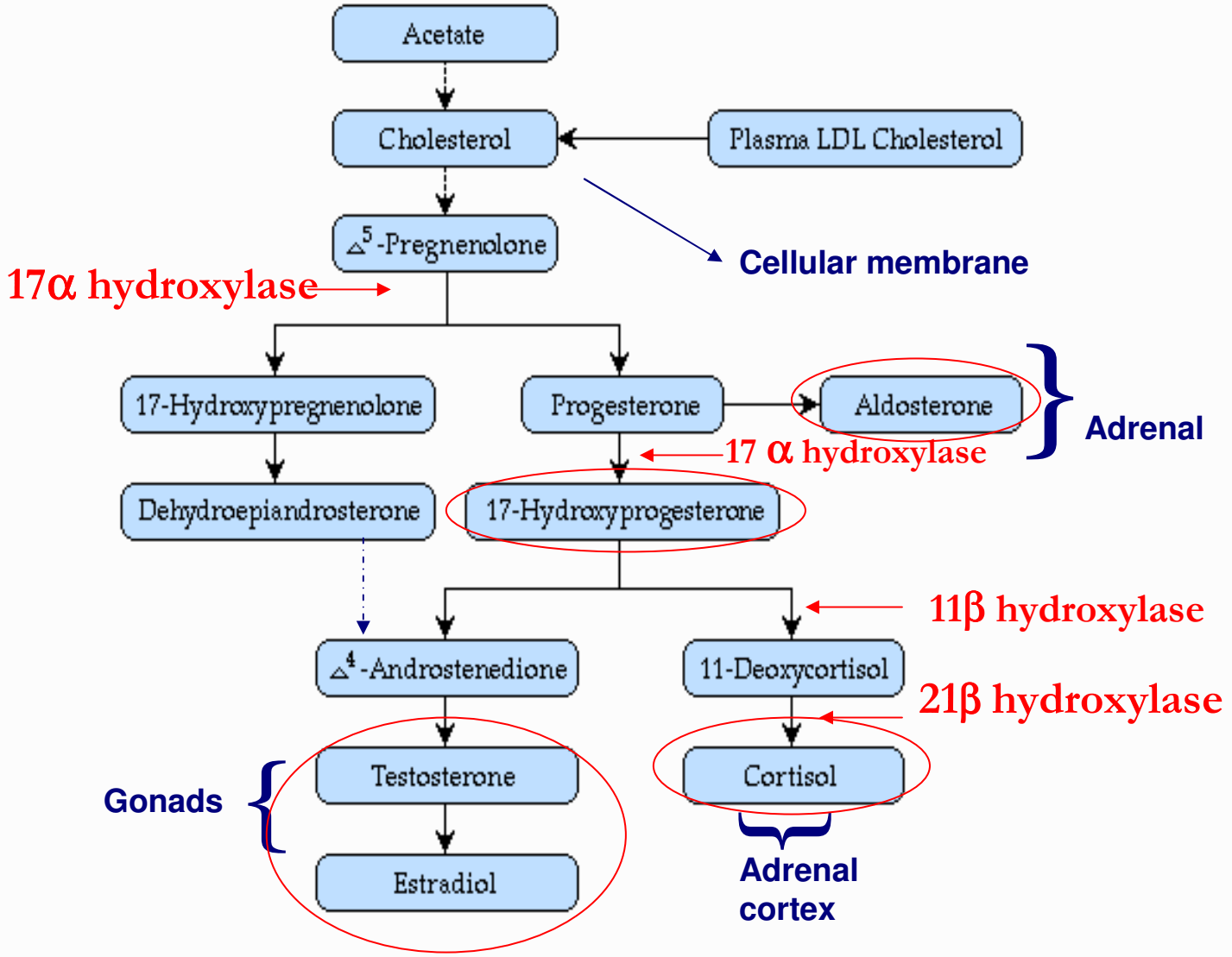
Hirsutism and Virilization

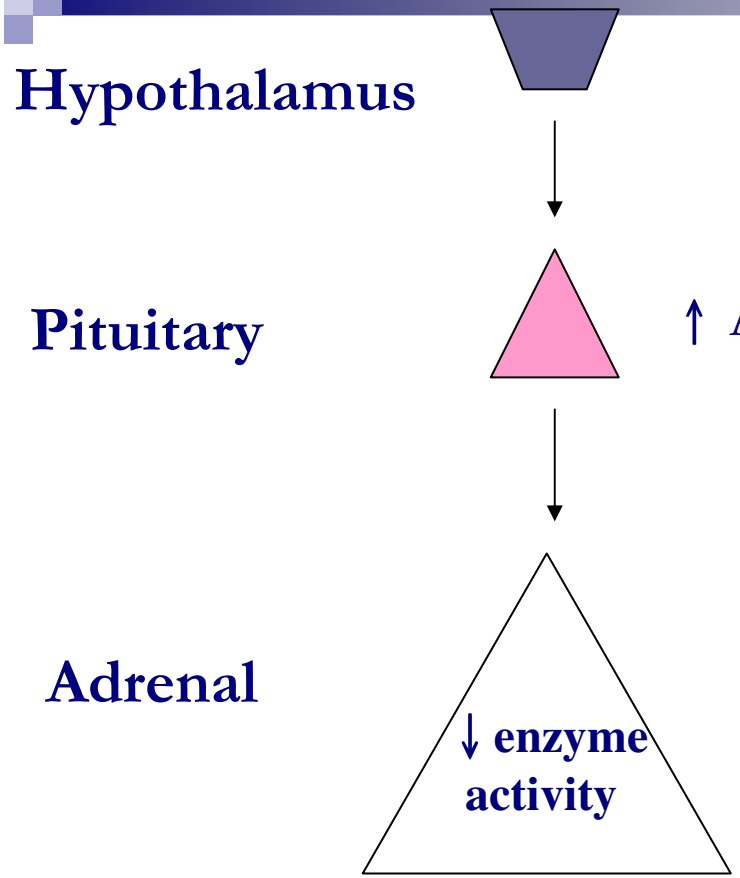
Hirsutism and virilization

- Hirsutism
  - excessive hair growth in androgen-sensitive areas
    - tip of nose, upper lip, chin, ear lobes, back, chest, areolae, axillae, lower abdomen, pubic triangle, anterior thighs
  - Interaction between androgen levels and sensitivity of hair follicles to androgen
  - Distinguish from hypertrichosis (generalised excessive hair in non-sexual areas and not due to excess androgen)
- Virilization
  - Severe hirsuitism associated with acne, irregular menses, signs of masculinization

Steroidogenesis



Manifestations of CAH



↓ Aldosterone → Salt wasting Hypovolaemia

↑ Androgens → Virilisation Precocious Puberty

↓ Cortisol → Hypotension Dizziness Fatigue

↓ Adrenaline → Hypoglycaemia Cardiovascular instability

Sources of serum androgens in women

- Testosterone
  - 25% ovarian, 25% adrenal
  - 50% from peripheral conversion of androstenedione
- Androstenedione
  - 50% ovarian, 50% adrenal
- Dehydroepiandrosterone (DHEA)
  - 90% adrenal, 10% ovarian
- Dehydroepiandrosterone sulfate (DHEA-S)
  - 100% adrenal

