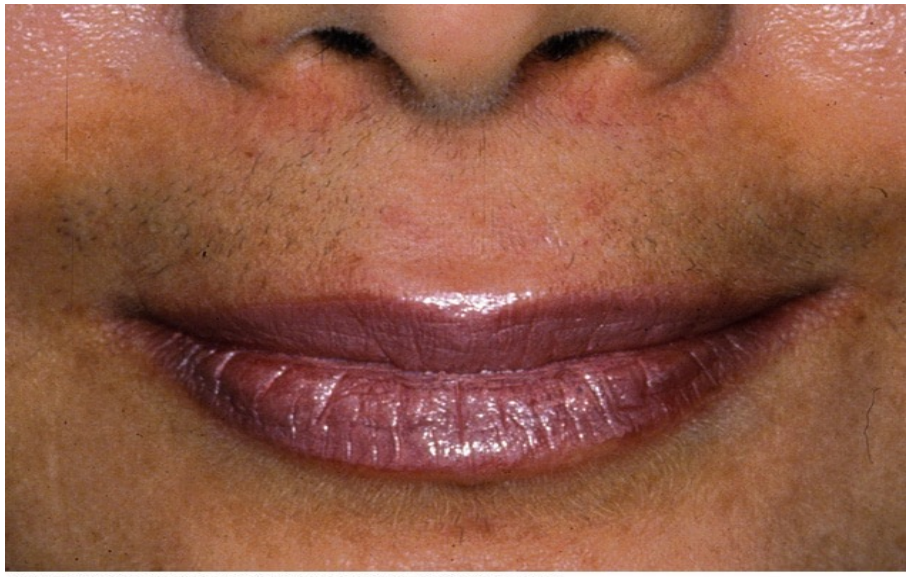
HIRSUTISM: excessive growth of androgen-dependant hair in an abnormal sites of female body (beard, nostrils, upper lip, chest, abdomen, extensors of arms & back of the trunk) associated with loss of cyclic menstrual pattern.

VIRILIZATION: is more severe condition of androgen excess in female; it includes combination of hirsutism & musculinity :clitoromegaly, deepening of voice, balding, and changes of body habitus (eg increased muscle mass, decreased breast size).

HYPERTRICHOSIS: excessive hair growth limited to a normal pattern of distribution. It is frequently associated with the use of medications such as antiepileptics.





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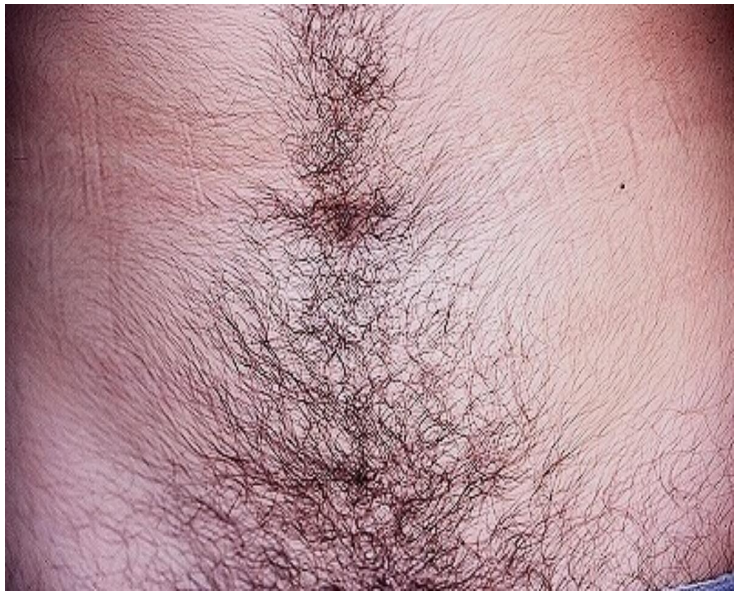

