Hyperandrogenism in women: Diagnosis and management

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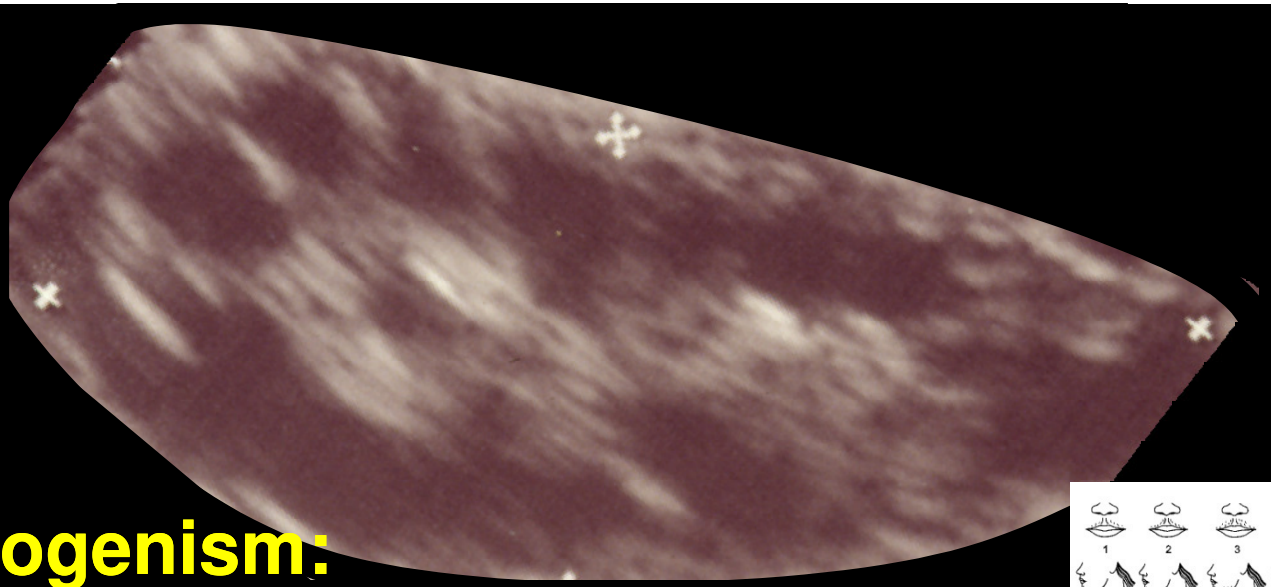
ESHRE Campus "Old and New Hormones"
Budapest 2009

Learning Objectives

1. Hyperandrogenism and new definitions of the polycystic ovary syndrome
2. Pathophysiology, genetics and ethnic variations
3. Approaches to management of HA

Causes of androgen excess

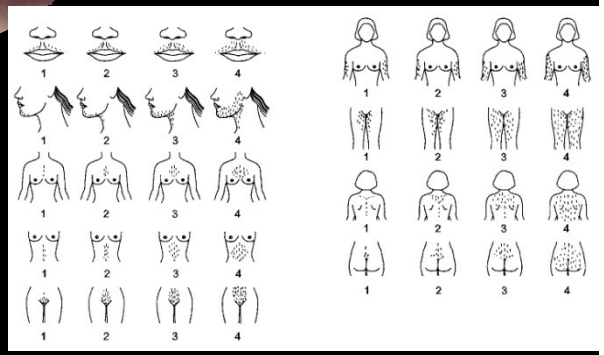
- PCOS
- Late onset congenital adrenal hyperplasia
- Androgen secreting tumours
- Cushing's syndrome



Hyperandrogenism:

Hirsutism: Subjective (patient and physician)
Quantify Ferriman Gallwey Score

Ethnic variations



Alopecia: Androgen mediated / iron deficiency

Acne…

54% of women over 25y have physiological acne

3% clinical acne

Correlates variably with hyperandrogenemia

Hirsutism – distribution varies,

F&G score – still subjective and observer variability
- not standardised

All symptoms and effect on QoL amplified by obesity and each other

Biochemistry of Hyperandrogenism

- Testosterone : free or total ? (< 5nmol/l)
- SHBG - surrogate for insulin resistance
- Free Androgen Index (T/SHBG)x100
- Androstenedione, DHEAS, 17-OH P …. ?

Kane et al, Ann Clin Biochem 2007; 44: 5-15
Barth & Balen, Clin Endocrinol 2007; 67: 811

Controversies

- How to assess HA biochemically?
  Mass spectrometry superior to immunoassays
- Variations:
  Diurnal (am > pm),
  Cyclical (luteal > follicular)
  Seasonal (summer > winter)
- Age-related changes
- Ethnic differences

The Rotterdam ESHRE/ASRM Consensus Group Revised 2003 Diagnostic Criteria for PCOS

2 out of 3 criteria required

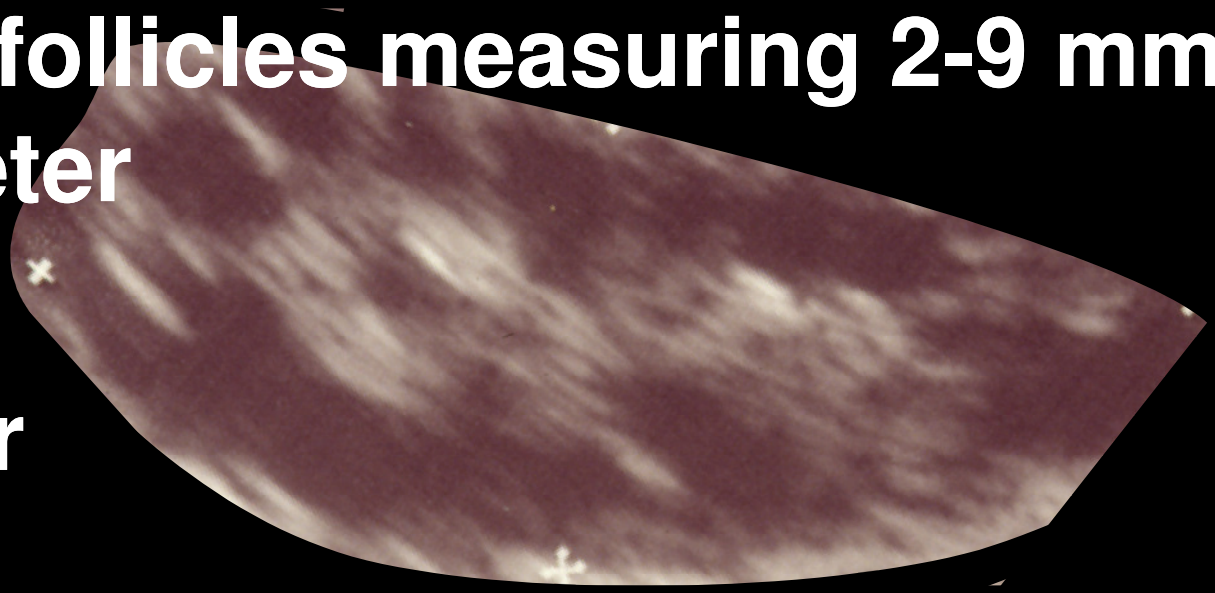
- **Oligo- and/or anovulation**
  i.e. oligomenorrhoea or amenorrhoea
- **Hyperandrogenism**
  - clinical and/or biochemical
- **Polycystic ovaries**

Exclusion of other aetiologies

Human Reproduction 2004; 19: 41-47. Fertility & Sterility, 2004; 81: 19-25.

