Polycystic ovary syndrome & Non-classical congenital adrenal hyperplasia

Dr Anju Joham
MBBS (Hons), FRACP, PhD

Head, Monash Health PCOS Service
Endocrinologist, Monash Health
NHMRC Early Career Fellow, Monash Centre for Health Research and Implementation (MCHRI)
School of Public Health and Preventive Medicine, Monash University
Disclosures

- Member of guideline development group 2018 PCOS guideline
- Novo education grants
- NHMRC fellowship
- PCOS CRE funding
Continuum of adverse lifestyle related diseases in women
Note:
Ultrasound should not be used < 8 years of menarche (high prevalence of PCO at this life stage)
PCOS prevalence

- Traditionally estimated at 4-8%
  - Older diagnostic criteria (NIH)
- Using Rotterdam diagnostic criteria
  - Prevalence 8-13%
  - Australian prevalence 12-18%
  - Indigenous populations up to 21%
- Major health and economic burden

Impact of excess weight

ALSWH: Longitudinal data 9% increased prevalence PCOS for 1 unit BMI

Teede, Joham et al Obesity 2013
PCOS pathophysiology

Genetics

Lifestyle

Hormonal changes

Obesity exacerbates hormonal changes

↑ Androgens

↑ Insulin

Ovarian follicles

Anovulation

↑ Oestrogen

Diabetes

Metabolic syndrome

Hirsutism

Acne

Menstrual disturbances

Sub fertility

Cardiovascular risk

Psychosocial issues: body image, self esteem, depression, anxiety

Genetics of PCOS

- Familial clustering / 1st degree relatives
  - 25% risk of PCOS
- Twin studies
  - Higher concordance in PCOS characteristics between monozygotic twin sisters c/w dizygotic twins
- Recent genome wide association studies (GWAS) identified several genetic variants being genome wide significantly a/w PCOS
  - In or near LH and FSH receptor genes
  - Variant in the FSH-β gene

Yilmaz et al, Fert Ster, 2018; Vink et al, JCEM, 2016; Laven, Frontiers Endo, 2019
Hyperandrogenism in PCOS

- **Prenatal exposure** (Abbott, Walters, others)
  - Mechanistic models
  - Human relevance unclear

- **Peripubertal exposure** (Marshall, McCartney, others)

- **Hyperandrogenism - feature of PCOS**
  - 80% affected
  - Increased thecal secretion
  - Increased responsiveness to androgens
Obesity and IR: clamps

- Integral link between obesity, reproductive and metabolic features
- Intrinsic vs extrinsic IR

WHO criteria for IR
<25th centile on clamp studies

IR was present in:
- 75% lean PCOS
- 62% obese controls
- 95% obese PCOS women

Hutchison et al, JCEM 2011
Stepto, Human Reprod 2013
PCOS clinical features

Reproductive
- Anovulation/cycle irregularity
- Polycystic ovaries
- Hyperandrogenism
- Subfertility

Metabolic
- Insulin resistance
- Obesity
- Dyslipidemia
- GDM/prediabetes/diabetes
- Cardiovascular risk

Psychological
- Depression and/or anxiety
- Negative body image
- Low self esteem
- Psychosexual dysfunction
- Eating disorders
- Poor quality of life

Obesity and PCOS

- Obesity affects ~60% of women with PCOS
- Role in pathophysiology of hyperandrogenism, chronic anovulation and metabolic abnormalities

**PCOS phenotypes**

- Significant clinical heterogeneity

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Diagnostic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Hyperandrogenism</td>
</tr>
<tr>
<td></td>
<td>Ovulatory dysfunction</td>
</tr>
<tr>
<td></td>
<td>PCOM</td>
</tr>
<tr>
<td>B</td>
<td>Hyperandrogenism</td>
</tr>
<tr>
<td></td>
<td>Ovulatory dysfunction</td>
</tr>
<tr>
<td>C</td>
<td>Hyperandrogenism</td>
</tr>
<tr>
<td></td>
<td>PCOM</td>
</tr>
<tr>
<td>D</td>
<td>Ovulatory dysfunction</td>
</tr>
<tr>
<td></td>
<td>PCOM</td>
</tr>
</tbody>
</table>

