M08: Evaluation and Management of Hirsutism

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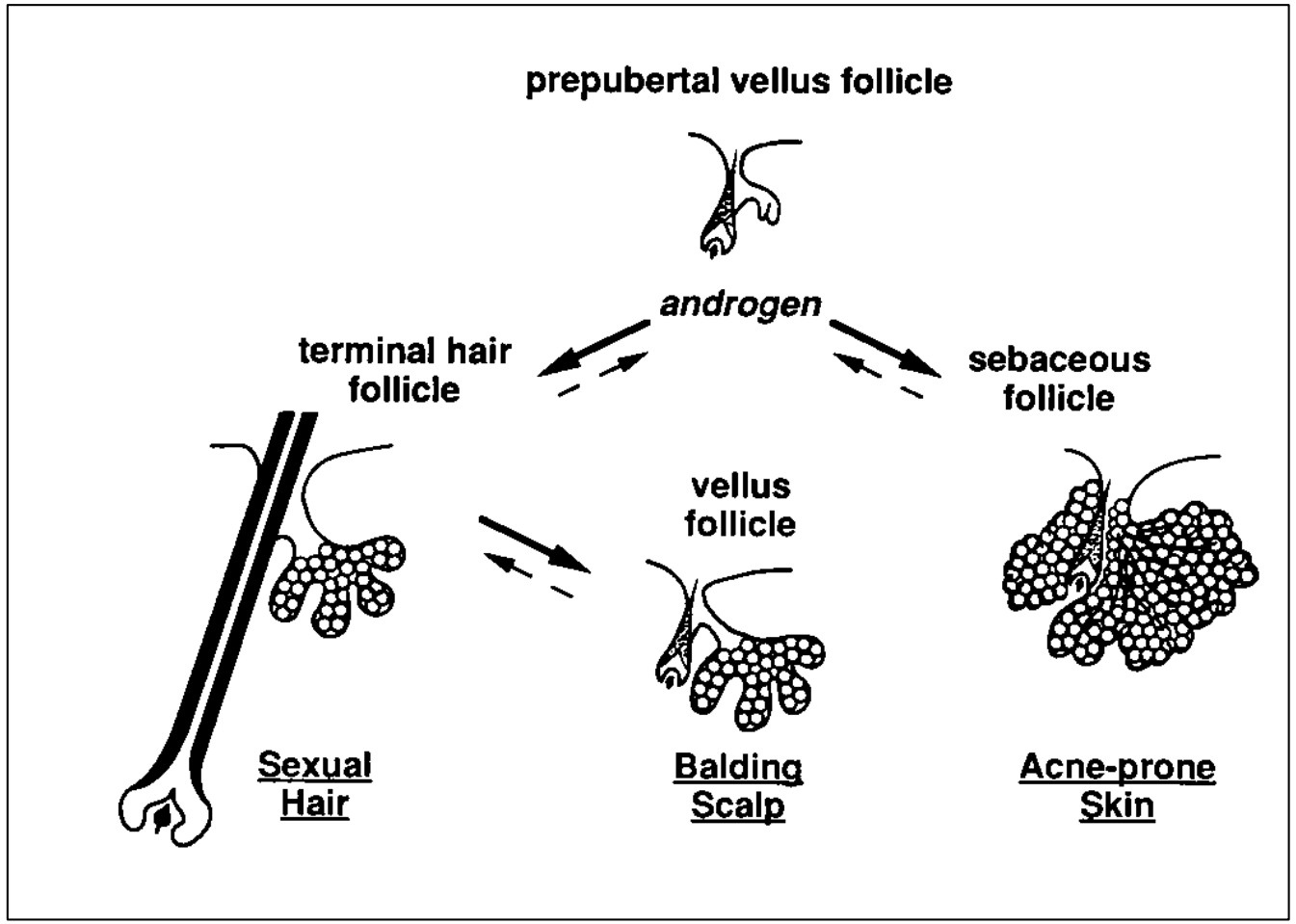
Term	Definition
Hirsutism	Excessive terminal hair that appears in a male pattern (excessive hair in androgen-dependent areas, ie sexual hair) in women.
Modified Ferriman-Gallwey Score	The gold standard for evaluating hirsutism. Nine body areas most sensitive to androgen are assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score.
Local Hair Growth	Unwanted localized hair growth in the absence of an abnormal total hirsutism score.
Patient-important Hirsutism	Unwanted sexual hair growth of any degree that causes sufficient distress for women to seek additional treatment.
Hyperandro-genism	Hyperandrogenism is defined by clinical features that result from increased androgen production and/or action.
Idiopathic Hirsutism	Hirsutism without hyperandrogenemia or other signs or symptoms indicative of a hyperandrogenic endocrine disorder

Evaluation and Treatment of Hirsutism



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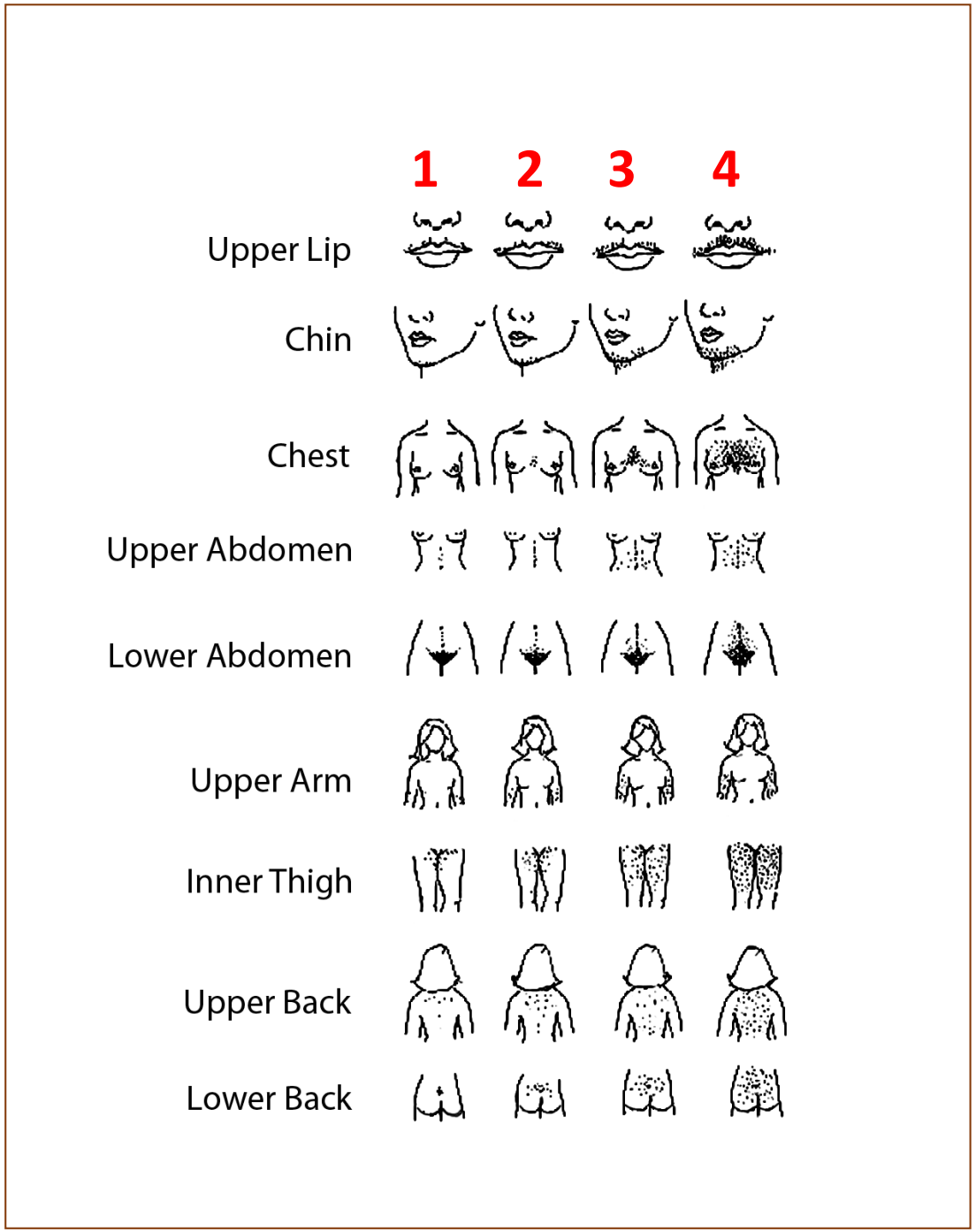