Ultrasound Assessment of the Polycystic Ovary: International Consensus Definitions

The polycystic ovary contains 12 or more follicles measuring 2-9 mm in diameter



and/or

increased ovarian volume (>10 cm^3)

Balen, Laven, Tan & Dewailly; Hum Reprod Update 2003
ESHRE/ASRM Consensus 2003

Polycystic Ovary Syndrome: Investigations

1. Androgen profile:
   Testosterone
   (SHBG,
   17OH-P, adrenal profile)
2. FSH, LH, ± oestradiol, AMH?
3. Prolactin / TFTs
4. Ultrasound scan

5. Assessment glucose tolerance / insulin resistance: GTT, lipid profile

Testosterone / DHEAS

- ↑ DHEA in brothers of women with PCOS
- Tight feedback of T in men, via ACTH, but not DHEA
- Neither T nor DHEA regulated by feedback in women

Oligomenorrhoea:	> 90% PCOS
Amenorrhoea:	~ 30 – 50% PCOS
Anovulatory infertility:	> 90% PCOS
Acne in women:	> 95% PCOS
Hirsutism:	> 95% PCOS

Female caucasian population:	20 – 33% PCO
	15 – 25% PCOS
U.K. South Asian population:	50% PCOS

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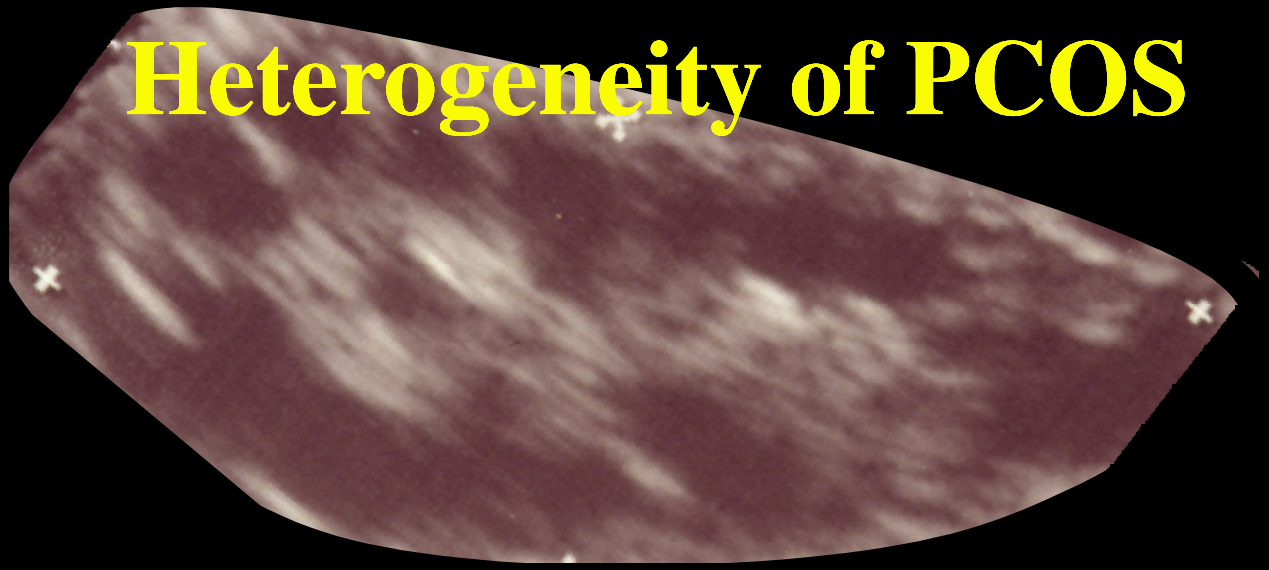
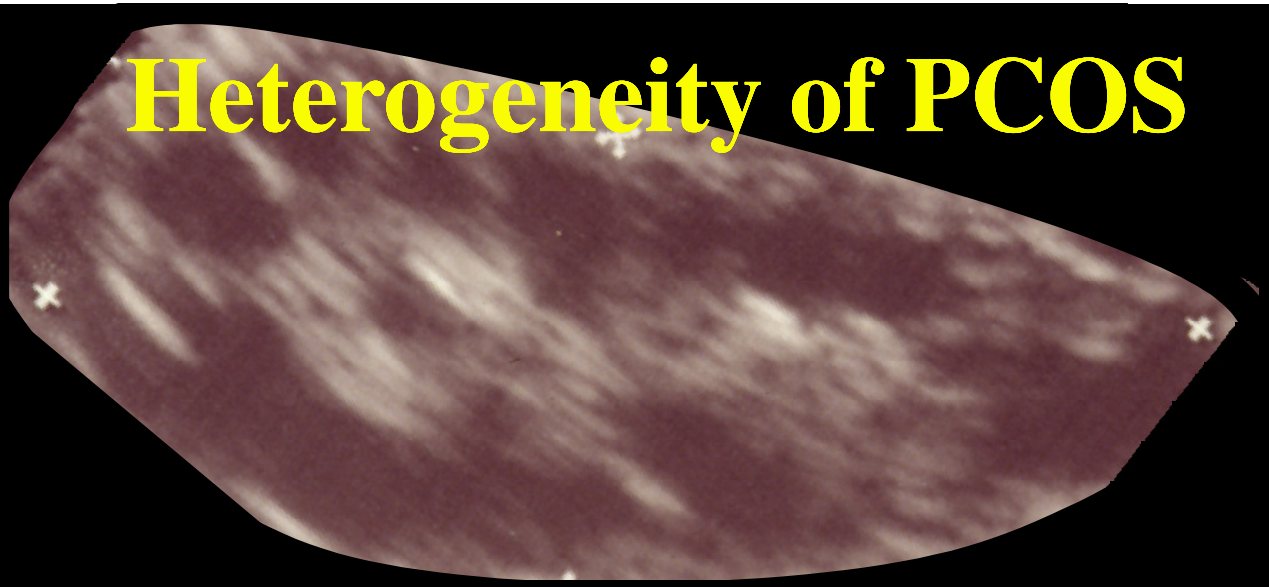
Heterogeneity of PCOS