- Consider ethnic variation:
  - Milder phenotype in Caucasians
  - Higher BMI in Caucasians (esp N America and Australia)
  - More severe hirsutism in Middle Eastern, Hispanic and Mediterranean women
  - Increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians
  - Lower BMI and milder hirsutism in East Asians
Glycaemic abnormalities in PCOS

- Earlier onset of glycaemic abnormalities
- May convert more rapidly from IGT to T2DM
- ↑ prevalence of IGT and T2DM

<table>
<thead>
<tr>
<th></th>
<th>PCOS</th>
<th>Non-PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGT</td>
<td>31.1%</td>
<td>10.3%</td>
</tr>
<tr>
<td>T2DM</td>
<td>7.5%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

- 2.9 fold ↑ risk of GDM
- 3.3 fold ↑ risk of IGT and a 2.9 fold ↑ risk of T2DM

Kakoly, Joham et al, HRU, 2018; Boomsma et al, HRU, 2006
Diabetes risk by BMI categories

**Figure 2**—The incidence rate of type 2 diabetes in women with and without PCOS by class of BMI, including healthy weight/lean, overweight, and obese.
Clinical assessment - examination

- Weight, height, BMI
- Waist circumference
- Blood pressure

- Assess:
  - Hirsutism
  - Acne
  - Alopecia
  - Acanthosis nigricans

- Screen clinically for:
  - Signs of virilisation if concerning hyperandrogenism (depending on rate of change of symptoms/signs, severity and if out of context)
    - Voice changes, cliteromegaly
  - Cushing’s syndrome

- Psychological screening often useful
Psychological screening

2.2.5 CPP  Assessment of anxiety and or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened according to regional guidelines, or by using the following stepped approach:

Step 1: Initial questions could include:

Over the last 2 weeks, how often have you been bothered by the following problems?

- feeling down, depressed, or hopeless?
- little interest or pleasure in doing things?
- feeling nervous, anxious or on edge?
- not being able to stop or control worrying?

Step 2: If any of the responses are positive, further screening should involve:

- assessment of risk factors and symptoms using age, culturally and regionally appropriate tools, such as the Patient Health Questionnaire (PHQ) or the Generalised Anxiety Disorder Scale (GAD7) and/or refer to an appropriate professional for further assessment.
Hirsutism

- Distressing symptom of PCOS
- Often the most concerning symptom for patients
- Can affect body image, self esteem and quality of life
Clinical assessment - hirsutism

Figure 1 Schematic representation of the mFG score. Nine body areas (upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper back, lower back and thighs) are scored from 1 (minimal terminal hairs present) to 4 (equivalent to a hairy man). If no terminal hairs are observed in the body area being examined the score is zero (left blank). Clinically, terminal hairs can be distinguished from vellus hairs primarily by their length (i.e. >0.5 cm) and the fact that they are usually pigmented. Reproduced with permission from R. Azziz (Yildiz et al., 2010). Copyright Oxford University Press, 2010.
Clinical assessment - hirsutism

- Terminal hair growth (> 5mm length, usually pigmented)
- Score ≥ 4-6 indicative of hirsutism
- But terminal hair growth has considerable ethnic variability – FG score ≥ 3 – hirsutism (South East Asian women)