Modified Ferriman – Gallwey Hirsutism Scoring System

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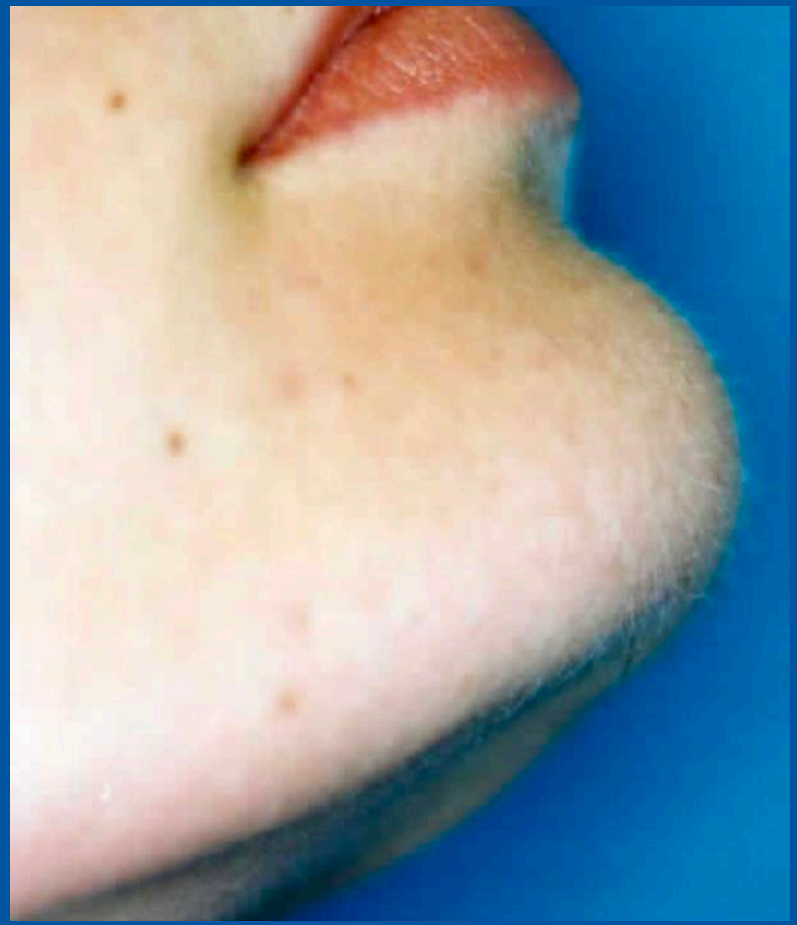
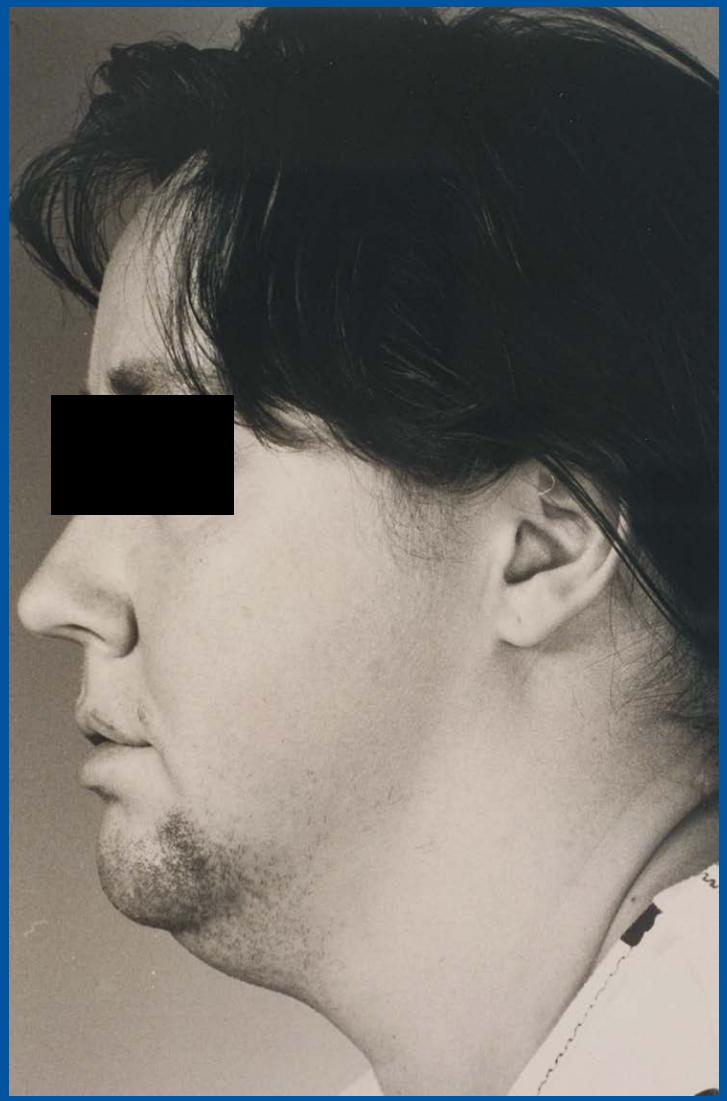
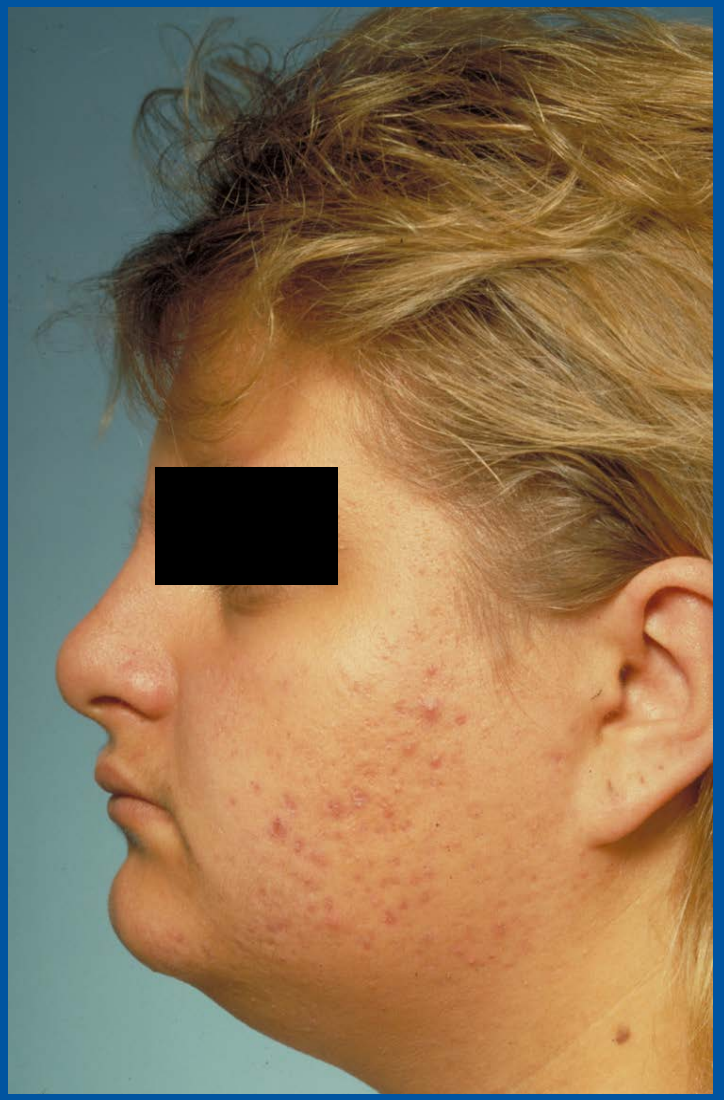
Evaluation



