Polycystic Ovary Syndrome

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Disclosures

- Novo education grants
- No advisory boards
- No industry funding
- Contracted research: funds to institution
Outline

• PCOS overview
• Insulin resistance in PCOS
• Hyperandrogenism in PCOS
• AMH
• Management of PCOS
Obesity

• Obesity is a major chronic disease
• Rising prevalence of obesity
• Growing health and economic burden
• Obesity, mediated via ↑ IR, is a/w ↑ risk of:
  – Impaired reproductive health
    • PCOS, infertility, GDM
  – Increases IR states such as T2DM
  – Hypertension
  – Dyslipidaemia
  – Cardiovascular disease (CVD)
Obesity in the modern world

Endocrine Society statement: “The Task Force agrees with the opinion of prominent medical societies that scientific evidence supports the view that obesity is a disease”
Continuum of adverse lifestyle related diseases in women

Teede  TEM 2007
Polycystic Ovary Syndrome

- PCOS prevalence traditionally estimated at 4 - 8% - Greece, Spain, USA
  - Older diagnostic criteria (NIH)
- Australian (Rotterdam) prevalence 12-18%
- Indigenous populations ~21%
- Costs >$400 million/yr in Australia
- Major health and economic burden

PCOS diagnosis

Rotterdam diagnostic criteria requires two of:
1. Oligo- or anovulation;
2. Clinical and/or biochemical hyperandrogenism;
3. Polycystic ovaries;
and exclusion of other aetiologies

NIH diagnostic criteria requires:
1. Oligo- or anovulation; and
2. Clinical and/or biochemical hyperandrogenism;
and exclusion of other aetiologies

Teede et al MJA 2011
PCOS: complex clinical syndrome

Genetics

- Hormonal changes
  - Obesity exacerbates hormonal changes
  - ↑ Androgens
    - Hirsutism
    - Acne
  - Ovarian follicles
    - Anovulation
    - ↑ Oestrogen
    - Menstrual disturbances
      - Sub fertility
  - Diabetes
    - Metabolic syndrome
    - Cardiovascular risk
  - Psychosocial issues: body image, self esteem, depression, anxiety

Lifestyle

- ↑ Insulin

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

Impact of excess weight

ALSWH: Longitudinal data 9% inc risk PCOS for 1 unit BMI

Teede et al Obesity 2013
Weight gain in PCOS

| TABLE 1 Characteristics of women with PCOS and without PCOS at surveys 1 and 4^a |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | PCOS (n = 478)  | Non-PCOS (n = 8,134) | PCOS (n = 478)  | Non-PCOS (n = 8,134) |
| Age, y                          | 20.71 ± 0.07    | 20.82 ± 0.02     | 30.51 ± 0.07    | 30.62 ± 0.02     |
| Weight, kg^b                    | 67.4 ± 0.86     | 61.92 ± 0.14     | 73.16 ± 1.03    | 68.51 ± 0.19     |
| BMI, kg/m^2c                    | 24.49 ± 0.29    | 22.45 ± 0.05     | 27.83 ± 0.37    | 24.84 ± 0.07     |
| Type 2 diabetes, %^d            | 2.0             | 0.7              | 5.1             | 0.3              |
| Hypertension, %^g               | 7.1             | 4.2              | 5.5             | 2.0              |
| Current smokers, %^f            | 29.1            | 23.3             | 16.6            | 19.0             |
| COP use, %^g                    | 41.8            | 45.2             | 23.3            | 36.9             |

Teede et al, Obesity, 2013
## Obesity in PCOS and phenotype

<table>
<thead>
<tr>
<th></th>
<th>All women</th>
<th>Original NIH</th>
<th>Rotterdam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>100%</td>
<td>6.1%</td>
<td>19.9%</td>
</tr>
<tr>
<td>Non-obese</td>
<td>90%</td>
<td>5.1%</td>
<td>19%</td>
</tr>
<tr>
<td>Obese</td>
<td>10.2%</td>
<td>15%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Turkish government employees, prevalence of PCOS by BMI