Hyperandrogenism
Menstrual disturbances

↑ testosterone
↑ luteinising hormone

Heterogeneity of PCOS



Hyperandrogenism
Menstrual disturbances

↑ testosterone
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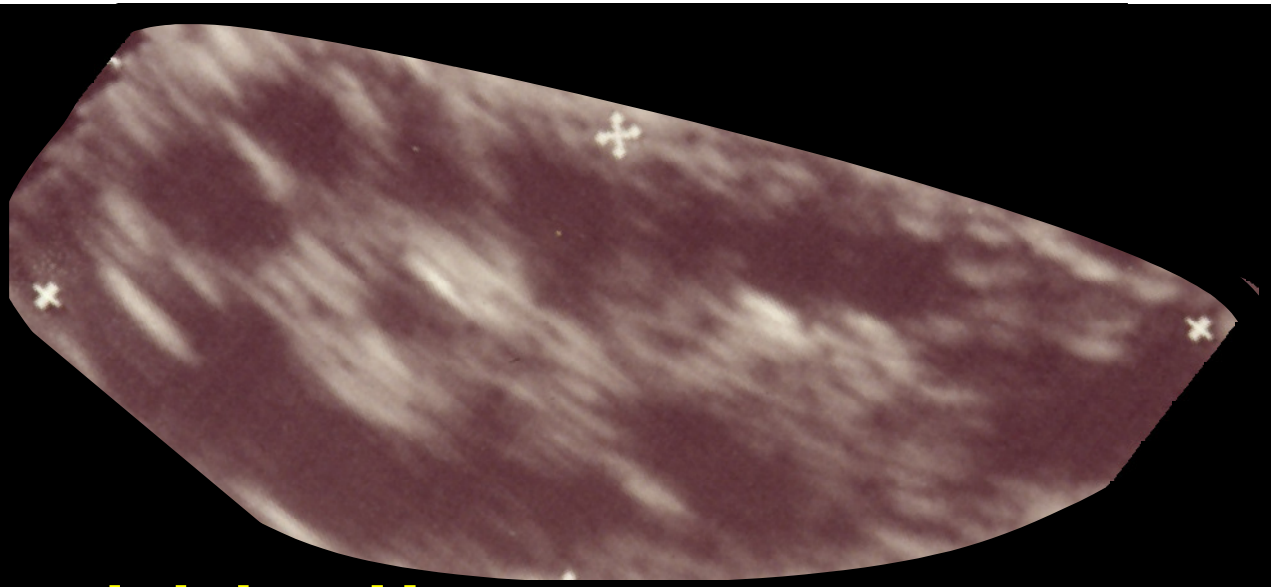
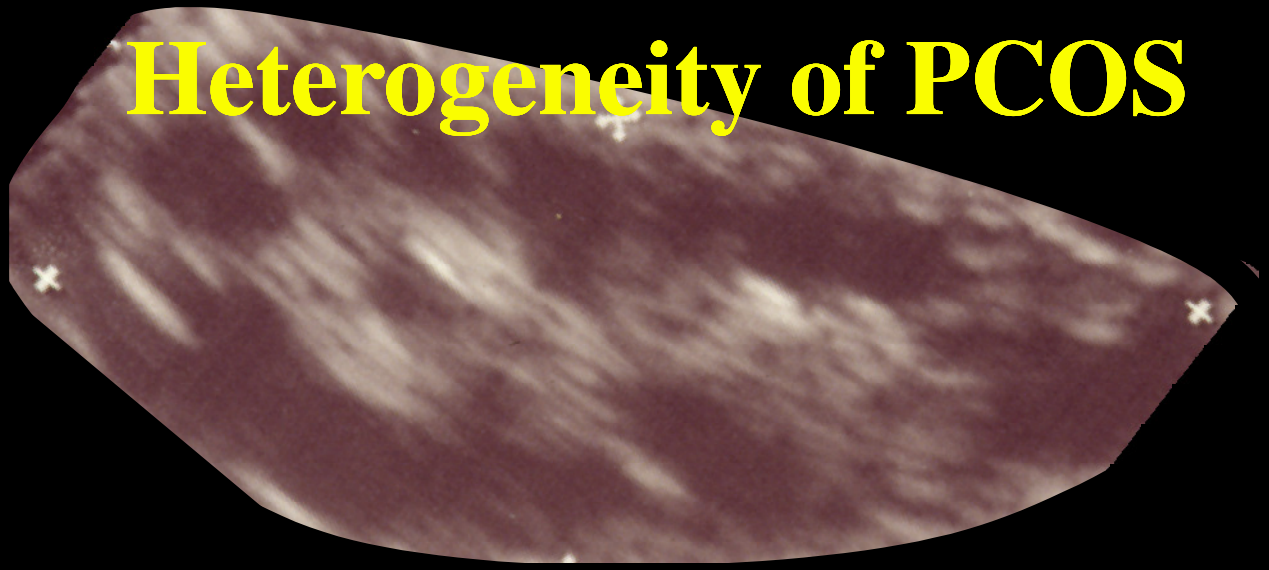


Elevated Luteinising Hormone:

- not mandatory for diagnosis, elevated in 40%
- most likely to be elevated in slim women
- may help predict outcome of fertility therapy:
    - Worse outcome after CC if elevated day 8
    - Better prognosis for response to ovarian drilling

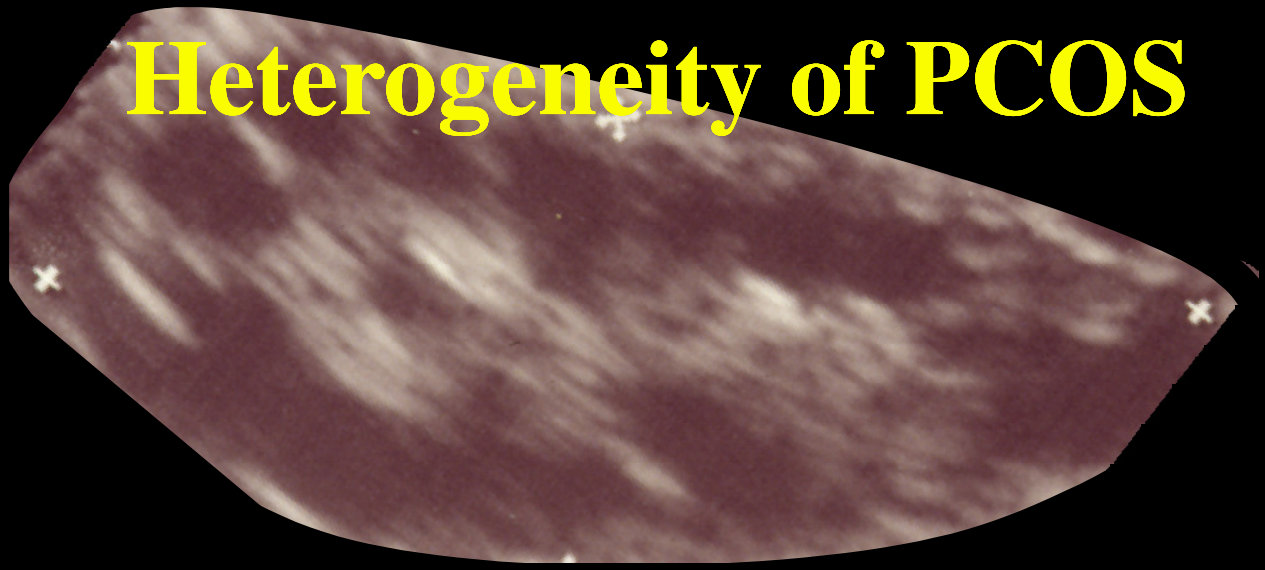
Heterogeneity of PCOS



Hyperandrogenism
Menstrual disturbances

↑ testosterone
↑ luteinising hormone
↑ insulin

Heterogeneity of PCOS



Hyperandrogenism
Menstrual disturbances

↑ testosterone, ↓ SHBG
↑ luteinising hormone
↑ insulin

Insulin Resistance and PCOS

- Failure of insulin action at receptor
- Selective insulin resistance:

  Glucose uptake by cells impaired

  Trophic actions of insulin continue

  Insulin augments LH $\rightarrow \uparrow$ testosterone

“Compensated” insulin resistance with normal glucose tolerance

Impaired glucose tolerance (IGT)