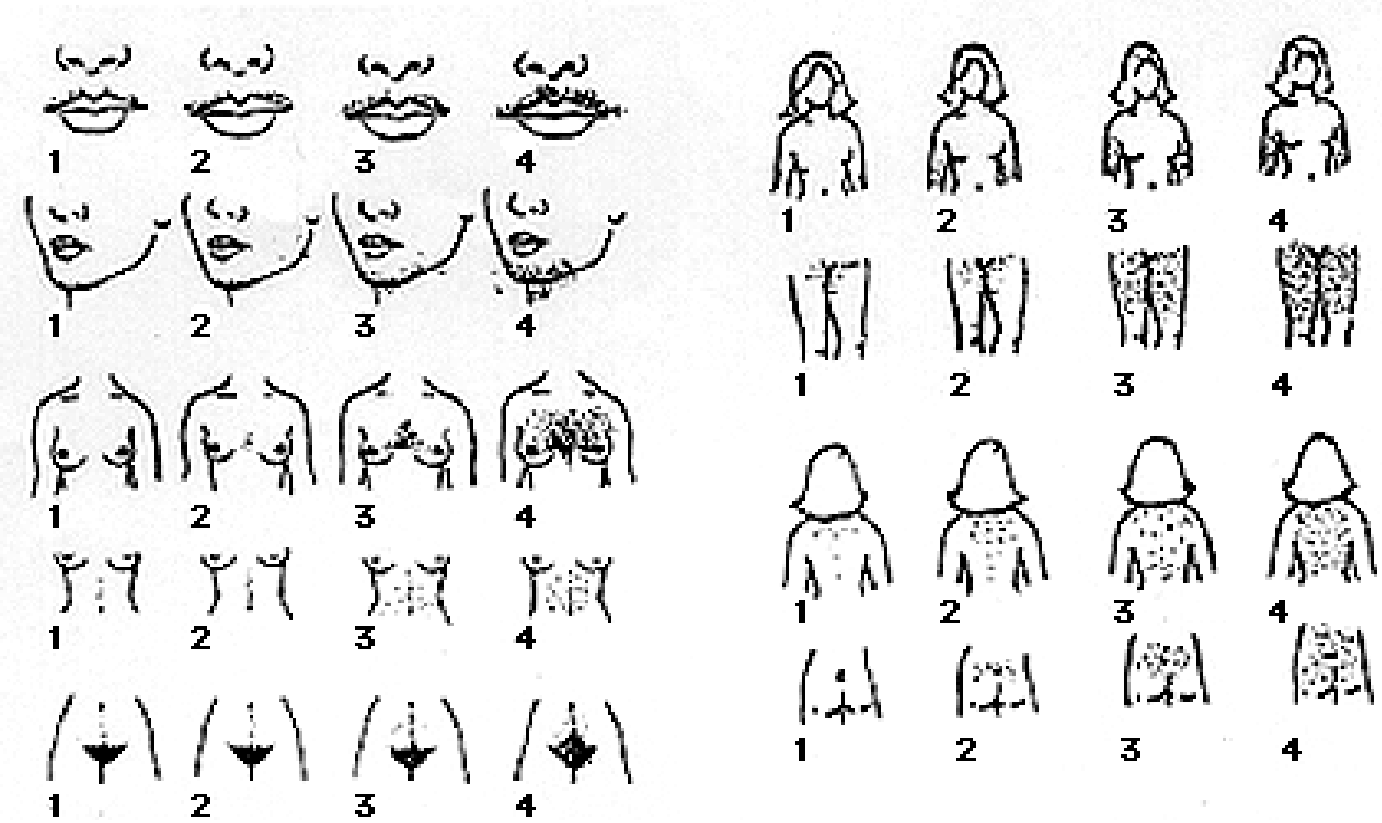
Hirsutism - Causes

- Over 50% of mild hirsuitism are not related to hyperandrogenism
- Look for causes due to hyperandrogenism
- Important causes :
  - Polycystic ovarian syndrome (PCOS)
  - Congenital adrenal hyperplasia (CAH) esp if FH+ or some ethnic groups
- Other causes
  - Medications (e.g. danazol, OCP with androgenic progestins)
  - Ovarian hyperthecosis (excessive insulin)
  - Cushing's syndrome
  - Ovarian tumours, adrenal tumours
  - Hypothyroidism
  - Prolactinoma

History taking

- Age of onset, progression, extent of growth
- Current measures of hair removal
- Age at menarche, regularity, fertility
- Change in libido, voice