Obstetrics & Gynecology Dept MUH

Biology of hair growth

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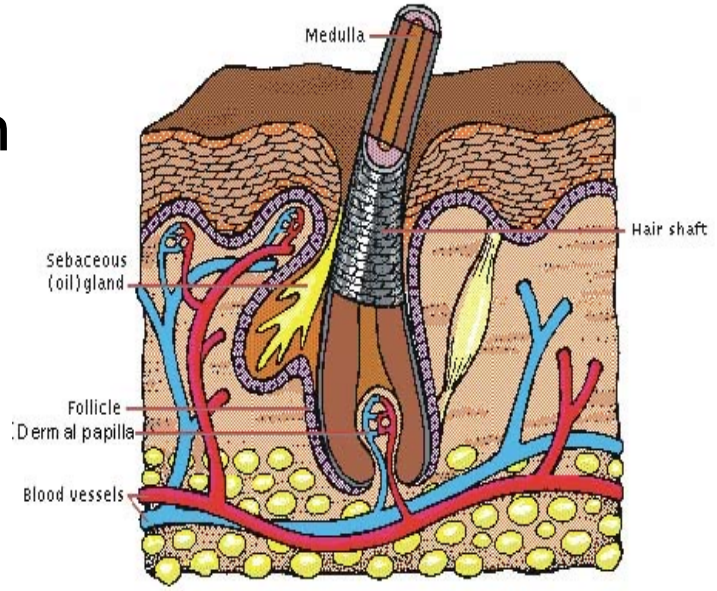
- ✓ Hair grows (at 8-10 weeks of gestation) from an individual hair follicle that are part of a pilosebaceous gland apparatus (hair follicle, sebaceous gland & arrector pili muscles)



- ✓ Number of hair follicles is set from birth
- ✓ Main difference between sexes is the degree of differentiation of hair
- ✓ Human hair growth is continuous
- ✓ Hair grows in a mosaic pattern (in a given area ,hair are in different stages of development)

Biology of hair growth

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Growth cycle of the Hair: ACT

Anagen : Growth phase,85- 90 % of the life cycle

Catagen : rapid involution Phase

Telogen : Quiescent phase

The growth phase or the anagen phase is primarily influenced by disorders that stimulate hair growth as well as therapeutic modalities.

Biology of hair growth

Three types of Hair :

Lanugo : Body hair seen in the fetus and newborn

Vellus : Fine (downy unpigmented) hair covering the body

Terminal hair : Thick pigmented hair of scalp and pubic area

Thickness of the terminal hair varies form one individual to other depending upon genetic, and possibly nutritional

Biology of hair growth

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HORMONAL FACTORS AFFECTING HAIR GROWTH

1. **Androgens**; particularly testosterone; initiate growth, increase the diameter & pigmentation in all but scalp hair.
2. **Estrogens**; act essentially opposite from androgens, retarding the rate & initiation of growth, leading to finer, less pigmented & slower growing hair.
3. **Progestins**; have minimal direct effect on hair.
4. **Pregnancy**; (high estrogen & progesterone) can increase the synchrony of hair growth leading to periods of growth or shedding

Biology of hair growth

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- **Androgen sensitive hair** : depend upon androgen input for hair growth. These include:

  Face, neck, chest, abdomen, axillary , upper arms ,inner thighs and pubic hair,+ part of the scalp hair.