Type 2 Diabetes

Volunteer Study of Women's Health

224 female volunteers, 17-25y

- 33% polycystic ovaries
- 80% with polycystic ovaries had a least one feature of PCOS

Michelmore et al, Clin Endocrinol 1999; 51: 779

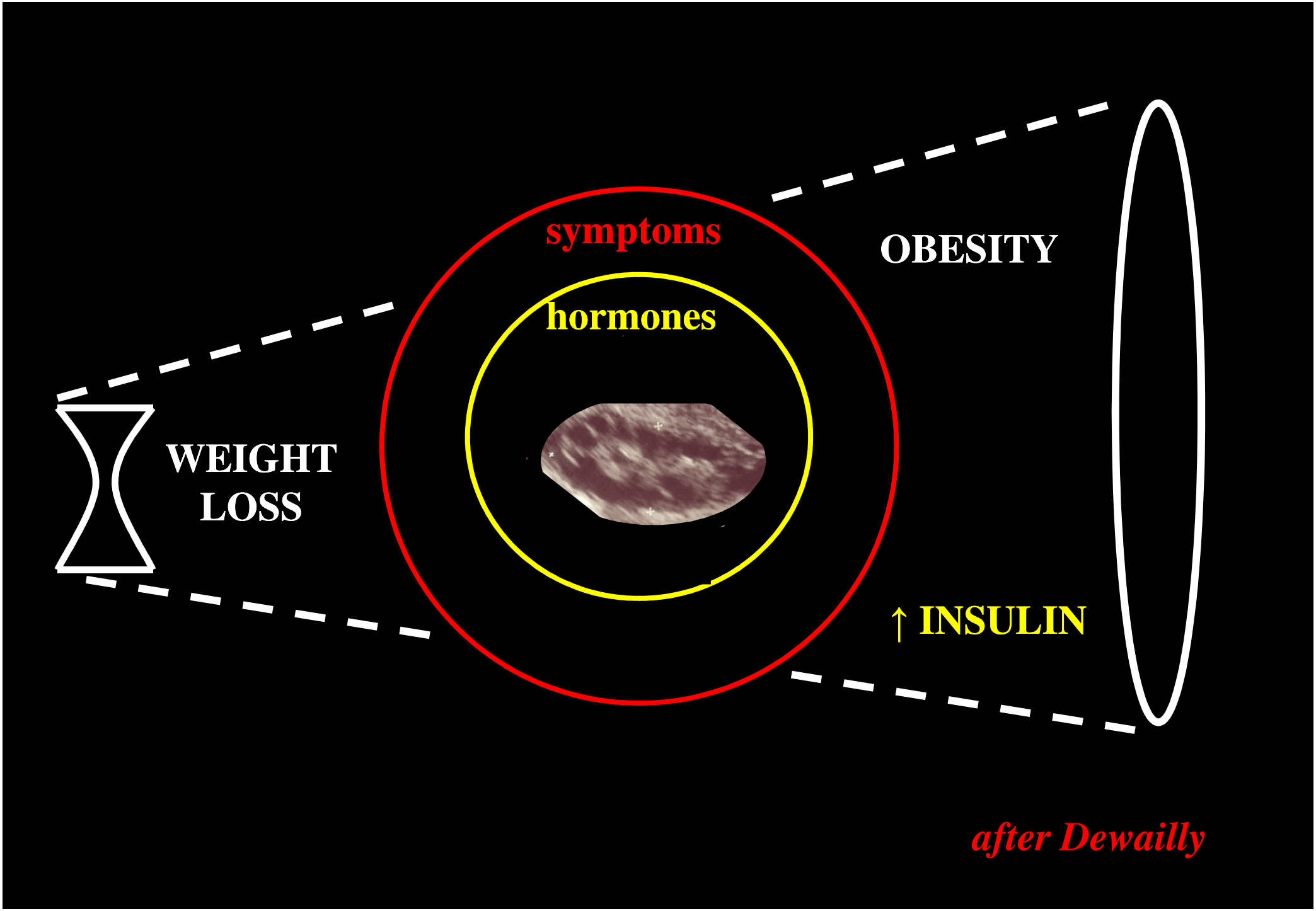
224 women 17-25y, 33% polycystic ovaries

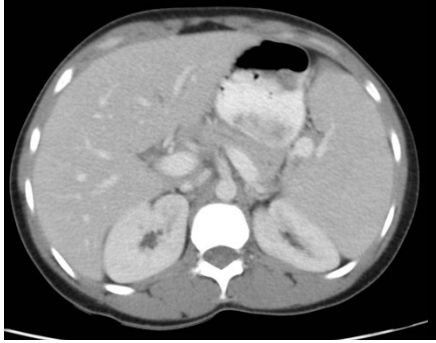
	PCO	Normal ovaries	P
BMI kg/m^2	23.3	23.1	n.s.
% body fat	30.4	29.4	0.048
Birthweight kg	3.49	3.28	0.004
Testo. nmol/l	2.67	2.47	0.03

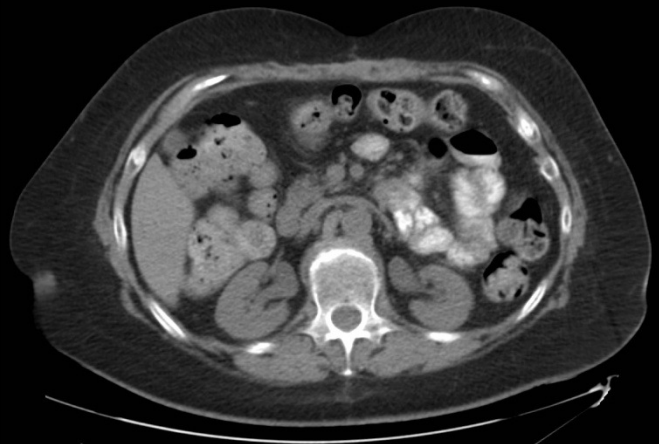
Differences between women with polycystic ovaries only and with polycystic ovary *syndrome*?

The presence of pco represents a milder end of the PCOS spectrum

Balen, Homburg, Franks, BMJ 2009


symptoms
hormones
OBESITY
WEIGHT
LOSS
↑ INSULIN
after Dewailly





The Genetics of PCOS

- Probably a complex genetic trait disorder
- Different combinations of genetic variants influence differential expression of the syndrome
- Multi-factorial - e.g. environmental influences:
  - in-utero programming of
    - hypothalamus
    - insulin homeostasis
  - lifestyle: diet / exercise

PCOS in South Asians and Caucasians living in the U.K.