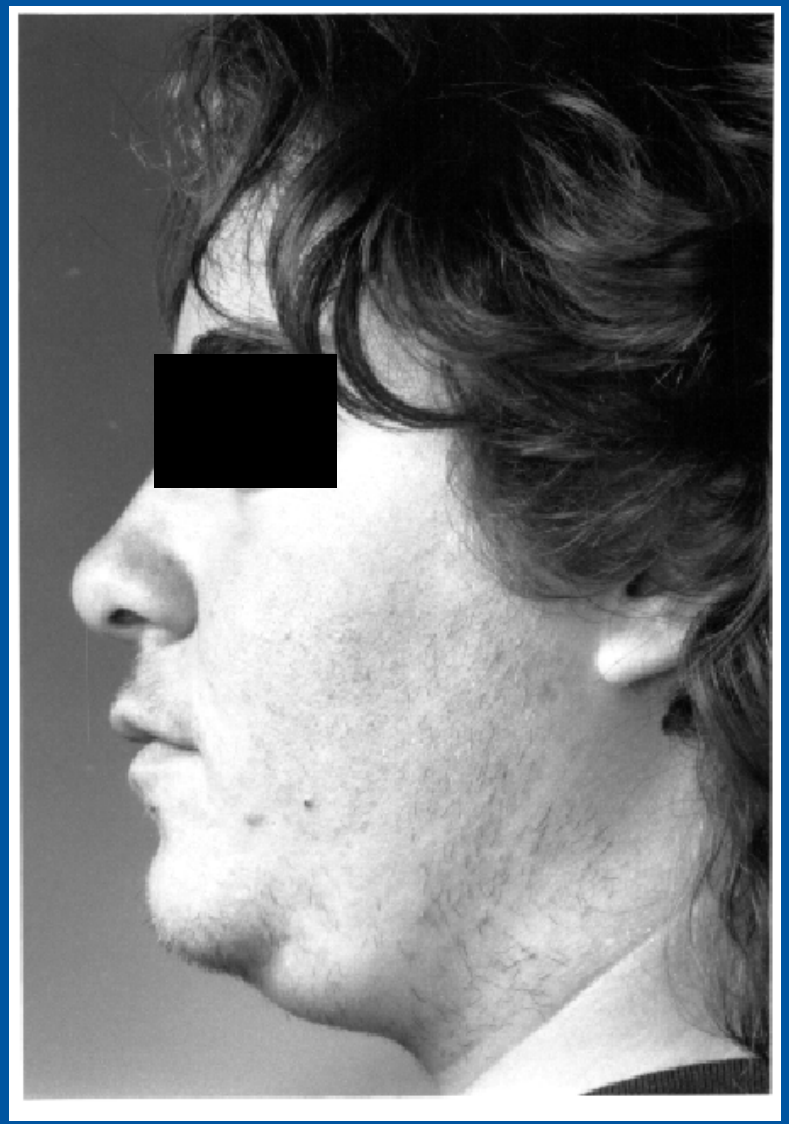
Hypertrichosis?
Treated Hirsutism?



Non-classic congenital adrenal hyperplasia (21-hydroxylase)