### Table 1: Suggested cut-offs for the mFG hirsutism score according to the 95 percentile in different unselected populations of premenopausal women.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Year</th>
<th>Country</th>
<th>Race</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Suggested mFG cut-off</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telesz and Frenkel (1995)</td>
<td>1995</td>
<td>Chile</td>
<td>White</td>
<td>Hispanic</td>
<td>236</td>
<td>≥ 6</td>
<td>236</td>
</tr>
<tr>
<td>Asuncion et al. (2000)</td>
<td>2000</td>
<td>Spain</td>
<td>White</td>
<td>Mediterranean</td>
<td>154</td>
<td>≥ 8</td>
<td>154</td>
</tr>
<tr>
<td>Sagsoz et al. (2004)</td>
<td>2004</td>
<td>Turkey</td>
<td>White</td>
<td>Middle Eastern</td>
<td>204</td>
<td>≥ 9</td>
<td>204</td>
</tr>
<tr>
<td>Cheewadhanaraks et al. (2004)</td>
<td>2004</td>
<td>Thailand</td>
<td>Asian</td>
<td>Thai and Chinese</td>
<td>531</td>
<td>≥ 3</td>
<td>531</td>
</tr>
<tr>
<td>DelUgarte et al. (2006)</td>
<td>2006</td>
<td>USA</td>
<td>White</td>
<td>Caucasian and Hispanic</td>
<td>283</td>
<td>≥ 8</td>
<td>283</td>
</tr>
<tr>
<td>Zhao et al. (2007)</td>
<td>2007</td>
<td>China</td>
<td>Asian</td>
<td>Chinese Han</td>
<td>623</td>
<td>≥ 2</td>
<td>623</td>
</tr>
<tr>
<td>Api et al. (2009)</td>
<td>2009</td>
<td>Turkey</td>
<td>White</td>
<td>Middle Eastern</td>
<td>121</td>
<td>≥ 11</td>
<td>121</td>
</tr>
<tr>
<td>Moran et al. (2010)</td>
<td>2010</td>
<td>Mexico</td>
<td>White</td>
<td>Hispanic</td>
<td>150</td>
<td>≥ 10</td>
<td>150</td>
</tr>
<tr>
<td>Noorbala and Kefae (2010)</td>
<td>2010</td>
<td>Iran</td>
<td>White</td>
<td>Middle Eastern</td>
<td>900</td>
<td>≥ 10</td>
<td>900</td>
</tr>
<tr>
<td>Kim et al. (2011)</td>
<td>2011</td>
<td>Korea</td>
<td>Asian</td>
<td>Chinese</td>
<td>1010</td>
<td>≥ 6</td>
<td>1010</td>
</tr>
<tr>
<td>Gambineri (2011, personal communication)</td>
<td>2011</td>
<td>Italy</td>
<td>White</td>
<td>Mediterranean</td>
<td>200</td>
<td>≥ 9</td>
<td>200</td>
</tr>
</tbody>
</table>

*aAs defined by the 95th percentile of an unselected population of premenopausal women.*
Clinical assessment - alopecia
Case study – Mrs FD

33 y o

Past medical history
- PCOS
- Obesity – BMI 34
- Trigeminal neuralgia
- Migraine, without aura
- L4/5 disc bulge
- G1P2-2
  - Primary infertility, IVF pregnancy 2018
  - MCDA twins, pregnancy loss 23 weeks
  - Open cervix, placental abruption and severe chorioamnionitis

Medications
- Magnesium
- Vitamin D
- Elevit

Social history
- Vet nurse
- Married
- Ex-smoker
Case study – Mrs FD

**PCOS history**
- PCO on ultrasound
- Menstrual cycles
  - Menarche aged 14
  - Cycles irregular every 3-4 months
  - Prolonged period of 2° amenorrhoea
- Severe hirsutism
- Mild alopecia
- Pustular acne
- No voice change
- Previous treatment:
  - COCP for 15 years
  - Metformin 1g bd
  - Spironolactone 100mg d

**Examination**
- BMI 43
  - Weight 134kg, height 175cm
- BP 145/90mmHg
- FG score 14
- Mild frontal alopecia
- Small dorsocervical fat pad
- Pale abdominal striae
- No other stigmata of Cushing’s or acromegaly
- No cliteromegaly
## Investigations

### Androgen profile
- **Total testosterone, SHBG, FAI**
  - LCMS / extraction immunoassay
  - Preferably during early follicular phase
  - Ideally off interfering medications for 3 months (e.g. COCP, anti-androgens)

### Exclude secondary causes
- TFTs, prolactin, 17-OH progesterone
- If clinical suspicion of secondary cause, consider Cushing’s screen, DHEAS or androstenedione, LH, FSH, estradiol (amenorrhoea)

### Anti-müllerian hormone (AMH)
- Serum AMH levels should not yet be used as an alternative for the detection of PCOM or as a single test for the diagnosis of PCOS.