- Family history of hirsutism
- Symptoms of Cushing's, prolactinoma, thyroid disease
- Medications

Ferriman-Gallwey score for hirsutism



Each of the nine body areas most sensitive to androgen is assigned a score 0 (no hair) to 4 (frankly virile) to give a total sum

8-15 mild hirsutism; >15 moderate hirsutism ; patient-important hursutism

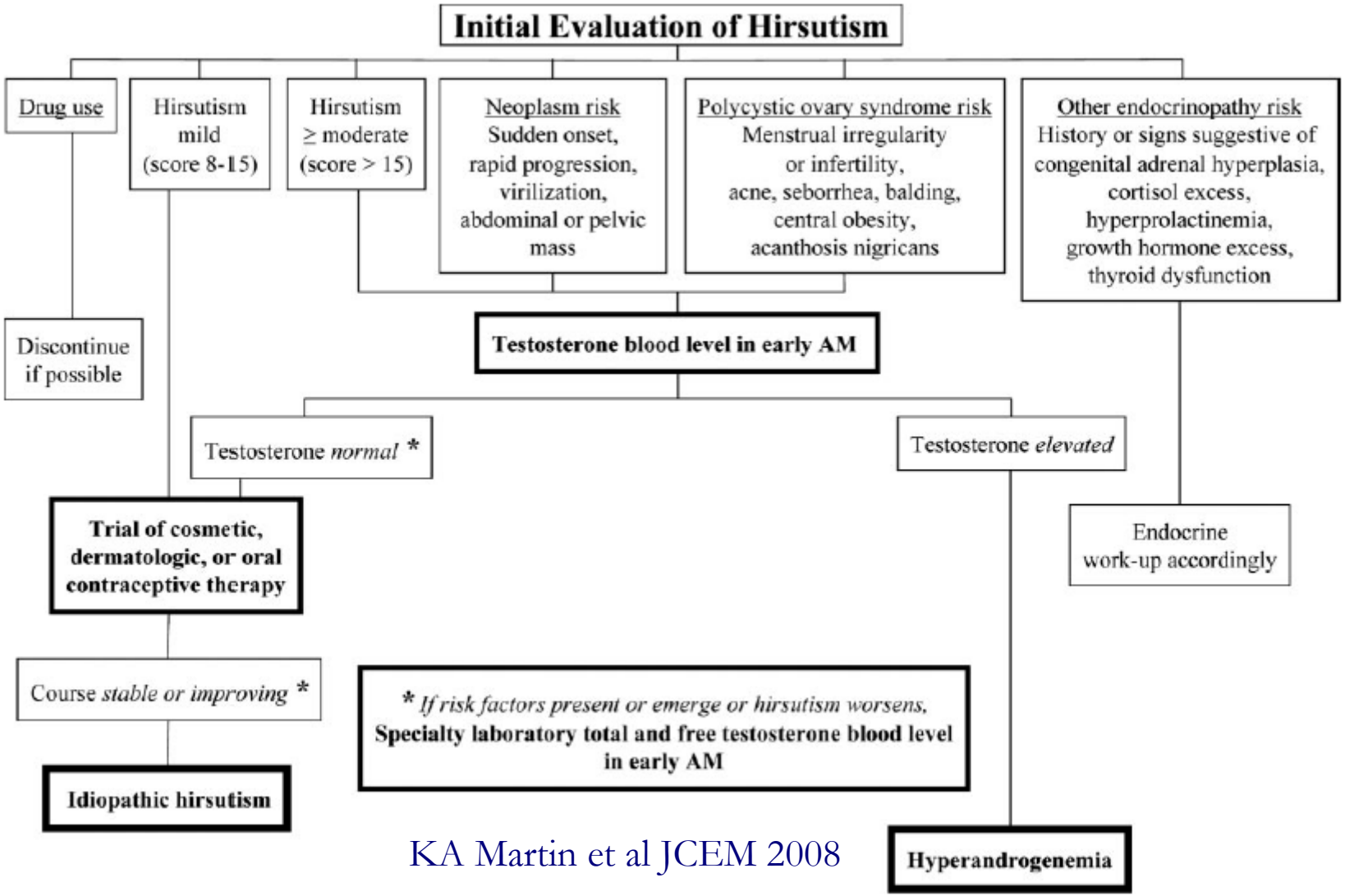
Physical Examination

- **Distribution and degree of hirsuitism**
- ↑muscle mass, temporal balding, clitoromegaly, acne
- Obesity
- Acanthosis nigricans
- Visual field defects
- Moon facies, plethora, features of Cushing's
- Galactorrhoea
- Goitre, loss of lateral eyebrows
- Abdominal or pelvic mass