Yildiz, Human Reprod 2012
Obesity and PCOS

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

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
Clinical assessment

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
• Score ≥ 8 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.

| Author, year | Year | Country | Race | Ethnicity | Sample size | Suggested mFG cut-off
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Teitelz and Frenkel (1995)</td>
<td>1995</td>
<td>Chile</td>
<td>White</td>
<td>Hispanic</td>
<td>236</td>
<td>≥ 6</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>
</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>
</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>
</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>
</tr>
<tr>
<td>Delugarte et al. (2006)</td>
<td>2006</td>
<td>USA</td>
<td>Black</td>
<td>African American</td>
<td>350</td>
<td>≥ 8</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>
</tr>
<tr>
<td>Apri et al. (2009)</td>
<td>2009</td>
<td>Turkey</td>
<td>White</td>
<td>Middle Eastern</td>
<td>121</td>
<td>≥ 11</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>
</tr>
<tr>
<td>Noorbala and Kefaei (2010)</td>
<td>2010</td>
<td>Iran</td>
<td>White</td>
<td>Middle Eastern</td>
<td>900</td>
<td>≥ 10</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>
</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>
</tr>
<tr>
<td>Escobar-Morreale (2011, personal communication)</td>
<td>2011</td>
<td>Spain</td>
<td>White</td>
<td>Mediterranean</td>
<td>291</td>
<td>≥ 10</td>
</tr>
</tbody>
</table>

*As defined by the 95th percentile of an unselected population of premenopausal women.
Clinical assessment - alopecia
Investigations

• Androgen profile
  – Total testosterone, SHBG, FAI
  – (DHEAS or androstenedione not routinely recommended)

• Exclude secondary causes
  – TFTs, prolactin
  – If clinical suspicion, consider
    • 17-hydroxyprogesterone
    • Cushings’ screen

• AMH not recommended at this stage

• Metabolic screening
  – Fasting lipids
  – 75g OGTT
  – (No need to do insulin levels – assay variability & inaccuracy)
Investigations

• Pelvic ultrasound
  – Ovarian morphology
    • Presence of $\geq 12$ follicles in the ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL) – PCO if involving 1 or both ovaries
  – Endometrial thickness
Key points: overview of PCOS

• PCOS affects 12-21% of reproductive aged women
• Key hormonal abnormalities
  – Insulin resistance
  – Hyperandrogenism
• Metabolic, reproductive and psychological clinical features
• Obesity increases PCOS risk and severity
Outline

• PCOS overview
• Insulin resistance in PCOS
• Hyperandrogenism in PCOS
• AMH
• Management of PCOS
Insulin resistance

• Integral link between obesity, reproductive and metabolic features
• Gold standard measurement is hyperinsulinaemic euglycaemic clamps – direct measure
  – Difficult to perform in clinical setting
Insulin resistance in PCOS

- Intrinsic IR inherent to PCOS
- Obesity related extrinsic IR

- IR \rightarrow \uparrow \text{hyperinsulinaemia}
- Pancreatic $\beta$-cell dysfunction $\rightarrow$ IGT and T2DM
- 4-8 fold increase in diabetes in PCOS
Mechanisms of IR in PCOS

Post receptor defect in early stages transduction

Diamanti-Kandarakis, Dunaif Endo Reviews 2012
Insulin resistance in PCOS

Insulin Sensitivity and Effects of Obesity in PCOS

Freq sampled IVGTT

Legro  adapted from Dunaif, Sem Reprod Med 2012
Obesity and IR: clamps

Hutchison et al, JCEM 2011
Insulin resistance, PCOS and obesity

WHO criteria for IR
<25th centile on clamp studies

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

Overall 85% IR in PCOS

Stepto, Human Reprod 2013
Effect of obesity in PCOS

Table 3: Results of meta-analyses for studies comparing overweight and obese (BMI ≥ 25) to normal weight (BMI < 25) women with PCOS