Case control study of anovulatory PCOS:

47 South Asian PCOS and 11 controls

40 Caucasian PCOS and 22 controls

Wijeyaratne et al, Clin Endocrinol 2002; 57: 243

S. Asians had significantly:

↓ age onset hirsutism	p < 0.01
↑ hirsutism, acne & acanthosis nigricans	p < 0.001
similar BMI & W:H	
similar total Testosterone	
↑ insulin and ↓ SHBG	p < 0.001

Wijeyaratne et al, Clin Endocrinol 2002; 57: 243
Wijeyeratne et al, Clin Endocrinol 2004; 60: 560
Palep-Singh et al. J Reprod Med 2008; 53:117

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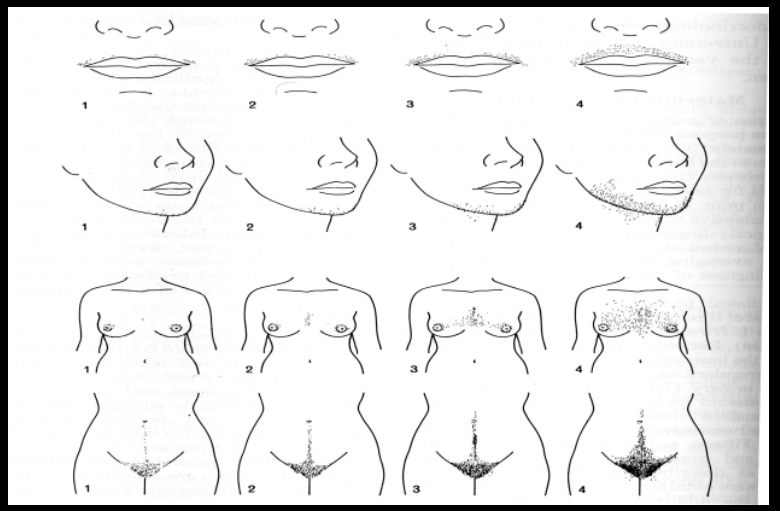
Hyperandrogenism:

Alopecia:

Hirsutism: subjective
Ferriman Gallwey Score



Acne:

Hyperandrogenism

- Acne
- Hirsutism
- Alopecia

Negative impact on self esteem, social interaction,
Ability to achieve at work

Combined with menstrual/fertility problems
- negative feelings about feminity

The PCOS Health-Related Quality of Life Questionnaire (PCOSQ)

Women and adolescents with PCOS

Worst health concerns:

- weight
- infertility
- emotional limitations and poor energy
- hirsutism

Jones *et al,* Human Reprod 2004; 2007;
Hall *et al,* ESHRE 2007
Jones *et al,* Hum Reprod Update 2008; 14:15

Acne

Androgens

Seborrhoea

Comedone formation

Changes in ductal micro environment

P-*acne* (ductal) colonisation

Inflammation

Acne in PCOS

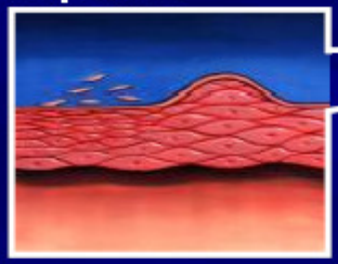
- Seborrhoea
  - an indicator of poor response to antibiotics
- Persistent
- Refractory to therapy
- Later onset
- Associated with
  - Irregular menses
  - Hirsutism
  - Obesity
  - Androgenic alopecia

Acanthosis Nigricans HAIRAN

- Mucocutaneous eruption
  - Axillae, flexures, nape of the neck
  - Increased pigmentation and papillomatosis
- Cutaneous marker associated with insulin resistance and compensatory increased secretion
- May present more commonly in adolescents with PCOS – incidence 1-3%

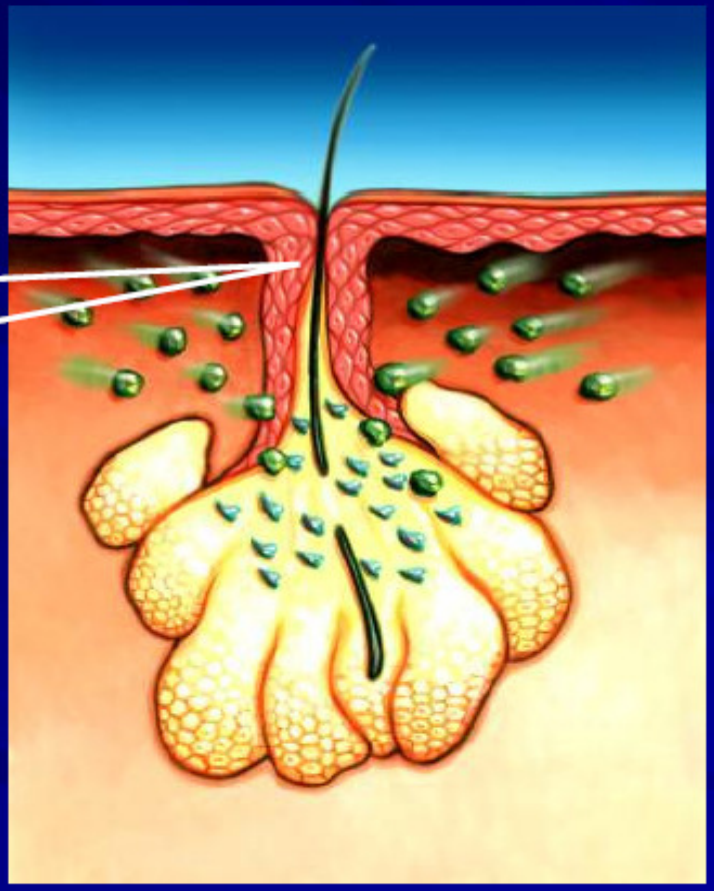
Actions of Anti-Acne Therapies

Topical retinoids:
- ✓ Normalise desquamation
- ✓ Reduce inflammatory response



Antibiotics:
- ✓ Reduce micro organisms
- ✓ Reduce inflammatory response

Benzoyl peroxide:
- ✓ Kills microorganisms



Oral Isotretinoin:
- ✓ Reduces sebum
- ✓ Normalise desquamation
- ✓ Inhibits *P acnes* growth
- ✓ Reduces inflammatory response

Hormones:
- ✓ Reduce sebum production
- ✓ Normalise desquamation

Anti-Acne Therapies

Hormones reduce sebum production

Antibiotics reduce inflammation and micro-organisms

Topical benzoyl peroxide kills micro-organisms

Topical retinoids reduce inflammation

Hirsutism

1-2% adult female population have severe hirsutism

80% of women in UK concerned about unwanted hair

Definition:

Excessive facial and / or body terminal hairs in a male pattern distribution

Results from excess androgen and the sensitivity of hair follicle to androgen

The impact of androgens on body hair

Vellus hair develops into terminal hair (secondary sexual hair)

Starts at puberty (adrenarche)

Occurs over several hair cycles

Irreversible
– treatments aim to destroy the stem cell population in hair follicles or to suppress androgen production

The impact of androgens on scalp hair

Androgenic alopecia: progressive loss of terminal scalp hair in genetically susceptible women

Diffuse diminishing hair diameter, length and density

Pattern may embrace progressive thinning over the crown (Ludwig pattern) with preservation of hairline, or male-pattern with bitemporal recession

Management of Hyperandrogenism

Weight loss

Physical removal: electrolysis, laser therapy
shaving, depilatory creams

Eflornithine carboxylase

Anti-androgen medication: COCP
EE2 / cyproterone acetate
EE2 / drospirenone
Spironolactone
Flutamide, finasteride

Metformin

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Metformin

Management of Hyperandrogenism

Weight loss

Physical removal: electrolysis, laser therapy
shaving, depilatory creams
threading, plucking, epilators
bleaching,
camouflage, hairstyling
wigs

Electrolysis / Electrical depilation

Only permanent method, may take 24 months

Galvanic depilation: needle inserted into hair follicle and direct current applied which causes chemical reaction with salts in the tissue and destroys follicle