Hyperandrogenism and hirsutism

- Moderate or severe hirsutism
- Hirsutism of any degree when it is sudden in onset, rapidly progressive, or when associated with any of the following:
  - Menstrual irregularity or infertility
  - Central obesity
  - Acanthosis nigricans
  - Rapid progression
  - Clitoromegaly
- Measure serum testosterone

Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline



KA Martin et al JCEM 2008

Investigations

- Testosterone
  - (SHBG, Free testosterone, DHEA-S)
- LH, FSH
- sTSH
- Prolactin
- Ultrasound scan ovaries/adrenals
- Fasting 17 OH progesterone
- Short synacthen test with 17OH progesterone at 60 mins

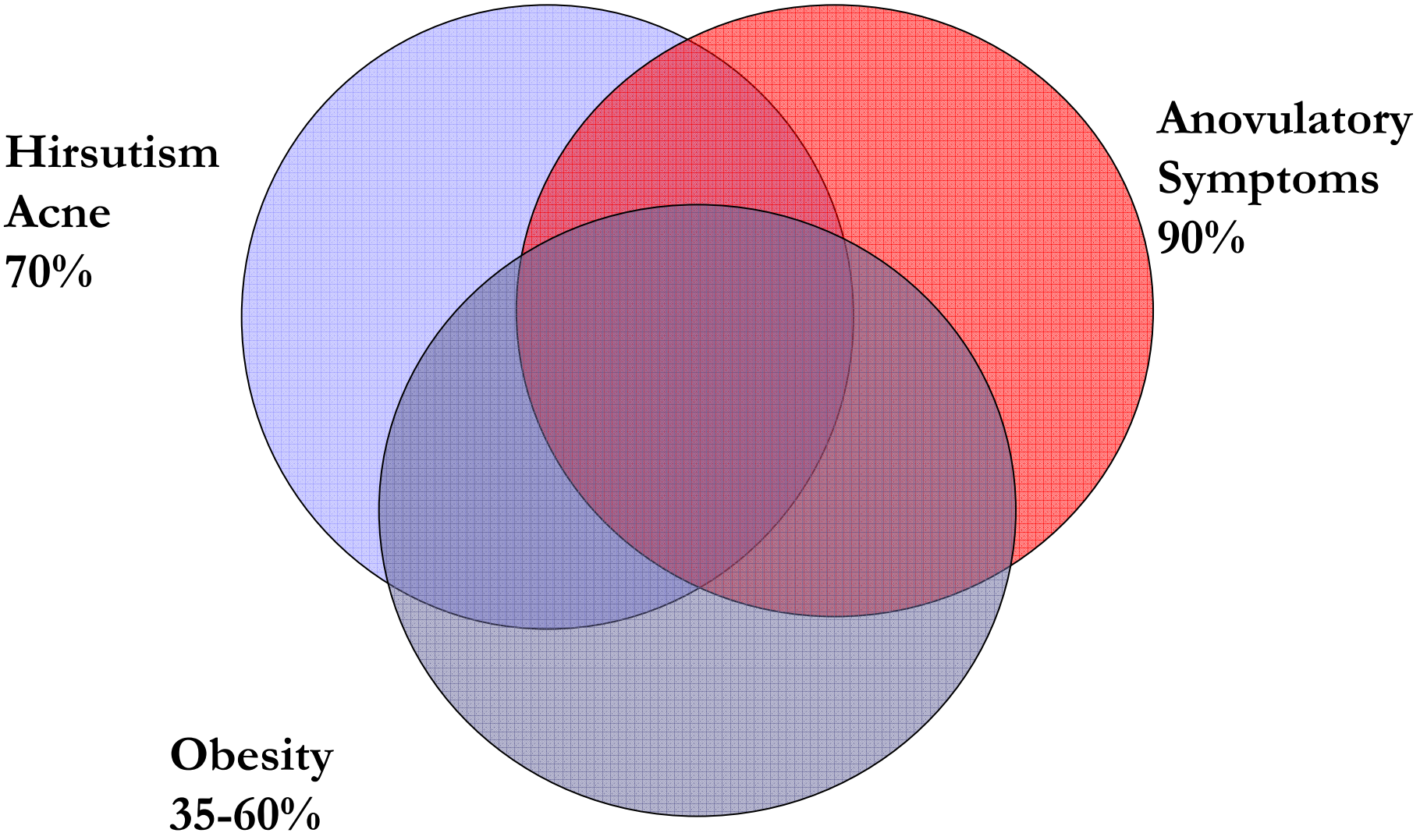
	Hirsutism	LH/FSH	Androgens	Others
PCOS	Onset puberty Progressive	↑ LH/FSH	↑ testosterone ↑ DHEAS (30%)	No virilization Normal 17OHP
Ovarian Hyperthecosis		Normal or low	↑ testosterone Androsten, DHT	Insulin resistant U/S scan appearance
NCCAH	Early onset		↑ testosterone ↑ DHEAS	↑ 17OHP Abnormal SST
Androgen tumours	Rapidly progressive		↑ testosterone ↑ ↑ DHEAS	Virilization
Idiopathic			Normal T, DHEAS	N 17 OHP