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Studies</th>
<th>Participants</th>
<th>Mean difference (95% CI)</th>
<th>Statistical model, P value</th>
<th>$\chi^2$ (P value)</th>
<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol L⁻¹)</td>
<td>7</td>
<td>567</td>
<td>0.35 (0.07, 0.64), random, P = 0.01</td>
<td>19.09 (P = 0.004)</td>
<td>69</td>
<td></td>
</tr>
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<td>LDL-C (mmol L⁻¹)</td>
<td>4</td>
<td>201</td>
<td>0.35 (0.20, 0.50), fixed, P &lt; 0.001</td>
<td>5.53 (P = 0.14)</td>
<td>46</td>
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<td>5</td>
<td>384</td>
<td>-0.23 (-0.38, -0.07), random, P = 0.005</td>
<td>16.29 (P = 0.003)</td>
<td>75</td>
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<tr>
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<td>7</td>
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<td>0.37 (0.25, 0.50), random, P &lt; 0.001</td>
<td>35.72 (P &lt; 0.001)</td>
<td>83</td>
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Lim at al Obes Rev 2013
Measurement of IR and glycaemic abnormalities

- IR common in PCOS, but is not required for diagnosis
- Partly due to lack of accurate methods to measure IR in clinical setting
- Measurement of insulin levels not recommended in clinical setting due to assay variability and inaccuracy
Insulin assay

• American Diabetes Association task force - standardization of insulin assays in 1996
  – Wide variation in assay bias
  – Results for plasma and serum from the 17 assays studied varied by a factor of 2 (mostly RIAs)
  – Use of the same insulin reference preparation did not improve comparability, and the same assay method run in 2 laboratories yielded different results

• Confirmed by more recent studies
  – 2 fold variation

  Robbins et al, Diabetes 2006; Manley et al, Clinical Chemistry 2007
Glycaemic abnormalities in PCOS

- Earlier onset of glycaemic abnormalities
- May convert more rapidly from IGT to T2DM
- Prevalence of IGT and T2DM in PCOS compared to age and weight-matched women without PCOS

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

- 2.5 fold ↑ risk of IGT and a 4 fold ↑ risk of T2DM
- 2.94 fold ↑ risk of gestational diabetes (GDM)

Moran et al, Human Reproduction Update 2010
Boomsma et al, Human Reproduction Update 2006
Glycaemic abnormalities in PCOS

Moran et al, Human Reproduction Update, 2010
Glycaemic abnormalities in PCOS

Moran et al, Human Reproduction Update, 2010
Diabetes risk by BMI

Chan et al Diabetes Care
Role of OGTT in PCOS

• Impaired fasting glucose is a poor predictor of IGT in women in general and also particularly in PCOS
• Pre-diabetes presents vital prevention opportunity
• 90% with pre-diabetes missed on fasting glucose / HbA1c
• OGTT test of choice to detect pre-diabetes
  - reproductive aged women – pregnancy implications
  - opportunities for prevention of diabetes, guiding lifestyle
PCOS and diabetes screening

- Repeat OGTT every 2 years in women with PCOS
  - Consider repeat yearly in patients with additional risk factors
    - Age, gender, ethnicity, parental history of diabetes, history of high blood glucose, use of antihypertensive medications, smoking, physical inactivity, increased waist circumference
- Clinical practice point: If lean and young, frequency of testing could be reduced
Key points: PCOS, IR and obesity

• IR inherently increased in PCOS
• Exacerbated by obesity
• Impact of obesity on IR in PCOS more profound

• Clinical assessment
  – Insulin assay – variable and inaccurate
  – 75g OGTT for routine screening
Outline

• PCOS overview
• Insulin resistance in PCOS
• Hyperandrogenism in PCOS
• AMH
• Management of PCOS
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
Effect of obesity in PCOS