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1 EBR</td>
<td>Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.</td>
</tr>
<tr>
<td>1.2.2 EBR</td>
<td>High quality assays such as liquid chromatography–mass spectrometry (LCMS)/mass spectrometry and extraction/chromatography immunoassays, should be used for the most accurate assessment of total or free testosterone in PCOS.</td>
</tr>
<tr>
<td>1.5</td>
<td>Anti-müllerian hormone (AMH)</td>
</tr>
<tr>
<td>1.5.1 EBR</td>
<td>Serum AMH levels should not yet be used as an alternative for the detection of PCOM or as a single test for the diagnosis of PCOS.</td>
</tr>
<tr>
<td>1.5.2 CPP</td>
<td>There is emerging evidence that with improved standardisation of assays and established cut off levels or thresholds based on large scale validation in populations of different ages and ethnicities, AMH assays will be more accurate in the detection of PCOM.</td>
</tr>
</tbody>
</table>
Investigations

- Metabolic screening
  - Fasting lipids
  - 75g OGTT (or fasting glucose or Hba1c depending on metabolic risk profile)
    - OGTT recommended if high risk:
      - BMI > 25kg/m² or in Asians > 23kg/m²
      - History of IFG, IGT, GDM
      - FHx DM or hypertension or high-risk ethnicity
      - Pre-conception / early pregnancy
  - (No need to do insulin levels – assay variability & inaccuracy)
Anti-Mullerian hormone (AMH)

- Produced predominantly in ovarian granulosa cells of pre-antral and antral follicles
- Proposed as a marker of ovarian dysfunction
  - Disrupts folliculogenesis through diminishing follicular sensitivity to FSH
  - Inhibits follicle recruitment and growth
- AMH significantly higher in women with PCOS
- Limitations
  - Considerable overlap of levels with normal ovulatory women
  - Specific threshold of AMH in PCOS and PCOM is challenging
  - Heterogeneity between studies (assays, life stage and phenotypes)
AMH and PCOS phenotype

Tal et al AJOG 2014
AMH had strong diagnostic ability for amenorrhea in this study population
- 91.7% specificity
- 79.4% sensitivity
when the threshold AMH concentration was 11.4 ng/mL

Tal et al AJOG 2014
Imaging

Pelvic ultrasound

1.4.4 CCR Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be on either ovary, a follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10ml, ensuring no corpora lutea, cysts or dominant follicles are present.

- Ideally using endovaginal ultrasound transducers (frequency bandwidth that includes 8MHz)
- PCOM on either ovary
- Follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10ml

- Endometrial thickness
  - (Increased risk of endometrial hyperplasia and endometrial cancer)

- Ultrasound not recommended for adolescents < 8 years following menarche
## Mrs FD - Investigations

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total T</td>
<td>7.7 nmol/L (0.1-1.7)</td>
<td>7.2 nmol/L (&lt;1.5)</td>
<td>5.7 nmol/L (0.5-2.2)</td>
</tr>
<tr>
<td>Free T</td>
<td></td>
<td>89 pmol/L (1-34)</td>
<td>83 pmol/L (4-33)</td>
</tr>
<tr>
<td>SHBG</td>
<td>65 nmol/L (25-150)</td>
<td>65 nmol/L (25-150)</td>
<td>49 nmol/L (25-150)</td>
</tr>
<tr>
<td>FAI</td>
<td>11.9 (0.7-10.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>FSH</td>
<td></td>
<td>5.5 IU/L</td>
<td>6 IU/L</td>
</tr>
<tr>
<td>LH</td>
<td></td>
<td>8.2 IU/L</td>
<td>5 IU/L</td>
</tr>
<tr>
<td>Estradiol</td>
<td></td>
<td>297 pmol/L</td>
<td>228 pmol/L (follicular phase)</td>
</tr>
<tr>
<td>Progesterone</td>
<td></td>
<td>0.8 nmol/L</td>
<td>1.1 nmol/L</td>
</tr>
<tr>
<td>17-OH progesterone</td>
<td>3.4 nmol/L (0.6-2.0)</td>
<td></td>
<td>5.9 nmol/L (&lt; 12)</td>
</tr>
<tr>
<td>DHEAS</td>
<td>5.7 umol/L (0.6-7.2)</td>
<td>8.7 umol/L (2.7-11.7)</td>
<td>7.9 umol/L (2.2-7.9)</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>10.5 umol/L (1.2-7.4)</td>
<td>14.8 umol/L (1.6-11.8)</td>
<td>11.3 umol/L (1.3-4.6)</td>
</tr>
<tr>
<td></td>
<td>6.9 nmol/L (1.2-7.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LCMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMH</td>
<td>50.2 pmol/L (4-45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mrs FD - Investigations