“diabetes des femmes a barbe”

Diabetes in a beard woman

Achard & Thiers, Bull Acad Natl Med 1921

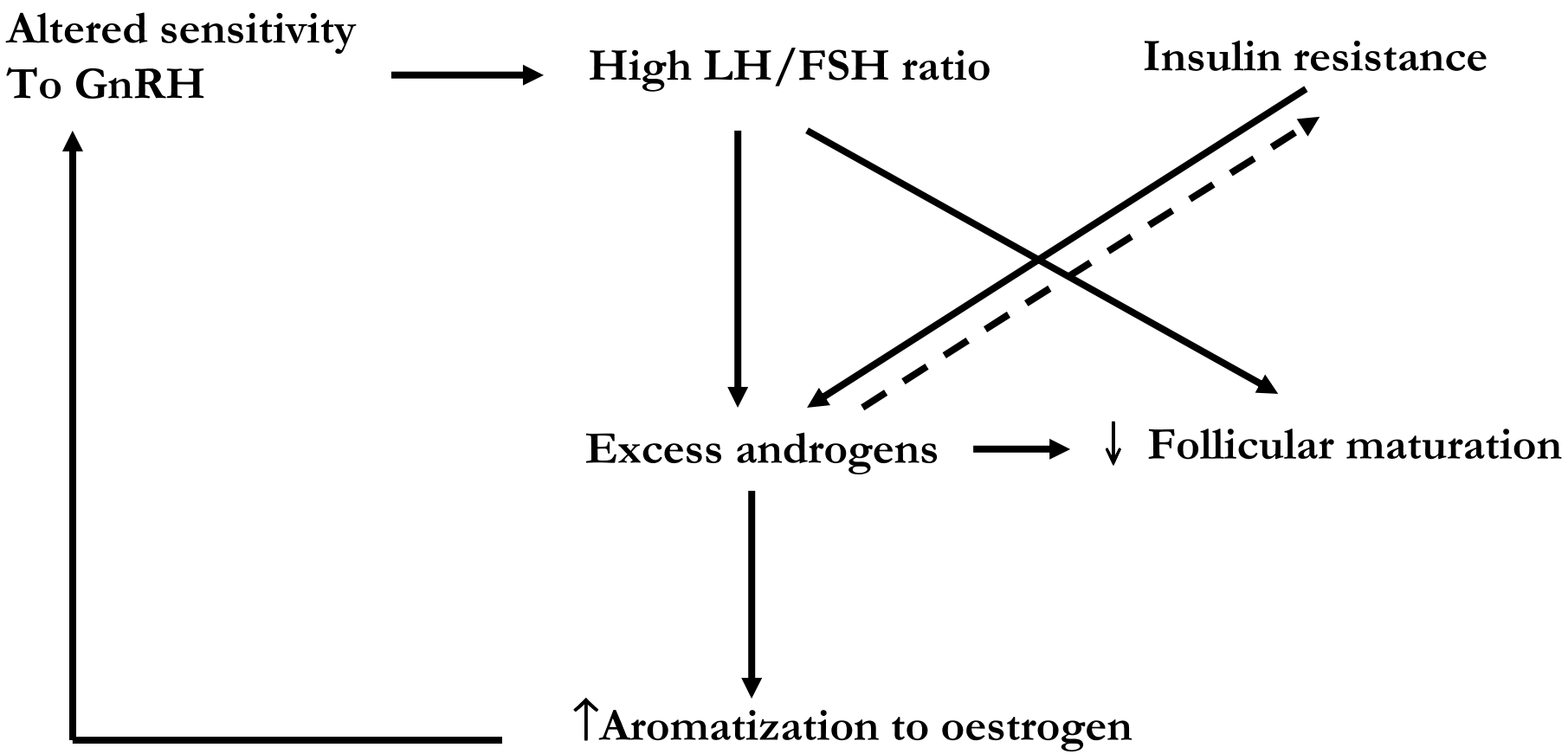
Polycystic Ovarian Syndrome (PCOS)



Polycystic Ovarian syndrome (PCOS)

- Common condition, affecting 6-10% women of reproductive age
- Presents with oligomenorrhoea, infertility, hirsutism
- Increased risk of diabetes, hypertension, CHD, endometrial carcinoma

Pathophysiology of PCOS

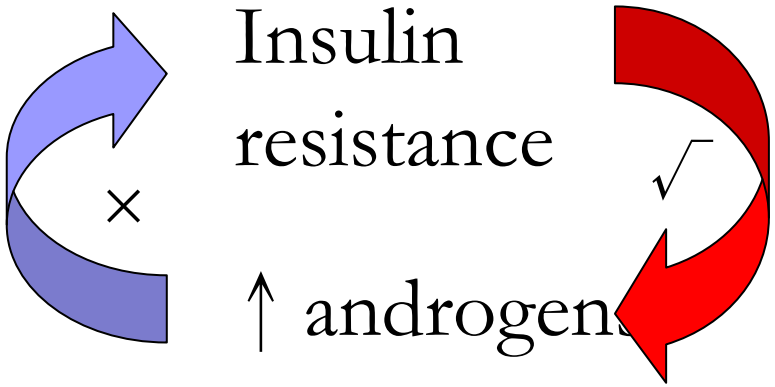


Insulin resistance and hyperandrogenism

1. Reducing androgens does not improve insulin resistance

2. Ovarian cautery, lowers androgen levels, no effect on Insulin resistance

3.Administration of androgens to oophorectomized women does not affect insulin levels