- **Less Androgen independent :**

  Forearms ,hands .lower limbs

ANDROGENS IN FEMALE

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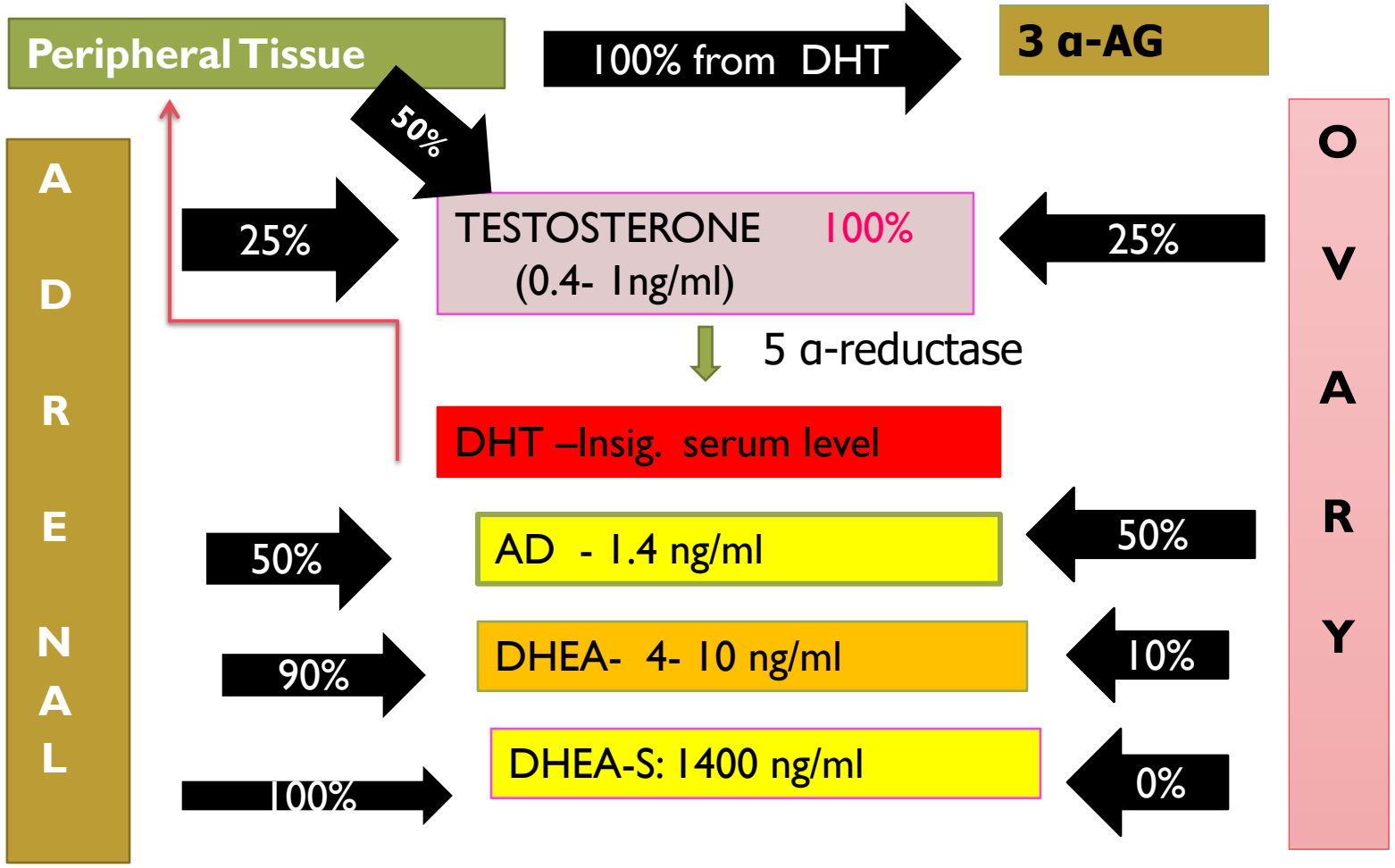
TYPES OF ANDROGENS IN FEMALES: 6

1. Androstendione (AD) = [1.4 ng/ml]
2. Dehydro-epiandrosterone (DHEA) =[4-10 ng/ml]
3. Dehydro-epiandrosterone sulfate (DHEA-S)=[1.4µg/ml]
4. Testosterone (T) = [0.4-1ng/ml]
5. Di-hydrotestosterone (DHT) =[0.1-0.3 ng/ml]
6. 3 alpha Androstenediole glucoronide (3 α-Diole G) OR (3 α AG)

ANDROGENS IN FEMALE- SOURCES



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ANDROGENS IN FEMALE

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- Testosterone level in male= 4-8 ng/ml [M> F]
- Androstendione in male= 0.8-1.2 ng/ml [F> M]