Polycystic ovary syndrome



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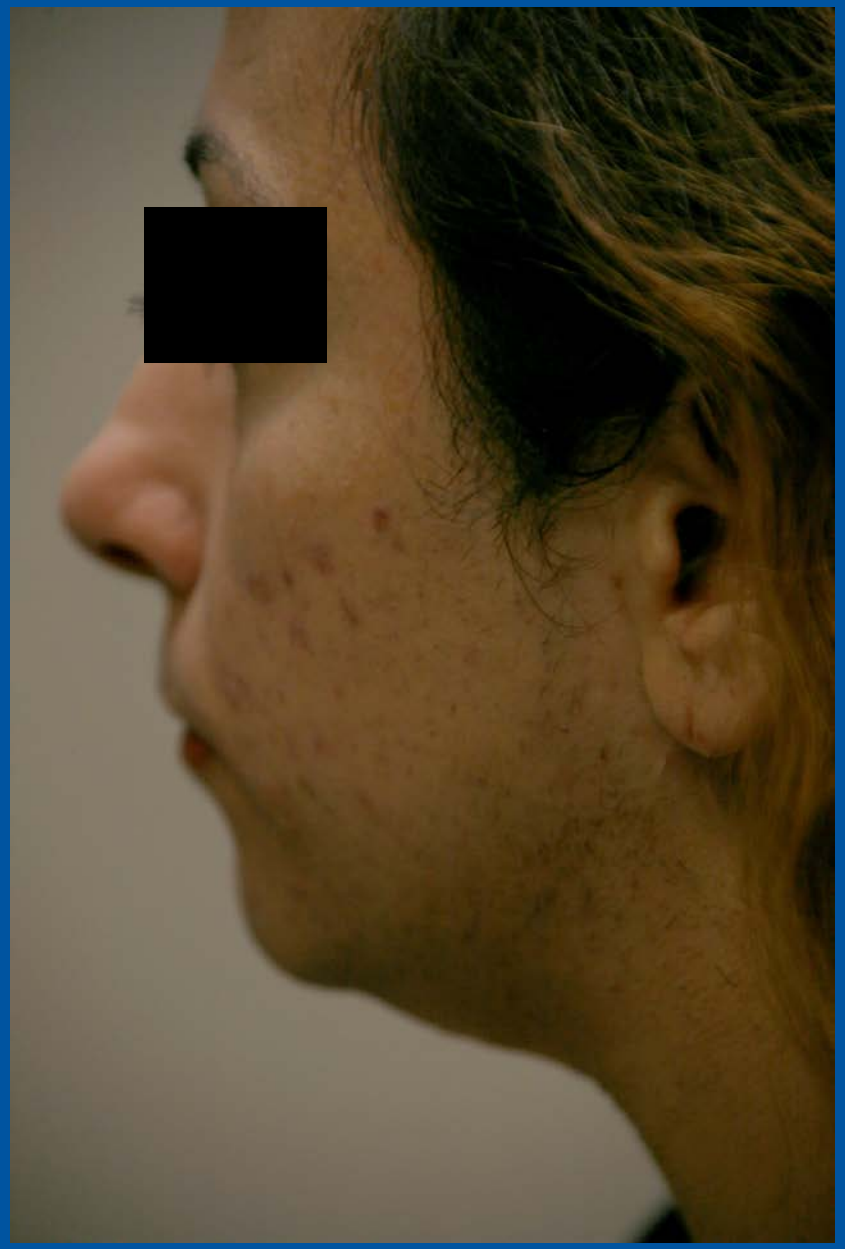
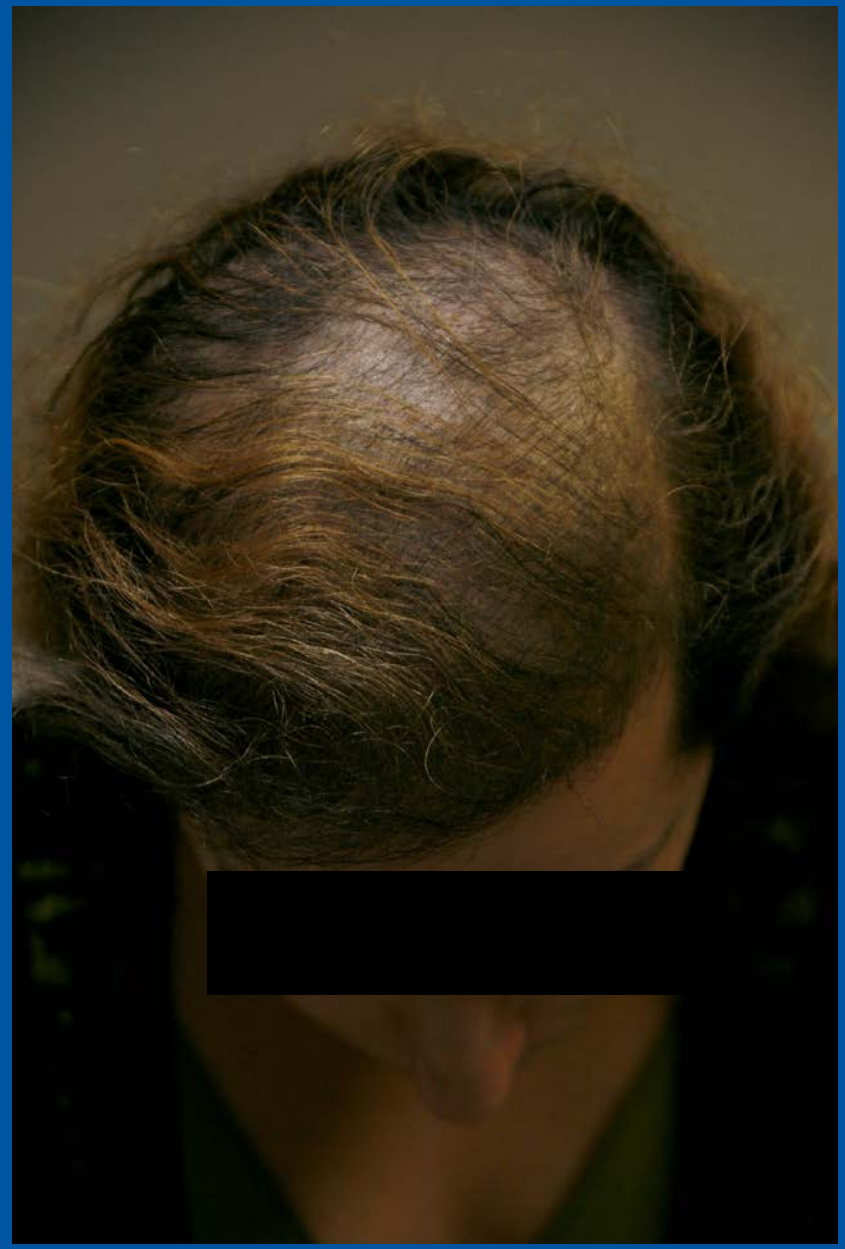
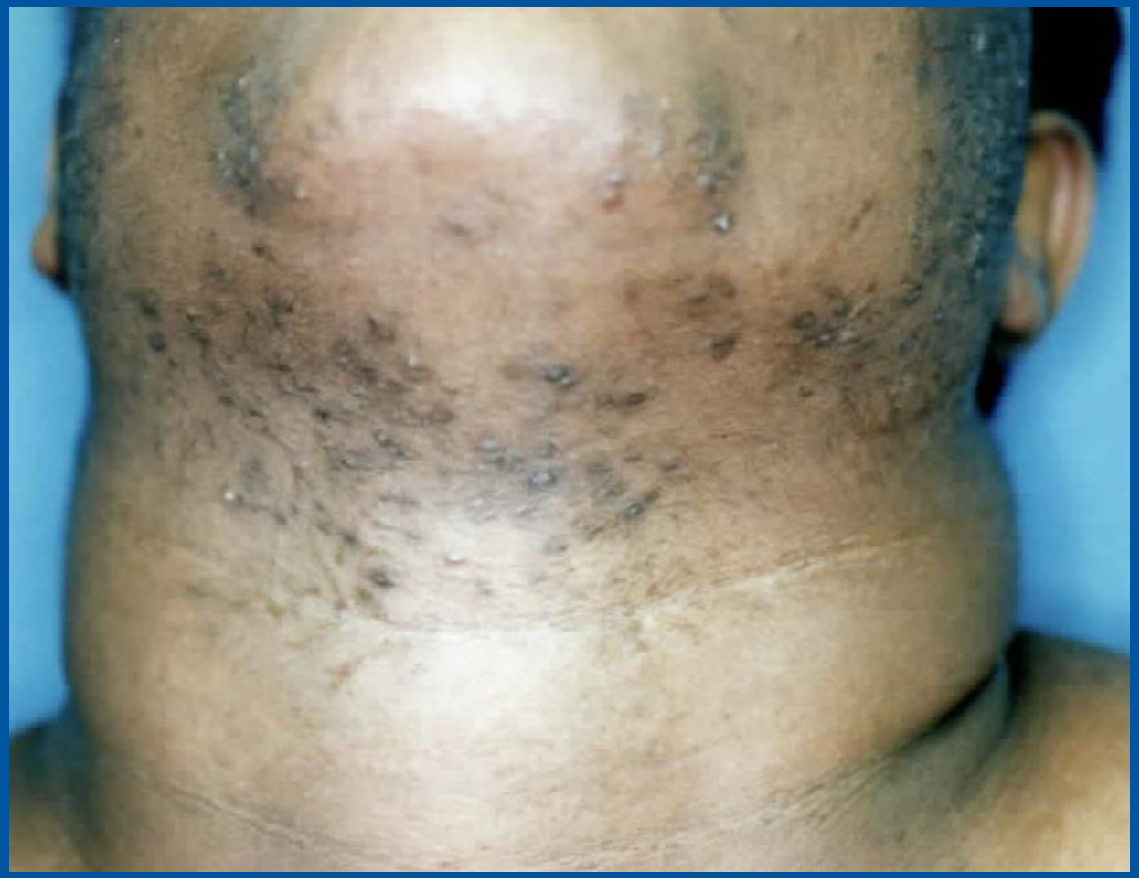