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<th>I² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-IRG (nmol L⁻¹)</td>
<td>12</td>
<td>986</td>
<td>-22.67 (-25.30, -19.75)</td>
<td>fixed, $P &lt; 0.001$</td>
<td>11.83 (P = 0.37)</td>
<td>8</td>
</tr>
<tr>
<td>Testosterone (nmol L⁻¹)</td>
<td>16</td>
<td>1,304</td>
<td>0.30 (0.05, 0.55)</td>
<td>random, $P = 0.02$</td>
<td>140.63 (P &lt; 0.001)</td>
<td>89</td>
</tr>
<tr>
<td>FAI</td>
<td>5</td>
<td>550</td>
<td>4.01 (2.28, 5.73)</td>
<td>random, $P &lt; 0.001$</td>
<td>11.97 (P = 0.02)</td>
<td>67</td>
</tr>
<tr>
<td>Hirsutism (FG score)</td>
<td>5</td>
<td>325</td>
<td>0.80 (0.22, 1.55)</td>
<td>fixed, $P = 0.009$</td>
<td>5.70 (P = 0.13)</td>
<td>47</td>
</tr>
<tr>
<td>Fasting insulin (pmol L⁻¹)</td>
<td>9</td>
<td>800</td>
<td>39.75 (29.95, 49.55)</td>
<td>random, $P &lt; 0.001$</td>
<td>20.40 (P = 0.09)</td>
<td>61</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>6</td>
<td>700</td>
<td>1.68 (1.06, 2.16)</td>
<td>random, $P &lt; 0.001$</td>
<td>46.10 (P &lt; 0.001)</td>
<td>89</td>
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<tr>
<td>Fasting glucose (nmol L⁻¹)</td>
<td>8</td>
<td>633</td>
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<td>2-h glucose (nmol L⁻¹)</td>
<td>2</td>
<td>364</td>
<td>0.95 (0.31, 1.59)</td>
<td>random, $P = 0.004$</td>
<td>4.80 (P = 0.03)</td>
<td>79</td>
</tr>
<tr>
<td>2-h insulin (mIU L⁻¹)</td>
<td>1</td>
<td>184</td>
<td>443.30 (303.69, 583.71)</td>
<td>fixed, $P &lt; 0.001$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>IFG/IGT, n</td>
<td>2</td>
<td>396</td>
<td>RR: 3.28 (0.21, 52.33)</td>
<td>random, $P = 0.39$</td>
<td>11.05 (P &lt; 0.001)</td>
<td>91</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>1</td>
<td>102</td>
<td>RR: 6.37 (0.38, 128.12)</td>
<td>fixed, $P &lt; 0.20$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total-C (mmol L⁻¹)</td>
<td>7</td>
<td>567</td>
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Lim at al Obes Rev 2013
Hyperandrogenism and obesity in PCOS

Ranasinha et al, Clinical Endocrinology, in press, 2015
Testosterone assays

• Testosterone assays originally developed to measure testosterone concentrations in the normal male range
• Reliable measurement of female testosterone concentrations is problematic
• Lack of precision and sensitivity of various commercially available testosterone assays
Testosterone assays

- RIA and chemiluminescence immunoassay
  - Most commonly used
  - Show good precision, but often show more bias, especially at lower range where they can be subject to increased interference and overestimation of steroid concentrations compared with other assays
- Extraction and chromatography methods preceding RIA
  - Advantage of removing interfering proteins and cross-reacting steroids.
  - Infrequently used in clinical practice because proper validation is lacking and extraction is labor intensive and time consuming
- Estimation of bioactive testosterone with calculation of FAI
  - FAI shown to correlate quite well with physical separation measures of female free testosterone
  - FAI is highly dependent on the quality of testosterone and SHBG assay measurements

Vermeulen et al, JCEM 1999; Stanczyk Steroids 2003; Rosner et al, JCEM 2010
Tandem mass spectrometry

- Tandem mass spectrometry preceded by gas or liquid chromatography assays for steroid measurement is emerging
  - Equal or better precision compared to immunoassays
  - No interferences due to chromatographic separation and mass spectrometry analysis