1. Reducing insulin levels (MF, glitazones Octreotide, diazoxide) Improves androgen levels

2. Hyperandrogenism present in states of extreme insulin resistance

3. Hyperinsulinaemia induced by valproate

Clinical features of PCOS

Hormonal profile	Hyper-androgenism	Reproductive Abnormalities	Metabolic disturbances
↑ LH/FSH	Acne	Irregular menses	Obesity
↑ Androgens	Hirsutism	Anovulation	Dysfibrinolysis
↓ E2	Seborrhoea	Infertility	Dyslipidaemia
PRL (↑)	Alopecia	Miscarriage	Diabetes
↓ SHBG	Acanthosis nigricans		Hypertension
↓ IGFBP-1		Preeclampsia	CVD
Hyperinsulinaemia			

Hyperandrogenism in PCOS

Acanthosis nigricans

Alopecia

Acne

Diagnostic Criteria for PCOS

NIH (1990) All 3 of	Rotterdam (2003) 2 out of 3	PWH >1 major, 1 minor
Chronic anovulation	Chronic anovulation	Chronic anovulation
Hyperandrogenism	Hyperandrogenism	Hyperandrogenism
	PCO on u/s	+/- ↑ LH
Exclude other causes	Exclude other causes	+/- PCO on u/s
		+/- IR/obesity

Polycystic ovary syndrome
Ovarian morphology on ultrasound

Overview of PCOS

- Diagnosis (PWH) - At least 2 of the criteria listed below including at least one of the major criteria
- Major criteria
  - Anovulation
  - Clinical signs of hyperandrogenism (hirsutism or acne) and/or hyperandrogenemia, with other causes of hyperandrogenemia excluded
- Minor criteria
  - Elevated early follicular phase LH (LH >10 IU/L)
  - Elevated LH/FSH ratio (>2.5)
  - Polycystic ovary on ultrasound scan
  - Obesity (BMI > 25) / Insulin resistance

Comparing PWH & Rotterdam criteria

PWH diagnostic criteria of PCOS	Proportion (%) of patients
Major criteria (with other endocrine causes excluded)	
Chronic anovulation	**89 / 90 (98.9%)**
Clinical or biochemical hyperandrogenism	**44 / 90 (48.9%)**
Minor criteria	
Increased serum concentration of LH	**61 / 90 (67.8%)**
Polycystic ovaries on ultrasound scan	**78 / 90 (86.7%)**
Obesity	**46 / 90 (51.1%)**
Insulin resistance *	**33 / 81 (40.7%)**

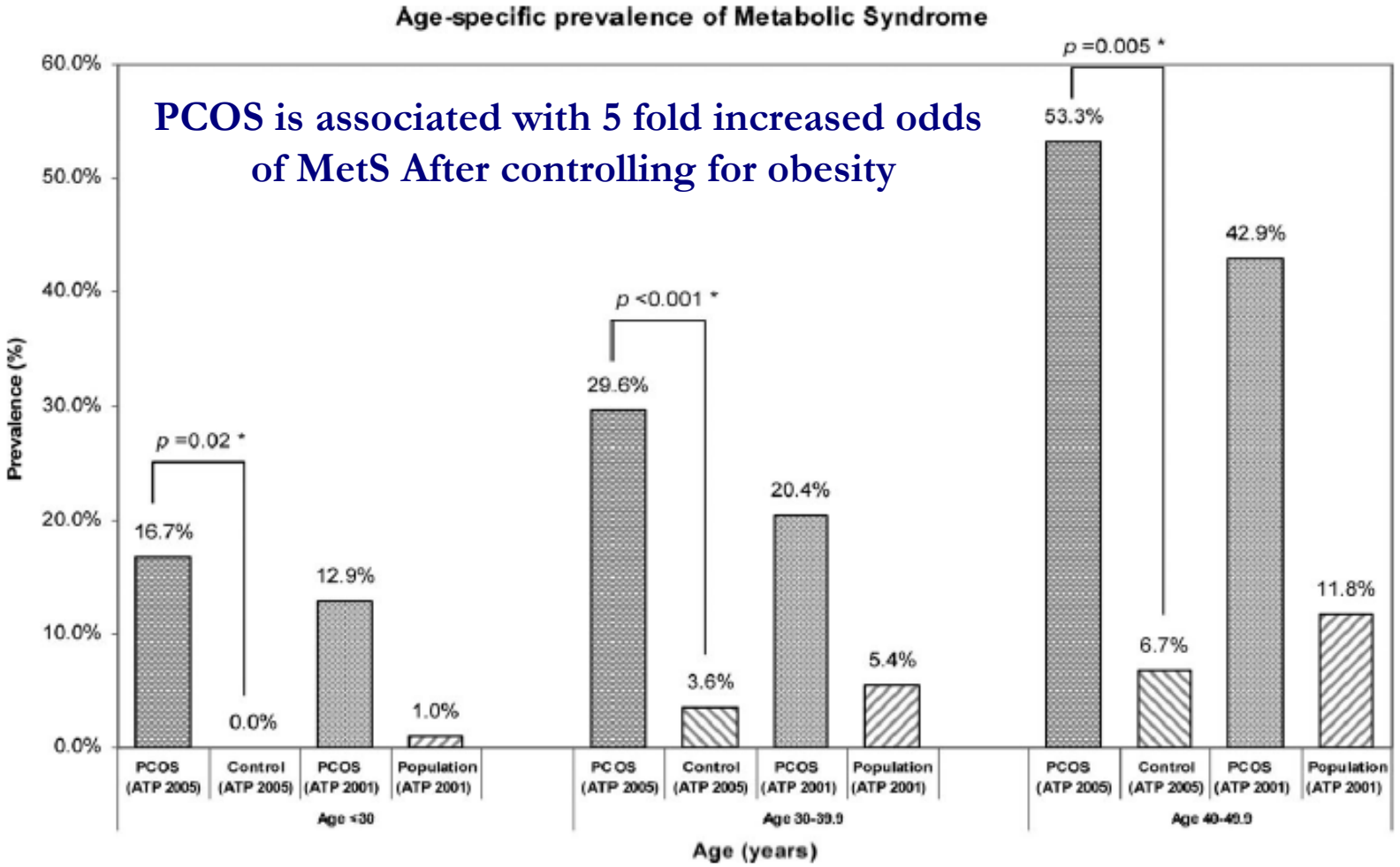
Lam E, Ma R et al, HKMJ 2005; 11: 336-41