- Testosterone : a measure of ovarian & adrenal activity

- DHEA-S- measure of adrenal activity

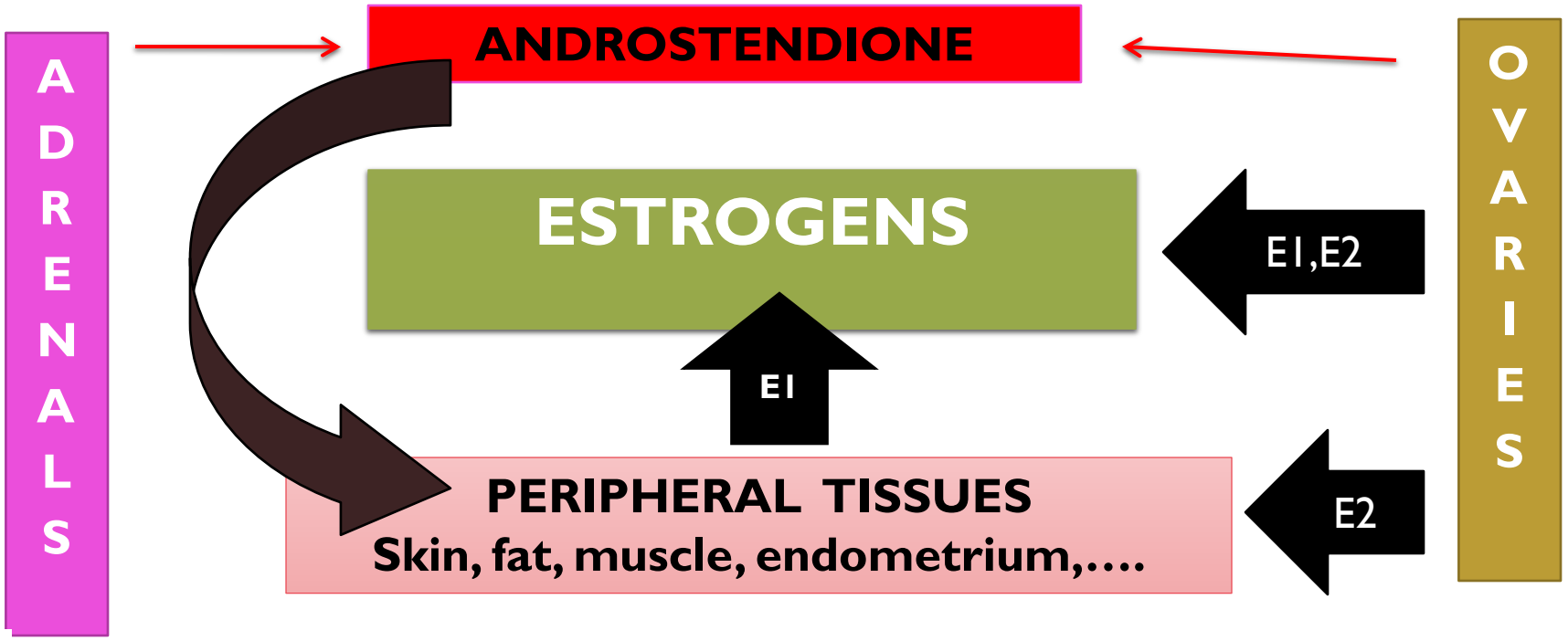
- Marker of peripheral target tissue androgen is 3 a-AG (not measured as routine; less clinical significant)

- DHT is the intracellular active form of T and it is twice potent as T and produced from T under the effect of 5 alpha reductase enzyme