Janse et al, European Journal of Endocrinology, 2013
Tandem mass spectrometry

Janse et al, European Journal of Endocrinology, 2013
Hyperandrogenism in PCOS LC-MS

Does not differentiate between PCOS and non-PCOS

Handelsman, Teede, unpublished data 2015
Key points: hyperandrogenism in PCOS

• Hyperandrogenism key feature of PCOS - 80% affected

• Relationship with IR:
  - Driven by insulin, directly and via SHBG effects

• Exacerbated by obesity

• Testosterone assays – lack of precision and sensitivity

• LC-MS emerging
Outline

• PCOS overview
• Insulin resistance in PCOS
• Hyperandrogenism in PCOS
• AMH
• Management of PCOS
Anti-Mullerian hormone (AMH)

- 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
- A growing body of literature reports ↑ AMH concentrations in PCOS
  - May be related to increased number of pre-antral and antral follicles or ↑ production of AMH by these follicles
  - Mechanisms in PCOS are poorly understood
  - Have been attributed to obesity, IR, hyperandrogenism, gonadotrophins and their complex interactions

Pigny et al, JCEM 2003
<table>
<thead>
<tr>
<th>Variable</th>
<th>Serum AMH, ng/mL</th>
<th></th>
<th>P value</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5-10 (n = 84)</td>
<td>&gt;10-14 (n = 30)</td>
<td>&gt;14 (n = 20)</td>
<td>5-10 vs &gt;10-14</td>
<td>5-10 vs &gt;14</td>
<td>&gt;10-14 vs &gt;14</td>
</tr>
<tr>
<td>AMH, ng/mL</td>
<td>6.8 (1.5)</td>
<td>11.65 (1.1)</td>
<td>22.95 (10.1)</td>
<td>.01</td>
<td>NS</td>
<td>.04</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3 (5.0)</td>
<td>27.2 (5.7)</td>
<td>24.6 (4.5)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Age, y</td>
<td>30.2 (5.2)</td>
<td>30.1 (5.7)</td>
<td>29.5 (4.6)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FSH, IU/L</td>
<td>5.4 (2.2)</td>
<td>5.4 (1.5)</td>
<td>5.2 (1.6)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LH, IU/L</td>
<td>5.3 (3.1)</td>
<td>8.6 (5.5)</td>
<td>11.9 (7.9)</td>
<td>.02</td>
<td>.002</td>
<td>NS</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>0.98 (0.6)</td>
<td>1.6 (1.0)</td>
<td>2.2 (1.1)</td>
<td>.01</td>
<td>.001</td>
<td>.04</td>
</tr>
<tr>
<td>Testosterone, ng/dL</td>
<td>42.8 (20.9)</td>
<td>56.2 (28.4)</td>
<td>75.9 (22.8)</td>
<td>.04</td>
<td>&lt; .001</td>
<td>.02</td>
</tr>
<tr>
<td>DHEAS, µg/dL</td>
<td>201.3 (93.6)</td>
<td>188.1 (85)</td>
<td>249.2 (104)</td>
<td>NS</td>
<td>NS</td>
<td>.05</td>
</tr>
<tr>
<td>Hyperandrogenemia, %</td>
<td>38</td>
<td>47</td>
<td>80</td>
<td>NS</td>
<td>&lt; .001</td>
<td>.03</td>
</tr>
<tr>
<td>Polycystic ovaries, %</td>
<td>54.2</td>
<td>97</td>
<td>100</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>NS</td>
</tr>
<tr>
<td>Menstrual regularity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular periods, %</td>
<td>49.4</td>
<td>17</td>
<td>15</td>
<td>.002</td>
<td>.005</td>
<td>NS</td>
</tr>
<tr>
<td>Oligomenorrhea, %</td>
<td>49.4</td>
<td>77</td>
<td>55</td>
<td>.009</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Amenorrhea, %</td>
<td>1.2</td>
<td>6.7</td>
<td>30</td>
<td>NS</td>
<td>&lt; .0001</td>
<td>.03</td>
</tr>
<tr>
<td>PCOS diagnosis, %</td>
<td>51.8</td>
<td>97</td>
<td>100</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>NS</td>
</tr>
<tr>
<td>Infertility cause if present in addition to PCOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male factor, %</td>
<td>40</td>
<td>36.7</td>
<td>33.3</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Tubal factor, %</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Endometriosis, %</td>
<td>1.2</td>
<td>3.3</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are given as mean (SD) or as percentages. Overall P values were determined by Kruskal-Wallis test. P value < .05 was considered statistically significant.