- TSH 1.36mIU/L (0.5-4.0)
- T4 16.2 pmol/L
- Prolactin 214 mIU/L (54-619)
- GH 0.9 mU/L (0-11.0)
- IGF-1 24.9 nmol/L (15.1-40.2)
- Synacthen stimulated 17-OHP 6.6 nmol/L (>30nmol/L → NCCAH)

- Fasting lipids
  - Chol 5.2 mmol/L
  - Trig 1.0 mmol/L
  - HDL 1.2
  - LDL 3.1 mmol/L
- Hba1c 5.0%
- 75g OGTT: 5.3 / 9.5 / 5.5
- 24 hour urine cortisol 77 nmol/day (<110)
- 24 hour urine steroid profile: androsterone slightly elevated, otherwise normal
Mrs FD - Investigations

- **Pelvic US**
  - Normal sized uterus
  - 8-9mm late proliferative endometrium
  - R ovary: 30 follicles
  - L ovary: 35 follicles
  - Antral follicle count 64
    - (AFC >19 ↑ risk to controlled ovarian stimulation)
  - No ovarian masses or discrete lesions

- **CT adrenals**
  - Normal appearance of adrenal glands
Assessment

- High testosterone levels out of keeping with PCOS
- Differential diagnoses
  - ? Secondary cause ? Androgen secreting tumour
  - ? PCOS
  - ? NCCAH
  - ? Ovarian hyperthecosis
Low dose dexa

- Glucocorticoid administration
  - Exclude patients with virilizing adrenal tumors
  - Identify source
    - Failure to suppress → suggestive of virilising adrenal tumour
    - Suppression → non-neoplastic adrenal source
    - Case reports of LDDST helping to identify patients with ovarian tumors

- Small series of 211 hyperandrogenic women
- 48-h low-dose dexamethasone-suppression test (LDDST) to exclude ovarian and adrenal tumors
  - Dexamethasone 0.5mg 6/24 for 48/24 with concomitant cortisol and testosterone levels

- Results:
  - No patients with tumors obtained > 40% reduction or normalization of T levels
  - 88% of patients without tumours suppressed > 40% or normalized T levels

- Lack of T suppression during LDDST - 100% sensitivity and 88% specificity
  - In distinguishing patients with ovarian and adrenal androgen-secreting tumors from patients with non-tumorous hyperandrogenism

Kaltsas JCEM 2003

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>7.2</td>
<td>7.5</td>
<td>8.9</td>
</tr>
<tr>
<td>ACTH</td>
<td>3</td>
<td>&lt;2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Cortisol</td>
<td>283</td>
<td>16</td>
<td>12</td>
</tr>
</tbody>
</table>
Mrs FD - Investigations

- $\alpha$FP: normal
- Inhibin: normal
- MRI ovaries
  - No masses

Assessment and progress
- Slow, indolent disease
- Desiring pregnancy
- Next step: ? ovarian vein sampling
Management PCOS
Gaps in PCOS care

- Can take 1/3 of women with PCOS > 2 years before a diagnosis of PCOS is established
- Often require ≥ 3 health professionals prior to PCOS diagnosis
- GPs report feeling ill equipped to manage PCOS
- Gynaecologists – often focus on reproductive features or fertility
- Women dissatisfied with care

- Addressing gaps for women and health professionals
  - PCOS International guideline development
  - Ask PCOS App
  - Multidisciplinary Monash Health PCOS Service

Gibson-Helm, JCEM, 2016; Teede, JCEM, 2014: PCOS EBG 2018
Available at: Monash PCOS

Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome

Helena J. Teede, M.B.B.S., Ph.D., FRACP, FAAHMS,a,b,c Marie L. Misso, Ph.D., B.Sc.(Hons.),a,b,c Michael F. Costello, M.B.B.S., M.Med.(RH&HG), FRANZCOG, C.R.E.I., D.Med.Sc.,a Anuja Dokras, M.D., Ph.D.,aJoop Laven, M.D., Ph.D.,a Lisa Moran, B.Sc.(Hons.), BND, G. Cert. Pub. Health, Ph.D.,a,b,c Terhi Piltonen, M.D., Ph.D.,a and Robert. J. Norman, FRANZCOG, FRCPA, FRCPath, FRCOG, C.R.E.I.,a,b,c on behalf of the International PCOS Network