ANDROGENS IN FEMALE

ANDROGEN CONVERSION INTO ESTROGENS

AROMATIZATION / AROMATASE ENZYME



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METABOLISM OF ANDROGENS

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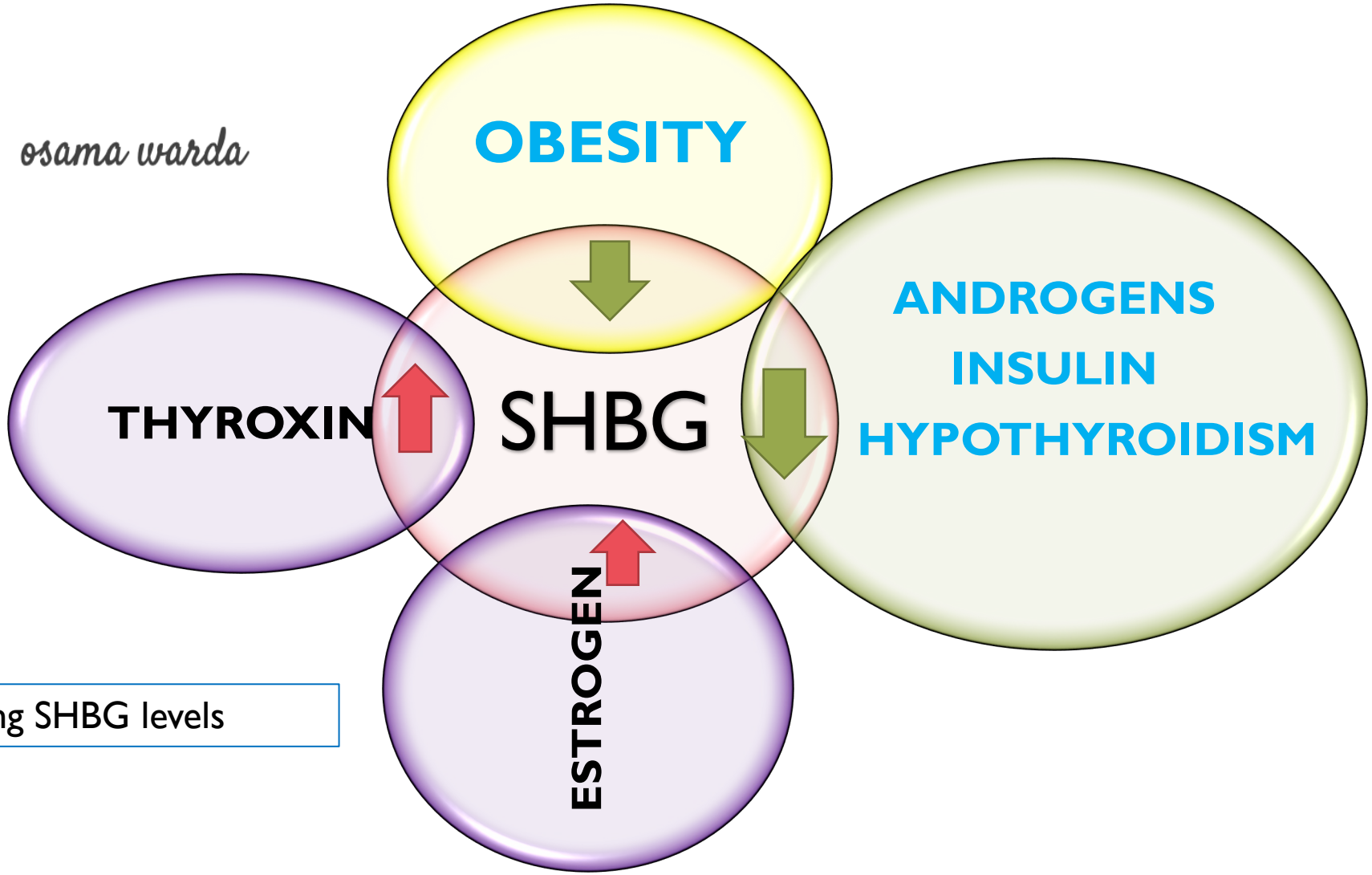
Androgens found circulating in 3 forms:

1. **bound to SHBG (80%)**
2. **bound to Albumen (19%)**
3. **free active form (1%)**

SHBG produced by liver ,plays important role in control of free active portion of Testosterone as follows:

- **NORMAL female = 1% Free TESTOSTERONE**
- **HIRSUTE female= 2% Free TESTOSTERONE**
- **VIRILIZED female or NORMAL male= 3% Free TESTOSTERONE**

METABOLISM OF ANDROGENS



Factors affecting SHBG levels

ETILOGY OF HIRSUTISM

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[1] 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 .

ETILOGY OF HIRSUTISM (cont'd)

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[2]. IDIOPATHIC HIRSUTISM:

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

1- normal menstrual pattern

2- normal or slightly increased androgens especially 3 α AG.