AMH, anti Müllerian hormone; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle stimulating hormone; LH, luteinizing hormone; NS, nonsignificant; PCOS, polycystic ovarian syndrome.
AMH

- 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
Fig. 1 Concentration of AMH is lean and overweight women with and without PCOS demonstrated by a box and whisker plot illustrating the median (central line), range (whiskers) and 25 and 75th percentiles (box). Abbreviations: OW, overweight. Significant difference $P < 0.05$ compared with the a lean control, b lean PCOS, c overweight control, d overweight PCOS group.
AMH

- ROC curve - ability of AMH to distinguish women with PCOS - threshold value of ≥ 30 pmol/l
- At this cutoff point, 79% specificity and 82% sensitivity

Cassar et al, Clinical Endocrinology, 2014
Key points: AMH

• AMH may be ↑ in women with PCOS
• AMH does not currently have a role in PCOS diagnosis
Outline

• PCOS overview
• Insulin resistance in PCOS
• Hyperandrogenism in PCOS
• AMH
• Management of PCOS
PCOS management

Figure 2 Summary of a targeted approach to therapy in polycystic ovary syndrome (PCOS). Reproduced with permission from [82].

Teede et al, BMC Medicine 2010
Cycle irregularity

- Lifestyle change (5-10% weight loss + exercise)
- Oral contraceptive pill (OCP)
- Cyclical progestins every 2-3 months
- Metformin (improves ovulation and cycles)

Teede et al BMC Medicine 2010
Infertility

- 60% get pregnant unaided
- Obesity independently exacerbates infertility and reduces effectiveness of interventions.
- Maternal and fetal pregnancy risks are greater
- Consider age related infertility
- Infertility therapies may include clomiphene, metformin, gonadotrophins and IVF

Teede et al BMC Medicine 2010
Hirsutism

• Cosmetic therapy first line
• Laser recommended
• Medical therapy
  – If concerned and cosmetic therapy ineffective, inaccessible or unaffordable
  – Primary therapy is the OCP
  – Anti-androgen (with contraception)
  – Trial therapies for $\geq 6$ months before changing
  – Combination therapy – if ineffective
• Hair loss on scalp – often triple therapy

Teede et al BMC Medicine 2010
Metabolic syndrome, prediabetes, diabetes and cardiovascular disease risk

- Lifestyle / exercise is critical
- Prevention of weight gain vital
- Screening and prevention is critical
- Lifestyle change 5% weight loss reduces diabetes risk by ~50-60% and metformin by ~50% in high risk
- Metformin has role to relieve symptoms and reduce metabolic risk in high risk women with PCOS
- Metformin may limit weight gain

Teede et al BMC Medicine 2010
OCP or hormonal therapies

• OCP reduces androgenism/hair excess
• Contraception
• Endometrial protection

• Low dose OCP best

• OCP not approved in PCOS
• However recommended by international/national specialist societies and is evidence based
Metformin

• Improves ovulation/ cycles, limited fertility impact
• Reduces glucose, insulin and blood pressure
• Reduces progression to diabetes
• May prevent weight gain
• Side-effects
  – Gastrointestinal side effects
  – Rare but serious adverse effect - lactic acidosis (LA)

• Metformin not approved in PCOS
• However recommended by international/national specialist societies and is evidence based
Key points: management

• Complex condition, common
• Lifestyle critical for all
• Targeted therapy for reproductive dysfunction
• Metabolic- screen, prevent and manage risk
• Lifelong chronic illness; education
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