Teede et al, Human Reproduction, Fertility and Sterility, Clinical Endocrinology 2018
Teede, Norman and Legro, Seminars in Reproductive Medicine 2018
Teede et al Medical Journal of Australia 2018
PCOS guideline translation program – APP

ASKPCOS.Admin@monash.edu

This work is supported by the NHMRC funded Centre for Research Excellence in Polycystic Ovary Syndrome (project number APP1078444).
Management - metabolic features

- Lifestyle / exercise is critical
  - No evidence for a specific diet
- 5% weight loss reduces diabetes risk by ~ 50-60%
- Prevention of weight gain is key
- Regular screening for metabolic complications
- Consider metformin
Medical therapy options

Algorithm 4: Pharmacological treatment for non-fertility indications

**COCP**
- Cycle control
- Contraception
- Reduces hyperandrogenism
- Endometrial protection

**Metformin**
- Improves ovulation/cycles, limited fertility impact
- Reduces metabolic risk in high risk women with PCOS
- May prevent weight gain
- Metformin not approved in PCOS
- Recommended by international/national specialist societies

**Anti-androgens**
- 2nd line
- Examples: Spironolactone, cyproterone acetate

**Second line pharmacological therapies**

**COCP + lifestyle + metformin**
- No COCP preparation is superior in PCOS.
- Should be considered in women with PCOS for management of metabolic features, where COCP + lifestyle does not achieve goals.
- Could be considered in adolescents with PCOS and BMI ≥ 25kg/m² where COCP and lifestyle changes do not achieve desired goals.
- Most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.

**COCP + anti-androgens**
- Evidence in PCOS relatively limited.
- Anti-androgens must be used with contraception to prevent male fetal virilisation.
- Can be considered after 6/12 cosmetic treatment + COCP if they fail to reach hirsutism goals.
- Can be considered with androgenic alopecia.

**Metformin + lifestyle**
- With lifestyle, in adults should be considered for weight, hormonal and metabolic outcomes and could be considered in adolescents.
- Most useful with BMI ≥ 25kg/m² and in high risk ethnic groups.
- Side-effects, including GI effects, are dose related and self-limiting.
- Consider starting low dose, with 500mg increments 1-2 weekly.
- Metformin appears safe long-term. Ongoing monitoring required and has been associated with low vitamin B12.

Notes:
- Other contraceptives don’t increase hepatic SHBG production with limited efficacy for hyperandrogenism.

Off label prescribing: COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

In those with a clear PCOS diagnosis or in adolescents at risk of PCOS (with symptoms)
Management - cycle irregularity

- Lifestyle change (5-10% weight loss + exercise)
- Oral contraceptive pill
  - Low dose (eg 20-30 mcg ethinyloestradiol or equivalent)
  - Avoid 35mcg+ ethinyloestradiol / cyproterone acetate preparations
    • ↑ adverse effects
- Cyclical progestins every 3 months
  - Eg MPA 10mg for 2 weeks
- Metformin (improves ovulation and cycles)
Management - hirsutism

- Cosmetic therapy first line
- Laser recommended
- Medical therapy
  - COCP – primary therapy
  - Anti-androgen (with effective contraception)
    - After at least 6/12 trial of COCP + cosmetic
    - Eg. Spironolactone, cyproterone acetate
    - Combination therapy
  - Eflornithine cream (Vaniqa)
    - May reduce hair growth
    - Only effective whilst being used
    - SEs: skin irritation, acne, folliculitis
- Alopecia
  - Often combination therapy
  - Minoxidil (topical solution)
  - Consider Dermatology referral
Laser hair removal

- Effective, permanent hair reduction
- Uses heat to target the hair follicle
- Multiple treatments required
  - Only hair follicle in anagen growth phase can be disabled
- Medical grade lasers most effective
- Suitability of patient for laser
  - Terminal hair (not vellous)
  - Needs to be dark / pigmented hair
  - Skin colour (Fitzpatrick scale) – suitability of laser wavelength
Laser hair removal