ETILOGY OF HIRSUTISM(cont'd)

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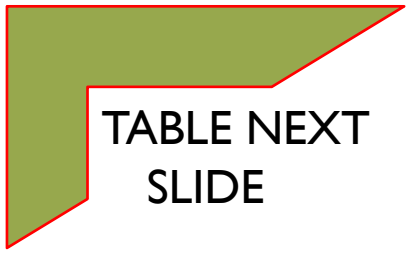
3- OVARIAN CAUSES:

(a). Polycystic ovary syndrome (PCOS)
(b). Hyperthecosis of the ovaries
(c). Androgen secreting ovarian tumors
(d). Lutoma 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

osama warda	PCOS	HYPERTHECOSIS
1. Inheritance	No	Autosomal dominant
2. Ovarian size	++ (vol.>9cm)	+ (vol. =7cm)
3. Follicles	Impaired growth (neclace)	Atretic
4. Stroma	Dense	Very dense
5. Capsule	Thick	Thick
6. Appearance	Hirsutism	Virilism
7. Menses	Oligo/amenorrhea	Oligo/amenorrhea
8. Hormones	T (N / +), 17OHP (N), LH/FSH (+ , ratio >3)	T(++ 8fold), 17OHP (++)
9. Histology (biopsy)	Theca cyst	no

ETILOGY OF HIRSUTISM(cont'd)

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ANDROGEN PRODUCING OVARIAN TUMORS; include

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

ETILOGY OF HIRSUTISM(cont'd)

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4. ADRENAL CAUSES:

A. Congenital adrenal hyperplasia (CAH): 3 forms/presentations:

- infantile CAH= female pseudohermaphrodite
- pre-pubertal = precocious puberty
- adult type= virilism

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

i. overproduction of ACTH by pituitary (Cushing's disease)
ii. Ectopic ACTH by non-pituitary tumor
iii. Autonomous secretion of cortisol by adrenal or ovarian tumors
iv. Ectopic corticotropin-releasing hormone production

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

ETILOGY OF HIRSUTISM(cont'd)

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5. OTHER CAUSES:

A. Iatrogenic (drugs): androgens, norgestrel, danazole, diazoxide, dilantin
B. Incomplete testicular feminization syndrome: (Refenstien's syndrome)
C. RARE TYPES : Acromegal, Porpheria, DES- exposed female infant

EVALUATION OF HIRSUTISM

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HISTORY TAKING:

1. Drug intake
2. Medical disorders
3. Rapid course may indicate tumors
4. Menstrual disorders
5. Epilation or shaving of hairs

EVALUATION OF HIRSUTISM

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PHYSICAL EXAMINATION

Cosmetically disturbing hirsutism is the end result of a number of factors:

1. **Number of hair follicle /unit skin area (eg. Asian women are rarely hisute even with androgen secreting ovarian tumor)**
2. **The degree to which androgen has converted resting villus hair to terminal adult hair.**
3. **The ratio of the growth to resting phases in affected hair follicles**
4. **The asynchrony of growth cycles in aggregates of hair follicles**
5. **The thickness and degree of pigmentation of individual hair**

EVALUATION OF HIRSUTISM

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PHYSICAL EXAMINATION

1. Distribution of excess hair growth; Casey's classification:

Type I: (FACE ONLY) upper lip, chin, complete beard & neck

Type II: FACE AND ABDOMEN

Type III: FACE ,ABDOMEN AND INTERMAMMARY AREA

Type IV: FACE, ABDOMEN, INTERMAMMARY AREA, AND BACK

EVALUATION OF HIRSUTISM

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PHYSICAL EXAMINATION

2. BODY BUILT , CONSTITUTION: trunk obesity, buffalo hump, breast size, reduced pelvic girdle

3. Signs of virilization: it includes combination of hirsutism & masculinity: clitoromegaly, deepening of voice, balding, and changes of body habitus (eg increased muscle mass, decreased breast size).

4. ABDOMINAL EXAMINATION: abdominal swelling as ovarian tuors

EVALUATION OF HIRSUTISM

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INVESTIGATIONS:

EACH PROPOSED ETIOLOGY IS SEARCHED FOR…..