Diathermic method: uses alternating current to induce heat reaction which coagulates hair follicle
(quicker but more regrowth)

www.electrolysis-bae-ltd.co.uk

Laser

Laser light (694-1064 nm) passes through skin
absorbed by melanin in the follicle,
converted to heat energy to destroy follicle

Target stem cell population where pigmented cells are populated

Most effective in anagen phase of hair growth

Complete hair loss rarely achieved

Laser

Ideal patient fair skin and dark hair

Dark skin: risk of epidermal damage, pigmentary change, scarring and more pain

RCT in 88 women with PCOS reported reduced facial hair, anxiety and depression after 6m

Clayton et al Br J Dermatol 2005; 152:986-992

Management of Hyperandrogenism

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Eflornithine

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EE2 / cyproterone acetate
EE2 / drospirenone
Spironolactone
Flutamide, finasteride

Metformin

Eflornithine HCl 11.5% cream (Vaniqa)

Irreversible inhibitor of ornithine decarboxylase, the rate limiting step in production of polyamines

Expressed in proliferating bulb cells of anagen hair follicles

Applied twice daily

Eflornithine

70% respond

Reduces visibility and coarseness

Eflornithine 11.5% cream

2 RCTs, published jointly
596 women (395 eflornithine vs 201 vehicle)
24 weeks

Significant improvement by 4-8 weeks

Overall success 33% vs 9%
(clear or almost clear of visible terminal hair)

Less effective in non-white women 22% vs 37%
Less effective in overweight

Wolfe et al Int J Dermatol 2007; 46:94

Management of Hyperandrogenism

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Metformin

Principles of hormone treatment

- Suppress adrenal & ovarian androgen production
- Increase binding of androgens to SHBG
- Impair peripheral conversion of precursors to active androgens
- Inhibit action of androgens at target tissue

Dianette EE2 35mcg + CPA 2mg

69.4% resolution in 140 women with PCOS for 60 cycles

Response takes 6-9 months

Check LFTS as rarely leads to liver damage

van der Spuy, Cochrane review 2003; 4:CD001125

Dianette (D) vs D+20mg CPA vs D+100mg CPA

CPA given days 1-10

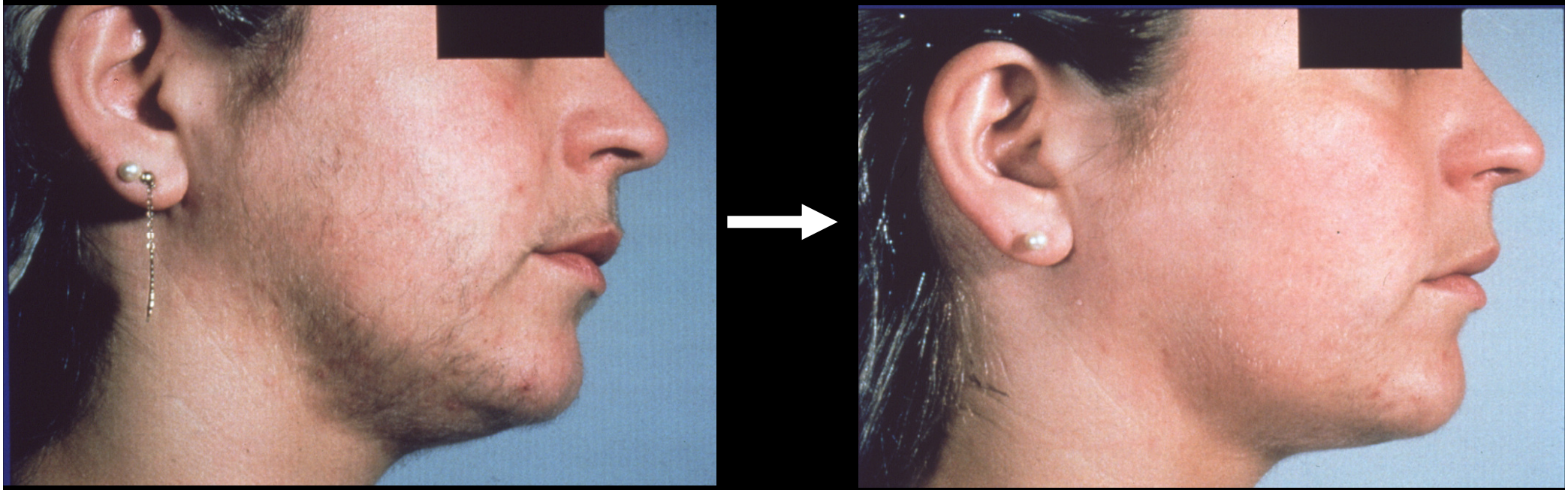
Significant fall in clinical hair growth scores
and hair diameter (face and body)

No significant differences between doses at 6 months

Trend towards a dose response

Barth et al Clin Endo 1991; 35:5

Hyperandrogenism



Yasmin (EE2 30 mcg + drospirenone 3mg)

Well tolerated

Significant fall in clinical hair growth scores by 67% at 6m and 78% at 12m

Batuka et al F & S 2006
Palep-Singh et al Br J Fam Plan 2004

Management of Hyperandrogenism

Weight loss

Physical removal: electrolysis, laser therapy
shaving, depilatory creams

Eflornithine carboxylase

Anti-androgen medication: COCP
EE2 / cyproterone acetate
EE2 / drospirenone
Spironolactone
Flutamide, finasteride

Metformin

Spironolactone vs Placebo

2 trials assessing hirsutism

F-G fell: WMD 7.20, 95% CI -10.98 - -3.42

Subjective improvement: OR 7.18, 95% CI 1.96-26.28

Farquhar et al Cochrane Database 2002
McLellan et al Postgrad MJ 1989
Moghetti et al JCEM 2000

Management of Hyperandrogenism

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Physical removal: electrolysis, laser therapy
shaving, depilatory creams

Eflornithine

Anti-androgen medication: COCP
EE2 / cyproterone acetate
EE2 / drospirenone
Spironolactone
Flutamide, finasteride

Metformin

Flutamide

Licensed for prostate cancer only

Supresses hirsutism,
but no better than other therapies

Fatal cases of cholestatic hepatitis

Risk-benefit ratio unacceptable for benign conditions

Osculati & Castiglioni Lancet; 2006; 367: 1140

Finasteride

Licensed for prostate cancer only

Supresses hirsutism,
but no better than other therapies

Management of Hyperandrogenism

Weight loss

Physical removal: electrolysis, laser therapy
shaving, depilatory creams

Eflornithine

Anti-androgen medication: COCP
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Metformin

