Hyperandrogenism in women: Diagnosis and management

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ESHRE Campus “Old and New Hormones”
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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
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

The polycystic ovary contains 12 or more follicles measuring 2-9 mm in diameter 
and/or 
increased ovarian volume (>10 cm$^3$)
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
1. Hyperandrogenism and new definitions of the polycystic ovary syndrome

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Heterogeneity of PCOS

- Hyperandrogenism
- Menstrual disturbances
  - ↑ testosterone
  - ↑ luteinising hormone

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Heterogeneity of PCOS
Heterogeneity of PCOS

Hyperandrogenism
Menstrual disturbances

↑:testosterone
↑:luteinising hormone
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 at least one feature of PCOS

Michelmore et al, Clin Endocrinol 1999; 51: 779
224 women 17-25y, 33% polycystic ovaries

<table>
<thead>
<tr>
<th></th>
<th>PCO</th>
<th>Normal ovaries</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>BMI kg/m²</td>
<td>23.3</td>
<td>23.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>% body fat</td>
<td>30.4</td>
<td>29.4</td>
<td>0.048</td>
</tr>
<tr>
<td>Birthweight kg</td>
<td>3.49</td>
<td>3.28</td>
<td>0.004</td>
</tr>
<tr>
<td>Testo. nmol/l</td>
<td>2.67</td>
<td>2.47</td>
<td>0.03</td>
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</tbody>
</table>
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
OBESITY

WEIGHT LOSS

↑ INSULIN

after Dewailly

symptoms

hormones

ultra sound

sound

hormones

symptoms

INSULIN

WEIGHT LOSS

OBESITY
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
1. Hyperandrogenism and new definitions of the polycystic ovary syndrome

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3. Approaches to management of HA
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-\textit{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

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

Antibiotics:
✓ Reduce microorganisms
✓ Reduce inflammatory response

Hormones:
✓ Reduce sebum production
✓ Normalise desquamation

Benzoyl peroxide:
✓ Kills microorganisms
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
Management of Hyperandrogenism

Weight loss

Physical removal: electrolysis, laser therapy, shaving, depilatory creams

Eflornithine

Anti-androgen medication: COCP

EE2 / cyproterone acetate
EE2 / drospirenone
Spironolactone
Flutamide, finasteride

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

Weight loss

Physical removal: electrolysis, laser therapy, shaving, depilatory creams

Eflornithine

Anti-androgen medication: COCP

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

Management of Hyperandrogenism

Weight loss

Physical removal: electrolysis, laser therapy, shaving, depilatory creams

Eflornithine

Anti-androgen medication: COCP

- EE2 / cyproterone acetate
- EE2 / drospirenone
- Spironolactone
- Flutamide, finasteride

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

Weight loss

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

Suppresses 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

Suppresses 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

EE2 / cyproterone acetate
EE2 / drospirenone
Spironolactone
Flutamide, finasteride

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
Mean change in FG score in different drug groups

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%
CHOLESTEROL

StAR → side chain cleavage

PREGNENOLONE 3β → 17α - hydroxylase → 17-HYDROXY-PREGNENOLONE → 17, 20 lyase (desmolase) → DEHYDROEPIANDROSTERONE 3β (DHEA)

3β hydroxysteroid dehydrogenase

DHEAS-SO4

PROGESTERONE 17α - hydroxylase → 17-HYDROXY-PROGESTERONE → 17, 20 lyase (desmolase) → ANDROSTENEDIONE

21 hydroxylase

DEOXYCORTICOSTERONE → 11-DEOXYCORTICOSOL → 11 β hydroxylase → CORTICOSTERONE → 1β oxidase

CMO-I

CMO-II

ALDOSTERONE → DIHYDROTESTOSTERONE

CORTICOSTERONE 11 β hydroxylase → CORTISOL → TESTOSTERONE 5α - reductase

(StAR = steroidogenic acute regulatory protein, delivers cholesterol to mitochondria)
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)
<table>
<thead>
<tr>
<th></th>
<th>Potency</th>
<th>Average daily dose (mg)</th>
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<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>20 - 30</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>0.8</td>
<td>25 - 37.5</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>5 - 10</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40</td>
<td>0.5 - 0.75</td>
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</tbody>
</table>
Congenital Adrenal Hyperplasia

Treatment usually with hydrocortisone

Monitor testosterone or androstenedione
(latter not bound to SHBG \( \therefore \) 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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