IDIOPATHIC HIRSUTISM:

1. Normal serum testosterone level
2. Normal serum DHEA-S level
3. Increased serum 3α- diol-G

EVALUATION OF HIRSUTISM

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PCOS:

1. Increased serum LH (≥25mIU/ml)
2. Increased LH/FSH ratio (3 or more)
3. Trans vaginal ultrasound: (diagnostic); increased ovarian vol. (> 9cm), neclace arrangement of 6-9follicles each 6-9mm /ovary
4. At laparoscopy: large ovaries, smooth surface, no stimata of ovulation

EVALUATION OF HIRSUTISM

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INVESTIGATIONS

ANDROGEN SECRETING OVARIAN TUMORS

1. Total serum testosterone > 2ng/ml
2. Pelvic ultrasound, CT, or MRI will diagnose presence of ovarian t.

EVALUATION OF HIRSUTISM

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INVESTIGATIONS

ADRENAL GLAND

- CAH: Early morning 17-OH progesterone > 8ng/ml

- ADRENAL TUMORS:
  - Increased serum DHEA & DHEA-S levels
  - Abdominal CT/MRI will show adrenal tumor
  - Increased urinary 17 ketosteroid > 35mg/24h (normal= 5-15mg/24hr urine)

KEY RECOMMENDATIONS FOR EVALUATION OF HIRSUTISM

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1. The lab. Evaluation of hirsutism consists of measurement of circulating levels of: (a) testosterone (b) 17-OH progesterone (c) TSH screen for thyroid function is indicated when alopecia is present.

2. The single-dose overnight dexamethasone test is used to screen for Cushing's syndrome. Abnormal results are confirmed by measuring the 24h urinary free cortisol

KEY RECOMMENDATIONS FOR EVALUATION OF HIRSUTISM

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3. A clinician should always consider the possibility of hyperinsulinemia :

All women who are hyperandrogenic should be assessed for insulin resistance & glucose tolerance with measurement of :

(a) Fasting blood glucose: fasting insulin ratio , a ratio of less than 4.5 is consistent with insulin resistance. This is followed by

(b) 2-h glucose level after 75gm glucose load:

- Normal = less than 140mg/dl
- Impaired= 140-199mg/dl
- Non-insulin dependant DM=200mg/dl or more

KEY RECOMMENDATIONS FOR EVALUATION OF HIRSUTISM

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4. Any patient with rapidly progressive virilization must be evaluated for androgen –secreting ovarian tumor regardless of the results of screening lab tests

KEY RECOMMENDATIONS FOR EVALUATION OF HIRSUTISM

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5. Incidentally discovered adrenal masses require evaluation as follows:

[A] screening tests for incidental adrenal masses:

- 24h urinary catecholamines & free cortisol
- Serum testosterone
- Renin activity, aldosterone, and electrolytes

[B] Provocative tests for subclinically active incidental adrenal masses:

- Dexamethasone overnight suppression test
- 17-OH progesterone response to ACTH
- Clonidine suppression test [clonidine 0.3mg p.o. in supine position, followed by plasma norepinephrine levels at 0,2, and 3 hrs. ; a level > 500pg/ml or 50% greater than the 0 level is a +ve result]

MANAGEMENT OF HIRSUTISM

Including the following measures…….

A- General measures

B-Antiandrogens:

1. cyproterone acetate (CPA)
2. Spironolactone (aldactone)
3. Flutamide
4. Ketoconazole

C- Ovarian suprression

1. COCs
2. GnRHa

D-Adrenal suppression

1- Finasteride

2 -Surgical measures

MANAGEMENT OF HIRSUTISM
A- GENERAL MEASURES

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1. TREATMENT OF THE CAUSE:

- Stop offending drugs
- Treat tumors by surgical removal
- Treat medical disorders

2. COSMETIC MEASURES:

Removal of the present hairs by shaving, waxing, epilation, electrolysis, lasers.