Metformin vs Placebo

Insufficient evidence to demonstrate a benefit

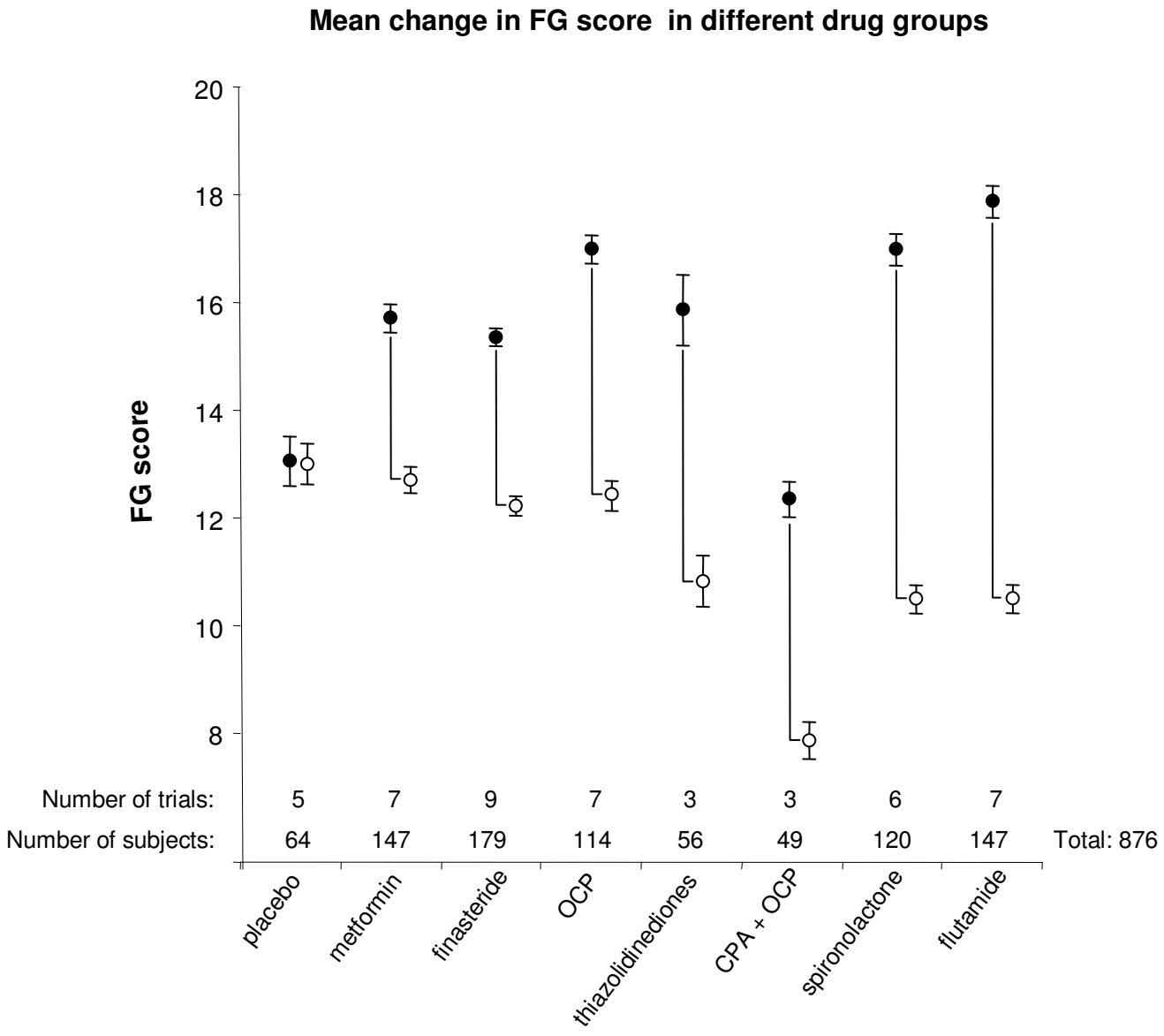
Metformin vs COCP

3 trials assessing hirsutism (F-G or subjective)

No difference (-0.18, 95% CI -0.67 - 0.32)

COCP better at suppressing androgen levels

Costello et al Hum Reprod 2007; 22: 1200
Tang, Norman, Balen Cochrane Database 2009



Meta-analysis, Conway *et al* 2007

Revised Cochrane Meta-analysis

No clear role for metformin in treatment of hyperandrogenism

Tommy Tang, Rob Norman, Adam Balen 2009

Treatment of androgenic alopecia

Minoxidil

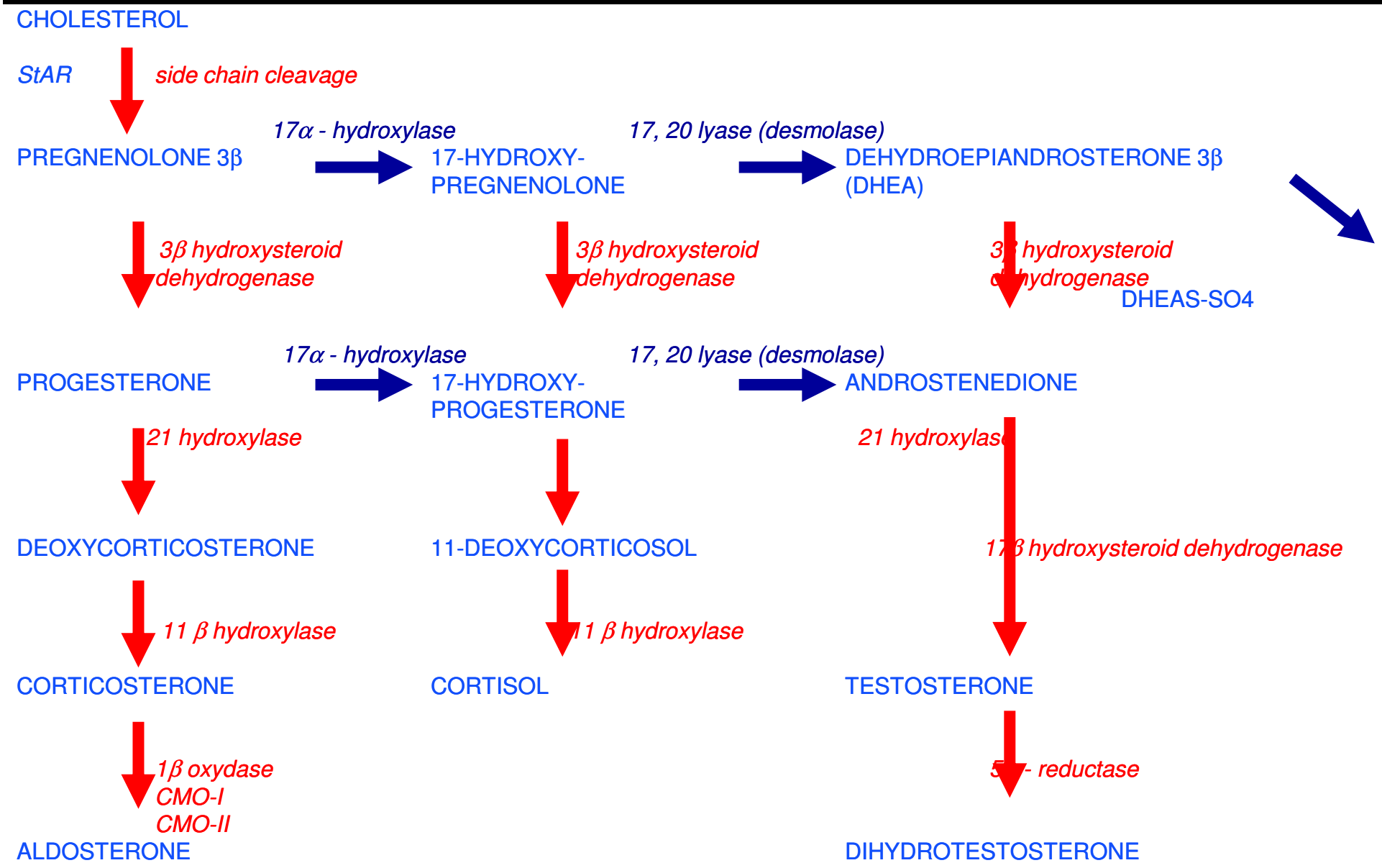
- increases duration of anagen, enlarges follicles
- 2% or 5% topical solution
- 1 ml to scalp twice daily, minimum 4 months
- up to 42.5% improvement over 32w