PCOS and metabolic syndrome

- PCOS
  - ↑ BMI
  - ↑ Waist circumference
  - ↑ Hypertension
  - ↑ Total cholesterol
  - ↑ LDL-C
  - ↑ TG
  - ↓ HDL-C

Wild et al, J Clin Endocrinol Metab 1985; 61: 946
Wild et al, Am J Obstet Gynecol 1988; 159: 423-7
Slowinska-Szrednicka et al, J Endocrinol Invest 1991; 14: 569
Dahlgren et al, Acta Obstet Gynecol Scand 1992; 71: 599-604

Rates of MetS in 295 Chinese women with PCOS



Cheung L, Ma RCW et al Hum Rep 2008

Clinical approach to PCOS

- History of anovulation
  - Exclude pregnancy
  - Measure LH/FSH ratio
- Assess obesity
- Measure androgen especially if hursutism
- Perform U/S scan to detect an ovarian neoplasm or a polycystic ovary
- Other investigations to exclude other causes
  - Prolactin dehydroepiandrosterone sulfate (DHEAS)
  - early morning 17-hydroxyprogesterone to exclude late onset CAH positive FH or right ethnic group
  - Assessment for thyroid dysfunction or acromegaly
  - Exclude Cushing's syndrome if indicated
    - Overnight dexamethasone suppression test

Clinical approach to PCOS

- Exclude diabetes and MetS and manage accordingly
- Correct insulin resistance
  - usually weight reduction
  - Metformin
- Treat diabetes
- Correct menstural irregularity and infertility
- Drug or cosmetic treatment for hirsuitism

Current recommendations for 'patient-important' hursutism

- Cosmetic Rx followed by at least 6 months of drug Px before adding or switching Rx
- Suggestions
  - OCP in premenopausal women
  - OCP or anti-androgen (who choose not to conceive or postmenopausal)
- NOT recommended
  - flutamide therapy
  - topical antiandrogen
  - insulin-lowering drugs (e.g. TZD)
  - GnRH agonist
  - Corticosteroids (unless confirmed non-classical CAH)
- Combination therapy
  - OCP+anti-androgen after 6 months of monotherapy
  - with adequate contraception in premenopausal women

Cosmetic treatment

- Temporary hair removal
  - Epilation (Waxing/plucking to extract hair from above hair bulb)
  - Depilation method (shaving/chemicals to remove hair from skin surface)
  - Bleaching
- Permanent hair reduction
  - Photoepilation (Laser & IPL to reduce hair production)
  - Electrolysis (Passing electric current to destroy hair follicles
- Topical treatment
  - Eflornithine (an irreversible inhibitor of ornithine decarboxylase, an enzyme that catalyzes the rate-limiting step for follicular polyamine synthesis necessary for hair growth)
- Side effects
  - Scarring, local irritation, folliculitis, allergic reactions, pain, depigmentation, costs

Estrogen (Oral contraceptive pills)

- Mechanisms
  - ↓LH
  - ↑SHBG and free androgen
  - ↓binding to androgen receptor
  - ↓ adrenal androgen production
- Side effects
  - ↑ IR, TG and BG in some women
  - ↑ risk of DVT especially in smokers

Anti-androgens

- Spironolactone
  - an aldosterone antagonist, ↓ androgen receptor and 5α-reductase activity
  - Dizziness and hyperkalaemia
- CPA (cyproterone acetate)
  - progestogenic compound, ↓ androgen receptor, 5 α -reductase activity, GnRH & androgen
  - Weight change, breast tenderness, depression
- Drospirenone
  - a progestin in several OCPs with weak antiandrogen effects
- Finasteride
  - inhibits type 2 5α -reductase activity
  - sexual dysfunction
- Flutamide
  - a pure antiandrogen with a dose-response inhibition of androgen receptor
  - Liver toxicity, PR bleeding, diarrhoea
- Anti-androgen cream
  - Weak actions (skin redness and irritation)

Other drugs

- Insulin lowering
  - Metformin
    - ↓hepatic glucose production
    - ↓IR ↓insulin ↓ovarian hyperthecosis, ↓androgen
  - TZD
    - Increase preadipocyte differentiation, ↓FFA, ↓IR
    - Weight gain, fluid retention and risk of HF
- Glucocorticoids
  - ↓ suppress adrenal androgens in women with CAH hyperplasia due to 21α hydroxylase deficiency (CYP21A2)
  - ↓hirsutism and maintain normal ovulatory cycles
- GnRH agonist
  - Chronic agonism of GnRH may ↓LH/FSH, ↓ovarian androgen production.