755nm

1064nm

IPL devices are non-specific and provide a broad range of wavelengths absorbed by a range of chromophores

Lasers utilize one wavelength to target a specific chromophore

- Alexandrite for lighter skin types (I-IV)
- Nd:YAG for all skin types (I-VI)

Image courtesy of Cutera
Sample results

Pre-Tx  8 Wks Post 3 Txs

Image courtesy of Cutera
Laser - adverse effects

- **Temporary**
  - Discomfort/pain
  - Redness/swelling
  - Bruising – less common

- **Hypo/hyperpigmentation**
  - Usually temporary, may be permanent (in rare cases)

- **Paradoxical hypertrichosis**
  - Stimulation of hair growth can occasionally occur within or adjacent to treated area

- **Burning**
  - Burning, blistering, crusting or scarring (rare)

- **Scarring**
  - Rare

- **Greying of treated hair can occur**
  - May be temporary or permanent
Key points - PCOS

- Complex, common condition
- IR inherently increased in PCOS, exacerbated by obesity
- Lifestyle management critical
- Educate and empower
- Targeted therapy based on features
- Metabolic - screen, prevent and manage risk
Non-classical Congenital Adrenal Hyperplasia
Non-classical CAH

- Usually due to 21-hydroxylase deficiency - encoded by CYP21A2
  - More rarely due to defects of:
    • 11β-hydroxylase (11-OH) activity (encoded by CYP11B1)
    • 3β-hydroxysteroid dehydrogenase (3β-HSD) (encoded by HSD3B2)
- Autosomal recessive disorder
- Prevalence ~ approximately 1 in 1000
  - Higher among specific ethnic groups such as Ashkenazi Jewish, Mediterranean, Middle-Eastern and Indian populations
  - More recent CYP21A2 genotype analysis ~ 1:200
- Global prevalence ~ 4.2% in women presenting with hyperandrogenism (from a meta-analysis)
- Mostly asymptomatic in pre-pubertal years
- Typically presents in late childhood, adolescence, or adulthood with hyperandrogenism

Non-classical CAH

Figure 1. Review of the enzymes comprising the steroidogenic pathway.
Clinical features

- Hirsutism (59-78%)
- Acne (33%)
- Alopecia (2-8%)
- Oligomenorrhea (30-50%)
- Decreased fertility (12%)
  - Majority conceive spontaneously
- Mild cliteromegaly (6-20%)
- May be asymptomatic

Witchel, Steroids, 2013; Carmina et al, HRU, 2017; Moran et al, Obs Gyn, 2000
Investigations

- 17-OH progesterone
  - Random levels may be N
  - Test early morning levels, ideally using LCMS
  - Follicular phase
  - Levels between 6-30 nmol/L need additional investigation

- Synacthen stimulation test
  - Gold standard to confirm decreased 21-hydroxylase activity
  - < 30 nmol/L – negative
    - Based on studies using RIA
    - Need studies using LCMS

Witchel, Steroids, 2013; Speiser et al, JCEM, 2018; Carmina et al, HRU, 2017
Investigations

Algorithm for the diagnosis of NCAH

- Patient presenting with clinical hyperandrogenism and/or hyperandrogenemia
- Detailed medical history and physical examination
- Exclusion of uncommon disorders (such as Cushing syndrome, acromegaly, adrenal and ovarian tumors) by clinical history, special tests and/or imaging as appropriate
- Routine measurement of early morning basal 17-OH Progesterone concentrations in the diagnostic work-up of androgen excess disorders (premature pubarche, idiopathic hirsutism, idiopathic hyperandrogenism, PCOS...)