3. WEIGHT REDUCTION : if BMI> 25KG/M^2

- **in hyper insulinemia**
- **obesity shares in etiology**

MANAGEMENT OF HIRSUTISM

B-1- **Antiandrogens :CPA**

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- Potent progestational agent that act by inhibition of gonadotropin & blocking androgen receptors.
- It has been used in an oral contraceptive agent called "Diane" [2mg CPA+50µg EE], Dianette or Dian 35 [2mg CPA+ 35 µg EE].
- When combined in OC it leads to inhibition of pituitary (⬇ LH), ovary (⬇ androgen), and ⬇ free testosterone due to ⬆ SHBG.

MANAGEMENT OF HIRSUTISM
B-1- Antiandrogens/CPA

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- **Mild cases (low dose): 10 day regimen of 21day cycle [low dose OC (30µg EE) + 2mgCPA**
- **Moderate cases: Dianette or Diane 35 (35 µg EE+2mg CPA) daily for 21 days.**
- **Severe cases: (Reversed sequential regimen/ high dose CPA):**

CPA: 50-100 mg daily on days 5-14, with EE 30-50 µg daily on days 5-25

- **The clinical response is the same in dianette and high dose with advantage of minimizing side effect with dianette (lower dose CPA).**
- **Significant improvement of facial hirsutism is expected by the 3rd month of treatment.**

MANAGEMENT OF HIRSUTISM
B-2- Antiandrogens/ Spironolactone

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- It is aldosterone- antagonist used as diuretic.
- It acts by : (1). inhibition of ovarian & adrenal steroidogenesis, (2). competes for androgen receptor in hair follicle . (3). directly inhibits 5α -reductase activity

Dose: 200 mg daily for 2weeks then maintenance dose 25-50mg daily for 6 months

-Effect on hirsutism is seen after 6 months, and is dose dependant

-Given when OC are not accepted, or their results are disappointing

- Unlike OC pregnancy can occur with it with the theoretical risk of feminization of male fetus.

- when given in combination with OC the results are not much better than single agent therapy

-Acne can be treated with a topical cream containing 2-5% spironolactone with no systemic absorbtion.

MANAGEMENT OF HIRSUTISM
B-3- Antiandrogens: Flutamide

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- Non-steroidal antiandrogen
- Acting on peripheral target tissue(hair follicle)
- Should be given in combination with COC.
- Dose is 500 mg orally daily

MANAGEMENT OF HIRSUTISM
B-4-Antiandrogens: *ketoconazole*

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- Synthetic imidazole derivative
- Blocks gonadal & adrenal steroidogenesis by inhibiting key enzyme steps in androgen biosynthesis.
- *Dose: 200 mg orally daily*
- Side effects include: alopecia, asthenia, nausea & vomiting

MANAGEMENT OF HIRSUTISM
C- OVARIAN SUPPRESION

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1- COMBINED ORAL CONTRACEPTIVES:

-Suppress FSH & LH

-Suppress ovarian androgen production

-E2 component : -*Suppresses gonadotropin production, . inhibits 5 α reductase activity, and stimulate SHBG synthesis, thus decreasing free testosterone*

- P4 component of the pill should have NO androgenic properties, so Desogestril & Gestoden –based pills are favored.

2- GnRH:

e.g. Leuprorelin 3.75 mg/monthly injections + COCs as backup

MANAGEMENT OF HIRSUTISM
D-1- ADRENAL SUPPRESION/Glucocorticoids

Glucocorticoids only have a place in the treatment of hirsutism when there is underlying adrenal component such as CAH

DEXAMETHAZONE (0.25-0.5 mg) taken at night suppress ACTH morning surge & adrenal production of androgens.

MANAGEMENT OF HIRSUTISM
D-2- ADRENAL SUPPRESION/Finasteride

- **Finasteride (Proscar)** is a synthetic 4-azasteroid compound, a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts testosterone into the active dihydrotestosterone. Used in cases of idiopathic hirsutism, and PCOS who do not want conception.
- ***Action*** *via exerting specific competitive inhibition with 5 α reductase thus decreases the conversion of testosterone into intra-celluar active DHT, decreasing hirsutism.*
- ***Dose***: One tablet 5mg orally /day/ 6 months
- ***Side effects***: severe or ongoing nausea,, difficulty breathing , swelling of face, lips, tongue or throat, breast lumps , breast pain, tenderness and discharge.

MANAGEMENT OF HIRSUTISM
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)

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