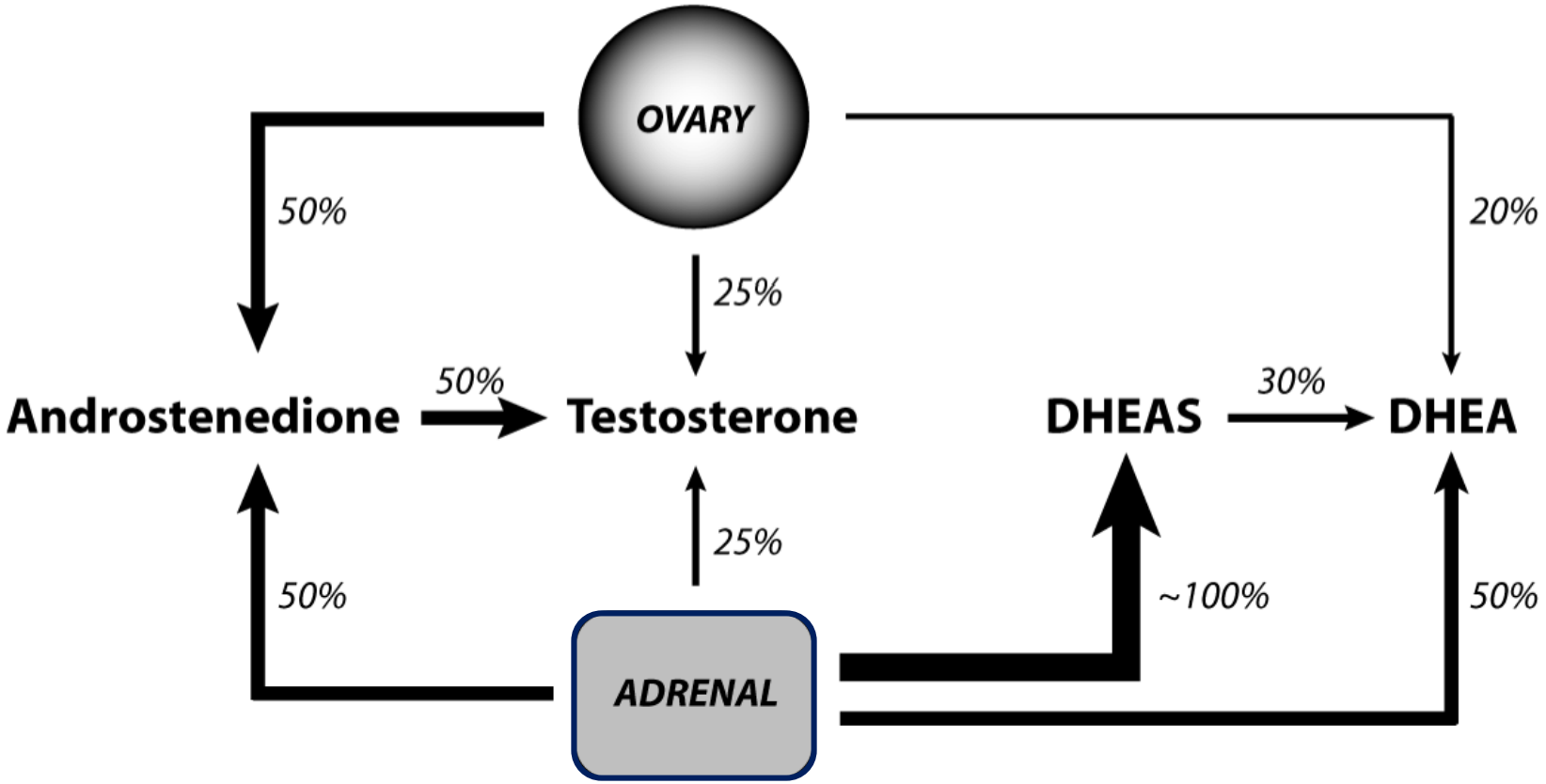
Hirsutism, Acne, and Androgenic Alopecia

Ovarian Neoplasm



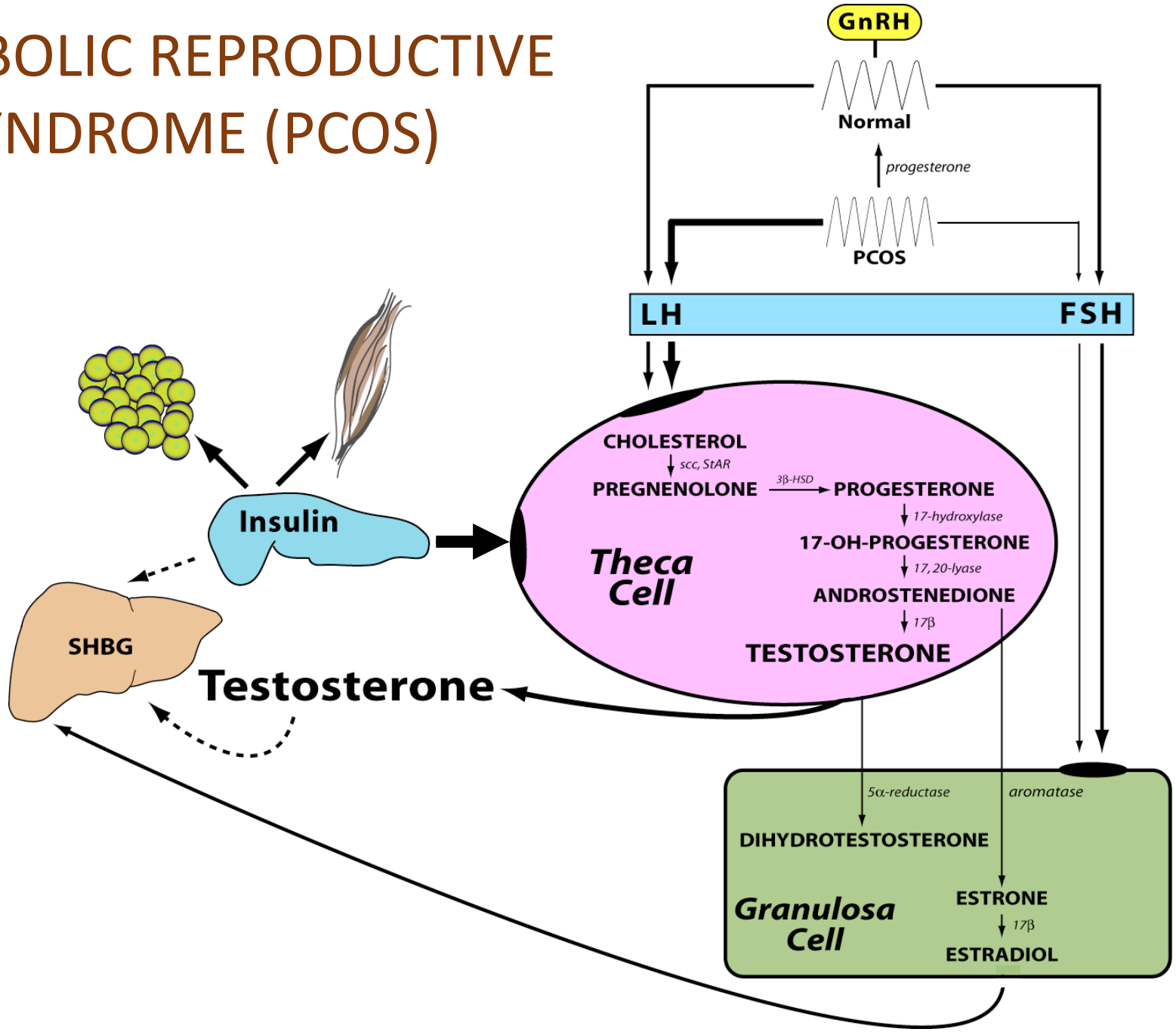
Hirsutism with Folliculitis Barbae

Androgen Production in Women



DIFFERENTIAL DIAGNOSIS OF HIRSUTISM/HYPERANDROGENISM			Distinguishing Features	
Condition	Hyperandro-genic	Irreg Menses	Clinical	Hormonal
Nonclassic 21-hydroxylaseCAH	Yes	Not typically	+FHx infertility, hirsutism; Eastern Europe Jewish (Ashkenazi)	High basal or ACTH stimulated 17-OHProg
Cushing's Syndrome	Yes	Yes	HTN, striae, easy bruising	Incr. 24hr urinary free cortisol
↑ Prolactin	No/Mild	Yes	Galactorrhea	Elevated prolactin level
Primary Hypothyroidism	No/Mild	May be present	Goiter, etc.	Elevated TSH, low T_4/FT_4
Acromegaly	No/Mild	Often	Acral enlargement, coarse features, prognathism	Increased IGF1
Primary Ovarian Insufficiency	No	Yes	Other autoimmune disorder, recurrent miscarriage	Increased FSH Low E2 Low AMH
Simple Obesity	Often	Variable	Dx of Exclusion	None
Virilizing Neoplasms	Yes, extreme	Yes	Clitoromegaly, extreme hirsutism, pattern alopecia	Extreme elevation of androgen levels
Medications	Variable	Variable	History	Variable