Congenital Adrenal Hyperplasia

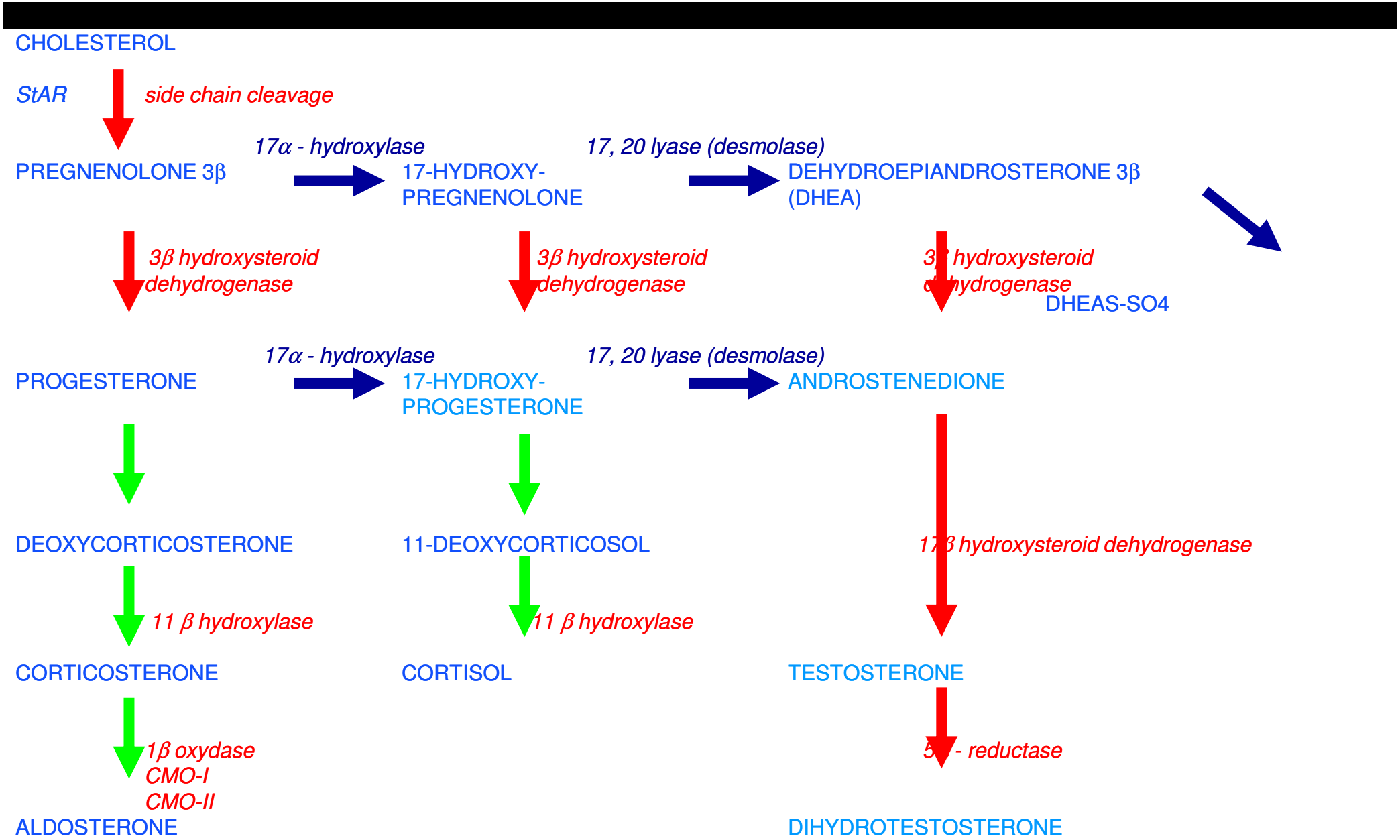
21 hydroxylase deficiency (95% of CAH)

1:5,000 – 1:20,000 births
carrier status in 1:80
racial differences

classical salt wasting ~ 60%
non-salt wasting ~ 20%
late onset ~ 20%



(StAR = steroidogenic acute regulatory protein, delivers cholesterol to mitochondria)


CHOLESTEROL
StAR
side chain cleavage
PREGNENOLONE 3β
17α - hydroxylase
17-HYDROXY-
PREGNENOLONE
17, 20 lyase (desmolase)
DEHYDROEPIANDROSTERONE 3β
(DHEA)
3β hydroxysteroid
dehydrogenase
3β hydroxysteroid
dehydrogenase
3β hydroxysteroid
dehydrogenase
DHEAS-SO4
PROGESTERONE
17α - hydroxylase
17-HYDROXY-
PROGESTERONE
17, 20 lyase (desmolase)
ANDROSTENEDIONE
DEOXYCORTICOSTERONE
11-DEOXYCORTICOSOL
17β hydroxysteroid dehydrogenase
11 β hydroxylase
11 β hydroxylase
CORTICOSTERONE
CORTISOL
TESTOSTERONE
1β oxydase
CMO-I
CMO-II
5α - reductase
ALDOSTERONE
DIHYDROTESTOSTERONE

Congenital Adrenal Hyperplasia

Adrenal medulla may be suppressed by overgrown cortex, but of no pathological significance

Simple virilizing: defect expressed only in zona fasciculata

Salt-wasting: z. fasciculata and z. glomerulosa

- ass. with HLA BW47 & DR7
- volume depletion, hypotension,
- reduced renal blood flow,
- raised PRA (suppression of PRA used to assess efficacy of treatment with fludrocortisone)

Congenital Adrenal Hyperplasia

Elevated 17OH-progesterone

May require 250mcg ACTH test:
cut-off 30 nmol/l

Congenital Adrenal Hyperplasia

Require corticosteroid
(hydrocortisone / prednisolone)

Fludrocortisone, if salt losing

May require additional COCP

Ovulation induction difficult if progesterone elevated
(suppress with additional prednisolone in follicular phase of cycle)

Relative strengths of glucocorticoids

	Potency	Average daily dose (mg)
Hydrocortisone	1	20 - 30
Cortisone acetate	0.8	25 - 37.5
Prednisolone	5	5 - 10
Dexamethasone	40	0.5 - 0.75

Congenital Adrenal Hyperplasia

Treatment usually with hydrocortisone

Monitor testosterone or androstenedione
(latter not bound to SHBG ∴useful if obese)

17OH-P fluctuates hourly and depends on previous dose of glucocorticoid

Prevention in pregnancy if previous history of affected child: Dexamethasone crosses placenta

Current Principals of Surgery in CAH

- Avoid vaginoplasty /clitoral reduction in infancy
  - careful counselling and support of parents
- Optimise endocrine control during childhood and puberty
- Surgery best performed post-puberty
  - full involvement of individual
  - avoid clitoral reduction

Summary

1. PCOS main cause of hyperandrogenism
2. Definitions still debated and ethnic variations important
3. Acne and hirsutism have major impact on QoL
4. Therapies combine physical and pharmaceutical approaches

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