- <2 ng/ml
  - NCAH excluded

- 2-10 ng/ml
  - Cosyntropin stimulation test
  - <10 ng/ml
    - NCAH excluded
  - >10 ng/ml
    - NCAH

- >10 ng/ml
  - If available genotyping

2ng/mL = 6 nmol/L
10ng/mL = 30 nmol/L

Witchel, Steroids, 2013; Speiser et al, JCEM, 2018; Carmina et al, HRU, 2017*
Genetic testing

- CYP21A2 locus is complex - compounds molecular genetic analysis
- Almost 300 mutations known
  - Most commercial assays: 10–12 most common mutations
- Disease severity correlates with allelic variation
- 1 allele can carry multiple mutations
- Most are compound heterozygotes (different mutations on each allele)
  - Majority carry 1 mutation causing severe enzyme deficiency in 1 allele and 1 mutation encoding a mild defect in the other
  - NCAH phenotype roughly reflects enzymatic activity encoded by the milder mutation

Witchel, Steroids, 2013; Speiser et al, JCEM, 2018; Carmina et al, JCEM, 2017
Genetic testing

- **Family studies**
  - In some instances, it is necessary to confirm that mutations are on opposite alleles.
  - To segregate the specific alleles, CYP21A2 genetic analyses can be obtained from parents to discriminate the specific maternal and paternal mutations.

- **Genetic studies may be useful for reproductive planning**
  - Essential for genetic counseling since many patients with NCAH carry a severe allele that might result in CAH in their offspring.

Witchel, Steroids, 2013; Speiser et al, JCEM, 2018
Heterozygote carriers

- High prevalence of heterozygote carriers (1:50)
- Basal and ACTH stimulated 17OHP often don’t discriminate carriers
  - But response to ACTH tends to be higher in carriers
- Genetic testing
  - Expensive
  - Not widely available
- 21-deoxycortisol
  - May simplify identification of CAH carriers
  - 11β-hydroxy-derivative of 17OHP
  - Production limited to the adrenal cortex
  - ↑ levels specific for 21OHD (production virtually nil in normal subjects)
  - ACTH stimulated 21-deoxycortisol*
    - Cut off point of 40 ng/dl can distinguish carriers with greater accuracy than ACTH-stimulated 17OHP (82% vs 53% sensitivity, for 100% specificity).
  - Need more studies in this area

Costa-Barbosa, Clin Endo, 2010*
Management

Glucocorticoid replacement – Consider in women who have not conceived spontaneously or with ovulatory dysfunction – Long-term GC replacement required only in select patients (based on synacthen testing). May require stress dosing.

COCP – Decreases ovarian androgen secretion – Restores menstrual cyclicity – Improves acne, slows progression of hirsutism

Hyperandrogenism – Cosmetic methods – Anti-androgens Eg. cyproterone acetate, spironolactone

Witchel, Steroids, 2013; Carmina et al, HRU, 2017∗
Summary: CAH

- Presents late with hyperandrogenism
- Baseline 17-OH progesterone
  - In all women presenting with hirsutism / hyperandrogenism
- Gold standard test: ACTH stimulated 17OHP
- Consider genetic testing
Acknowledgments

- Monash Health PCOS Clinic staff and patients
- Prof Helena Teede
- A/Prof Amanda Vincent
- MCHRI
The GRADE of the recommendation is determined by the GDG from structured consideration of the GRADE framework [15] including desirable effects, undesirable effects, balance of effects, resource requirements and cost effectiveness, equity, acceptability and feasibility and includes:

- Conditional recommendation against the option;
- Conditional recommendation for either the option or the comparison;
- Conditional recommendation for the option;
- Strong recommendation for the option.

Quality of the evidence is categorised (see table 2) according to:

- Information about the number and design of studies addressing the outcome;
- Judgments about the quality of the studies and/or synthesised evidence, such as risk of bias, inconsistency, indirectness, imprecision and any other considerations that may influence the quality of the evidence; key statistical data;
- And classification of the importance of the outcomes.

The quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation [15] and was largely determined by the expert evidence synthesis team.

**Table 2: Quality (certainty) of evidence categories (adapted from GRADE [15]):**

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>☄️ ☄️ ☄️ ☄️ Very confident that the true effect lies close to that of the estimate of the effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>☄️ ☄️ ☄️ Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different</td>
</tr>
<tr>
<td>Low</td>
<td>☄️ ☄️ ☄️ Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect</td>
</tr>
<tr>
<td>Very Low</td>
<td>☄️ ☄️ ☄️ ☄️ Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</td>
</tr>
</tbody>
</table>

GRADE note that quality of evidence is a continuum; any discrete categorisation involves a degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations [15].