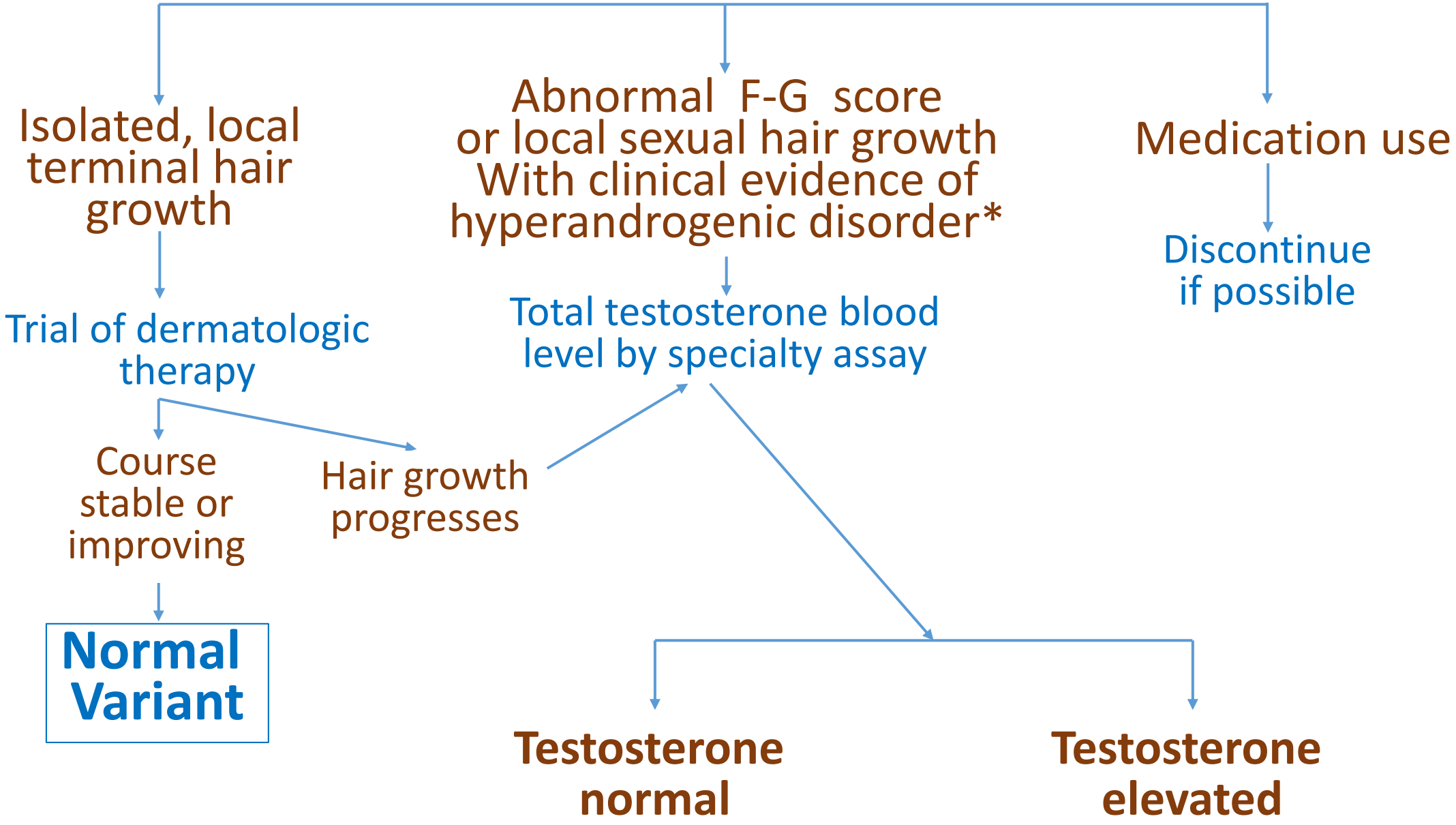
METABOLIC REPRODUCTIVE SYNDROME (PCOS)