Case 1

- P/E
  - Overweight
  - Acanthosis nigricans over neck
  - Hirsutism over face, abdomen and perineal region
- Investigations
  - TFT/prolactin normal
  - O/N dexamethasone suppression test normal
  - Abdo u/s scan
    - normal ovaries
  - LH:FSH ratio >3

Diagnosis: PCOS

Case 2

- 27F
- Single
- Type 2 DM on OAD
- Oligomenorrhoea
- Menarche aged 12, then only 2-3 times per year
- Took OCP for 1 year aged 16, then stopped
- FH+ for DM and HT

Case 2

- P/E
  - Overweight
  - BMI 32 kg/m^2
  - BP 130/88
  - Acanthosis nigricans
  - Mild hirsuitism

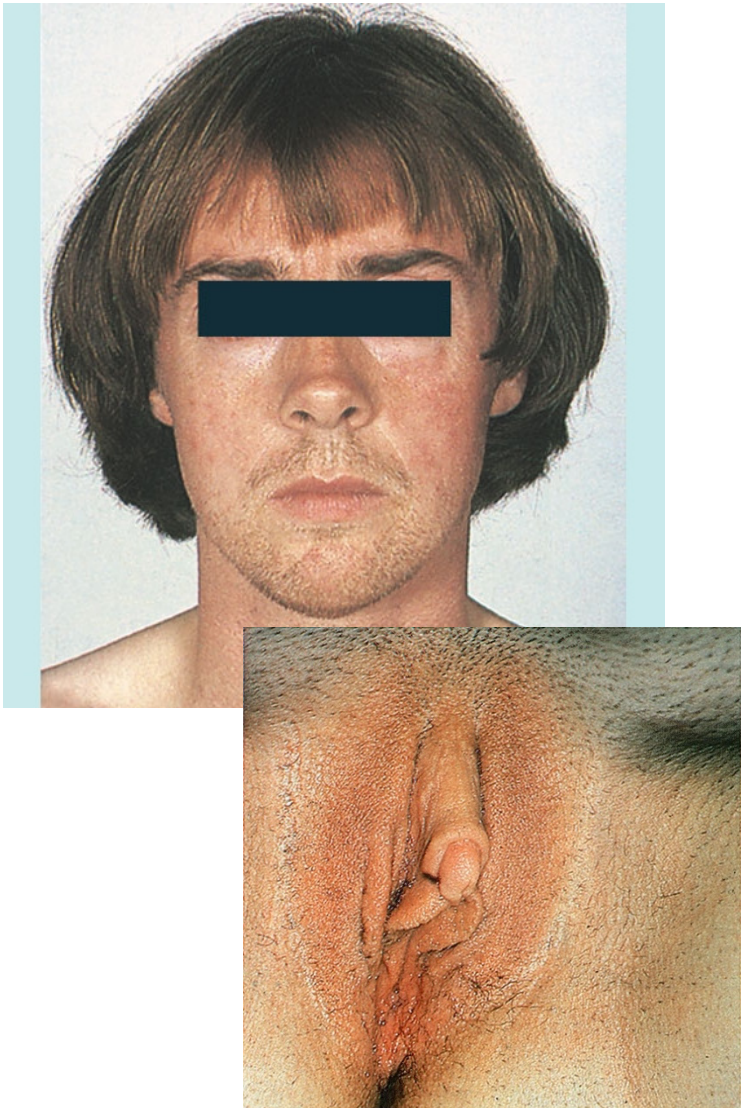
Diagnosis: PCOS

- Investigations
  - TFT normal
  - LH 3.5 IU/L
  - FSH 3.9 IU/L
  - Testosterone 3.2 nmol/l (normal <2.9)
  - DHEA-S normal
  - Prolactin normal
- Ultrasound scan ovaries
  - Multiple ovarian cysts

Case 3

- Prolactin normal
- Testosterone 3 nmol/l (normal <2.9)
- Laparoscopy
  - polycystic ovaries
- Semen analysis of partner normal
- Post-coital bleeding
- D/C - endometrial carcinoma

Case 4



- 22F
- Hirsutism since puberty, worsened in adolescence
- Menarche aged 12, irregular all along
- Requires shaving every 2 days
- Facial treatment every 2 weeks
- No hoarse voice
- Physical examination
  - marked virilism
  - enlarged clitoris
- Testosterone /DHEA-S↑ ↑ ↑
- Ultrasound scan: ovarian tumor

Take home messages

- Confirm hyperandrogenism if rapid onset or moderate hursutism
- Exclude
  - PCOS and CAH and treat accordingly
  - hyperprolactinemia and endocrinopathies
- Start with cosmetic Px followed by monotherapy of OCP or anti-androgen in patient- important hursutism
- Consider combination Rx (OCP+anti-androgen) after 6 months with adequate contraception
- Flutamide, GnRH, insulin lowering drugs not recommended
- Corticosteroid only if confirmed NCCAH

Reference:

KA Martin et al, Martin Recommended Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline Journal Clinical Endocrinology Metabolism 2008