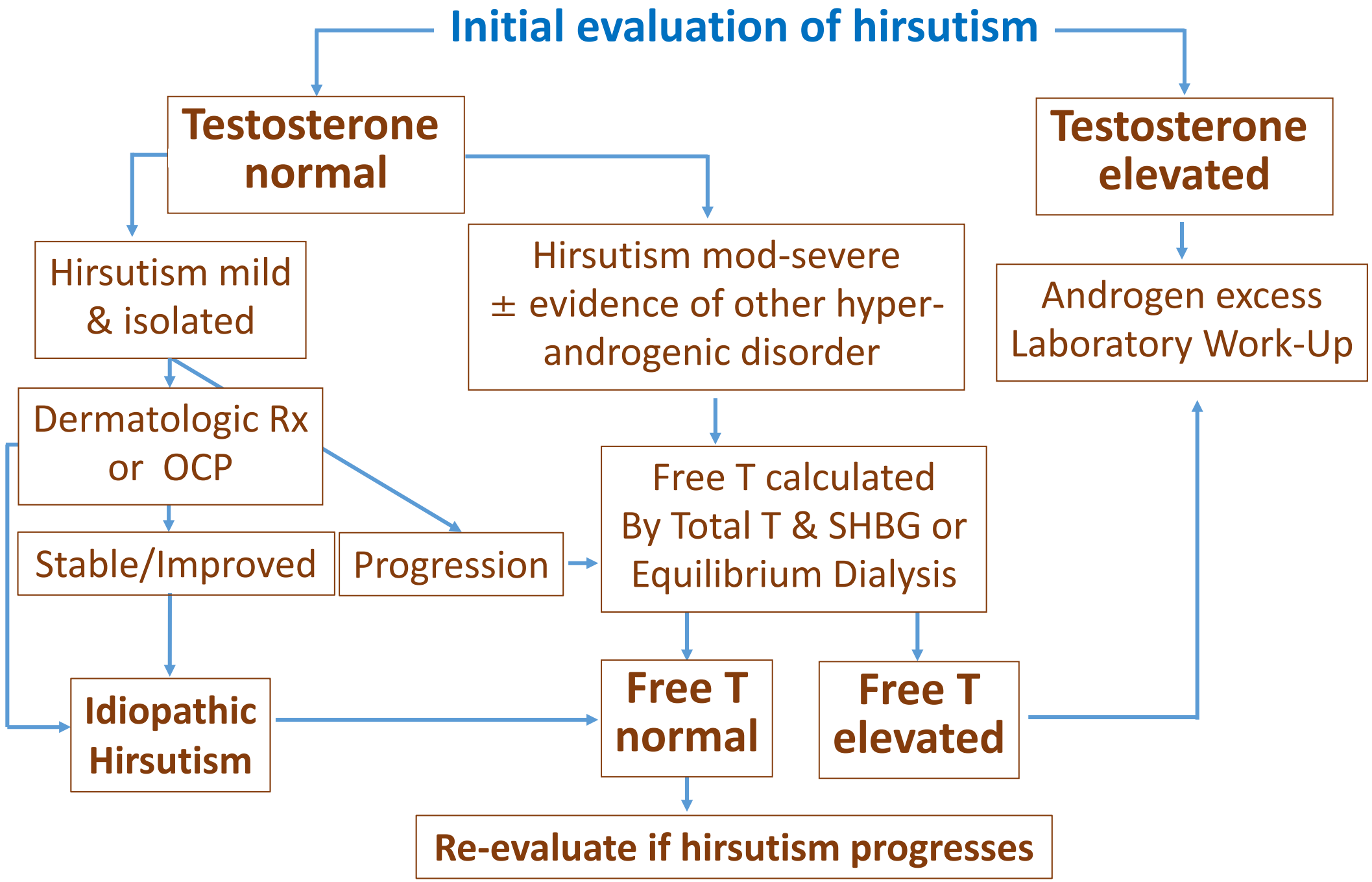


Metabolic Reproductive Syndrome (PCOS): Diagnostic Criteria

NIH consensus criteria (all required)	**Rotterdam criteria (two out of three required)**	**Androgen Excess PCOS Society criteria (all required)**
Oligo- or anovulation (<6-8 menses/yr)	Oligo- or anovulation (<6-8 menses/yr)	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction – oligo/anovulation (<6-8 menses/yr) and/or polycystic ovaries on ultrasound
Exclusion of other disorders: NCCAH, androgen-secreting tumors, etc.	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

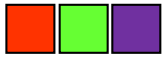
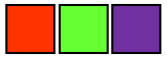
Initial evaluation of hirsutism

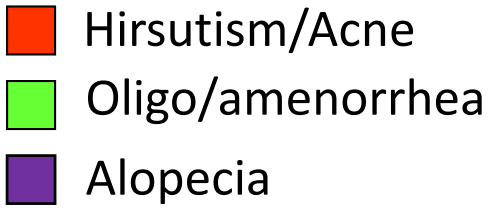



Initial evaluation of hirsutism
Testosterone normal
Testosterone elevated
Hirsutism mild & isolated
Hirsutism mod-severe ± evidence of other hyper-androgenic disorder
Androgen excess Laboratory Work-Up
Dermatologic Rx or OCP
Stable/Improved
Progression
Free T calculated By Total T & SHBG or Equilibrium Dialysis
Idiopathic Hirsutism
Free T normal
Free T elevated
Re-evaluate if hirsutism progresses

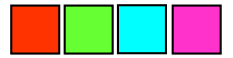
Treatment

Pharmacologic Therapy of PCOS (Hirsutism)

Agent	Mechanism(s)	Examples	Use(s)
Combination estrogen-progestin	Increase SHBG; suppress LH and FSH; suppress ovarian androgen production	• Ethinyl Estradiol • Mestranol *plus* • Progestin	
Antiandrogens	Inhibit androgens from binding to the androgen receptor	• Cyproterone acetate • Spironolactone • Flutamide	

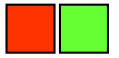
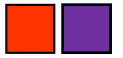


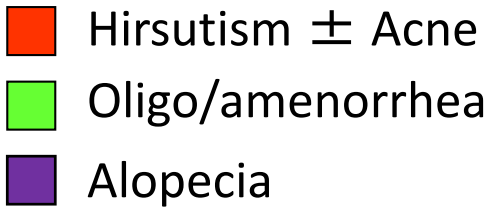
Pharmacologic Therapy of PCOS (Hirsutism)

Agent	Mechanism(s)	Examples	Use(s)
Biguanides (Metformin)	Reduce hepatic glucose production with 2° lowering of insulin levels; ?Direct effects on ovarian steroidogenesis	•Metformin (Glucophage, Glucophage XR)	

- Hirsutism/Acne: little evidence to support
- Oligo/amenorrhea: modestly effective
- Ovulation induction: modestly effective
- Insulin lowering: effective

Pharmacologic Therapy of PCOS (Hirsutism)

Agent	Mechanism(s)	Examples	Use(s)
Glucocorticoids	Suppress ACTH and adrenal androgen production	•Prednisone •Dexamethasone	
5α-reductase inhibitors	Inhibition of 5α-reductase	•Finasteride (5α-type2) •Dutasteride (5α-types 1 & 2)	
Ornithine decarboxylase inhibitors	Inhibition of ornithine decarboxylase	•Vaniqa (topical)	
Minoxidil	?antiandrogenic; vaso-dilatory, antiinflammatory	•Minoxidil	
Ketoconazole	Inhibits steroidogenesis; Decr. DHT in hair follicle	•Ketoconazole	



Conversion of Testosterone to Dihydrotestosterone (DHT) by 5α-reductase

Type 1: predominantly expressed in skin and annexes (sebaceous glands, sweat glands, and hair follicles).

Type 2: expressed in the epididymis, seminal vesicles, prostate, and genital fibroblasts.

Type 3: expressed both in benign and neoplastic prostate tissue, but overexpressed and more broadly distributed in advanced prostate cancer.

Relative Androgenic Activity of Progestins in OCPs

Highest Androgenic Activity	Moderate Androgenic Activity	Lowest Androgenic Acitivity
Levonorgesterel Norgesterel	Desogesterel Norethindrone Acetate Norgestimate	Ethynodiol Diacetate Dienogest Drosperinone

Table 2. Oral Contraceptives and Associated Venous Thromboembolism Risks

Progestin Generation	Progestin Relative Androgenicity	Progestin Relative VTE Risk[a,b]	Progestin Absolute VTE Risk[b,c]	Progestin/Dose	EE Dose (mcg)
1	Medium	2.6	7	Norethindrone 0.5–1.0 mg	20, 35
2	High	2.4	6	Levonorgestrel 0.15 mg	20, 30
2–3	Low	2.5	6	Norgestimate 0.25 mg	35
3	Low	3.6	11	Gestodene 0.075 mg	20, 30
3	Low	4.3	14	Desogestrel 0.15 mg	20, 30
4	Antiandrogen	4.1	13	DSP 3 mg	20, 30
—	Antiandrogen	4.3	14	CPA 2 mg[d]	35

[a]Relative risk compared with no OC use.

[b]Vinogradova *et al.* (72); Stegeman *et al.* (56).

[c]Extra cases VTE per 10,000 women treated with OCs per year.

[d]OCs containing CPA are not available in the United States.

Cases

Evaluation and Treatment of Hirsutism: Case 1

- An 18 yr old woman is concerned about increased hair growth on her face and lower abdomen. Menarche at age 11yr. For the first year post-menarche she had approximately 4 menstrual periods. Between 11 and 14yr, cycles remained unpredictable; approximately 6 - 7 menses/yr.
- At age 16 yr, developed acne on her face and upper back. A dermatologist recommended topical Clindamycin, then isotretinoin. She is now 17 yr old.
- Non-smoker. EtOH – social. Her father has T2DM; mother had a DVT with a pulmonary embolism.

Evaluation and Treatment of Hirsutism: Case 1

- Never used any form of contraception, but now sexually active; inquires about oral contraceptives.
- Physical exam: is 5’5’’ (1.65 m) in height, her weight is 211 lb (95.9 kg); BMI is 35.3 kg/m^2; moderate pustular acne on chin and upper back. BP 138/94 mmHg. HR is 104 bpm. She has centripetal obesity; no other signs of Cushing syndrome or lipodystrophy. Acanthosis nigricans on her neck. Her Ferriman-Gallwey score is 7. There is some thinning of her scalp hair but no alopecia.
- A transvaginal ultrasound showed a 2 cm cyst in the right ovary but no clear evidence of multiple follicles. The ovaries were of normal size.

Evaluation and Treatment of Hirsutism: Case 1

1. Does this patient have PCOS?
    a. Yes
    b. No
    c. Not sure, but does it matter?

Evaluation and Treatment of Hirsutism: Case 1

2. Are additional blood tests required before recommending treatment?

a. Yes
b. No
c. Optional

Evaluation and Treatment of Hirsutism: Case 1

3. In addition to lifestyle intervention, what treatment(s) would you recommend for her hirsutism and oligomenorrhea?

a. An oral contraceptive
b. Metformin
c. A progestin (levonorgesterel) containing IUD
d. Spironolactone alone
e. An oral contraceptive together with spironolactone
f. Finasteride
g. Photoepilation

Evaluation and Treatment of Hirsutism: Case 1

4. How will you monitor response to treatment?
    a. Measure serum testosterone level in 3 months
    b. Measure serum dihydrotestosterone level in 3 months
    c. Measure LH and FSH
    d. Use a patient-provided self-assessment

Evaluation and Treatment of Hirsutism: Case 2

- A 32 year old woman with a hx. of PCOS is referred for management. Menarche was at 10 yr. At age 19 yr, she was diagnosed with PCOS based upon her history of 9 years of oligomenorrhea together with a total serum testosterone that was 2.5X the upper limit of normal in the assay used.

- OCPs were taken intermittently but stopped after “migraine” headaches developed. A progestin releasing IUD was placed. She has persistent headaches, at times with vision disturbances. She is G0P0. She had photo-epilation of her facial hairgrowth, but is not satisfied with the result. She describes persistent fatigue and a recent weight gain of 12 lb (5.5 kg) over the last 6 – 8 mo.

Evaluation and Treatment of Hirsutism: Case 2

- Her BMI is 37.3 kg/m^2, BP 162/94 mmHg. Fasting labs: total cholesterol 258 mg/dl, HDL cholesterol 33 mg/dl, triglycerides 194 mg/dl, and LDL cholesterol (calculated) 187 mg/dl; HbA1c is 6.2%. The patient is taking atorvastatin 10 mg/day and amlodipine 10 mg/day.
On exam, she has centripetal obesity with a Ferriman-Gallwey score of 16 (nl < 8).

Evaluation and Treatment of Hirsutism: Case 2

1. Which, if any, of the following tests are appropriate at this time?

a. Polysomnography to exclude obstructive sleep apnea

b. Factor V Leiden assay

c. Prolactin level

d. MRI of the brain

e. A, B, C, and D

f. None of the above

Evaluation and Treatment of Hirsutism: Case 2

2. What is your treatment recommendation now?

a.Removal of her IUD

b.Start metformin with the aim of reaching 2000 mg/d

c.Start an oral contraceptive with close monitoring

d.Start spironolactone 100mg BID

e.Start dutasteride 0.5mg/d

f. A and D only

g.A, B, C, and D

Thank you!

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Evaluation and Treatment of Hirsutism

Causes of Hirsutism

Gonadal hyperandrogenism

- Ovarian hyperandrogenism
- Polycystic ovary syndrome
- Ovarian steroidogenic blocks
- Syndromes of extreme insulin resistance (eg, lipodystrophy)
- Ovarian neoplasms
- Hyperthecosis

Adrenal hyperandrogenism

- Premature adrenarche
- Functional adrenal hyperandrogenism
- Congenital adrenal hyperplasia (nonclassic and classic)
- Abnormal cortisol action/metabolism
- Adrenal neoplasms

Evaluation and Treatment of Hirsutism

Causes of Hirsutism

Other endocrine disorders

- Cushing's syndrome
- Hyperprolactinemia
- Acromegaly

Peripheral androgen overproduction

- Obesity
- Idiopathic

Pregnancy-related hyperandrogenism

- Hyperreactio luteinalis
- Thecoma of pregnancy

Medications

- Androgens
- Oral contraceptives containing androgenic progestins
- Minoxidil
- Phenytoin
- Diazoxide
- Cyclosporine
- Valproic Acid

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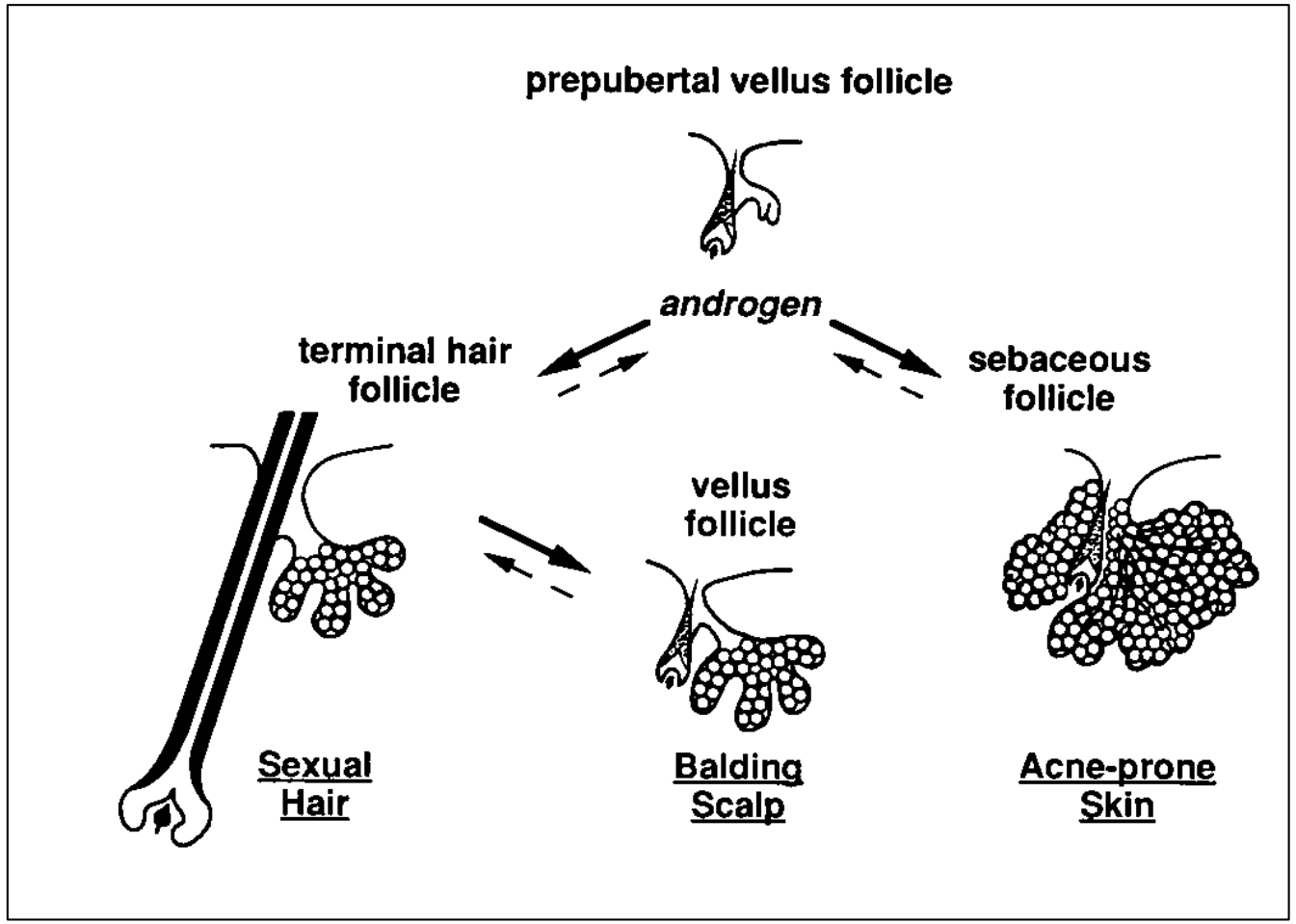

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