Polycystic ovary syndrome (PCOS)

Educational Slide Kit
Module 4
1. How frequently does PCOS occur in women of reproductive age?

A. 1 out of 3  
B. 1 out of 4  
C. 1 out of 5  
D. 1 out of 6
2. How often is amenorrhea related to PCOS?

A. 10 – 30% of cases
B. 30 – 40% of cases
C. 40 – 60% of cases
D. More than 60% of cases
3. Which PCOS phenotype(s) represents a higher risk for metabolic dysfunction?

A. A only
B. A and B
C. A, B and C
D. All phenotypes – A, B, C and D
4. Which of the following approaches is most relevant in the management of PCOS?

A. Lifestyle modification
B. Topical or cosmetic options
C. Pharmacological treatment
D. All of the above
Module content

• Defining polycystic ovary syndrome (PCOS)
• Presentation and prevalence of PCOS
• The burden of PCOS on health and quality of life
• Diagnosis and exclusion of other disease causes
• Treatment of PCOS and management of long term implications
Defining PCOS
Defining Polycystic ovary syndrome (PCOS)\textsuperscript{1}

Rotterdam (2003) Diagnostic criteria for PCOS - two out of three of:

- Clinical hyperandrogenism or biochemical hyperandrogenism \textbf{OR}
- Irregular menses \textbf{OR}
- Polycystic ovaries on ultrasound, after excluding other endocrine causes such as hyperprolactinemia

\textsuperscript{1}Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Hum Reprod 2004;19:41–7
The importance of phenotypic definition of PCOS

- Those with ‘classic’ PCOS phenotypes i.e. A and B are at greatest risk of metabolic dysfunction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phenotype A</th>
<th>Phenotype B</th>
<th>Phenotype C</th>
<th>Phenotype D</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS features</td>
<td>HA/OD/PCOM</td>
<td>HA/OD</td>
<td>HA/PCOM</td>
<td>OD/PCOM</td>
</tr>
<tr>
<td>Hyperandrogenism (HA)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ovulatory dysfunction (OD)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Polycystic ovarian morphology (PCOM)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Prevalence of different phenotypes varies widely

### Distribution of PCOS phenotypes in studies reported from unselected populations by countries (%)

<table>
<thead>
<tr>
<th>Country</th>
<th>Phenotype A</th>
<th>Phenotype B</th>
<th>Phenotype C</th>
<th>Phenotype D</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark n:447, PCOS: 86</td>
<td>4.7</td>
<td>4.7</td>
<td>72.1</td>
<td>18.6</td>
<td>Lauritsen, 2014</td>
</tr>
<tr>
<td>China n:15,924, PCOS:886</td>
<td>28.7</td>
<td>19.0</td>
<td>37.3</td>
<td>15.0</td>
<td>Li R, 2013</td>
</tr>
<tr>
<td>Australia n:728, PCOS:129.5</td>
<td>21.2</td>
<td>27.5</td>
<td>18.9</td>
<td>32.5</td>
<td>March, 2010</td>
</tr>
<tr>
<td>Mexico n:150, PCOS:10</td>
<td>70</td>
<td>20</td>
<td>0</td>
<td>10</td>
<td>Moran, 2010</td>
</tr>
<tr>
<td>Iran n:929, PCOS:136</td>
<td>12.9</td>
<td>22.4</td>
<td>49.4</td>
<td>15.3</td>
<td>Tehrani, 2014</td>
</tr>
<tr>
<td>Turkey n:392, PCOS:78</td>
<td>25.6</td>
<td>5.1</td>
<td>46.2</td>
<td>23.1</td>
<td>Yildiz, 2012</td>
</tr>
</tbody>
</table>

*Table adapted from Lizneva, 2016*
Presentation and prevalence of PCOS
The prevalence of PCOS

- PCOS is a common endocrine disorder affecting up to 1 in 6 women of reproductive age.*

  * When assessed using the Rotterdam criteria²

Variability in prevalence data for PCOS is due to:

- Different defining criteria of PCOS
- Geographic or ethnic variability of presenting symptoms
- Lack of specificity of symptoms to PCOS
- Variability in timing of symptom presentation

Polycystic ovary syndrome (PCOS) is a common cause of menstrual dysfunction$^1$

PCOS causes 85% of cases of oligomenorrhea...

...and 30-40% of cases of amenorrhea

Common presenting symptoms of PCOS include:

- Hirsutism
- Acne
- Menstrual cycle abnormalities
- Clinical elements of the metabolic syndrome
- Infertility$^2$

Primary presentation of PCOS symptoms may vary with age\textsuperscript{1-4}

Although PCOS presentation may be less clear in adolescents, the vast majority develop the phenotype clearly by the age of 18 years.\textsuperscript{4}

Long-term impact of PCOS extends to metabolic and reproductive risks

Clinical hyperandrogenic skin symptoms (hirsutism, acne, seborrhea, alopecia)\(^1,2\)

Type 2 diabetes\(^1\)

Insulin resistance\(^1\)

Cardiovascular disease\(^3\)

Menstrual dysfunction\(^1\)

Endometrial cancer\(^2,4\)

Infertility\(^1,3\)

The burden of PCOS on health and quality of life
PCOS has a negative impact on health-related quality of life1-5

Graph adapted from Elsenbruch S, 2003

Infertility contributes to quality of life impairment

- Women with PCOS are 3x more worried about their fertility than women with normal androgen levels\(^1\)

- Women with PCOS and fertility problems experience a 50% reduction in health-related quality of life\(^2\)

Women with PCOS have multiple long-term health implications\textsuperscript{1-3}

**CARDIOVASCULAR RISK**

At risk:
- Obesity
- Cigarette smoking
- Hypertension
- Dyslipidemia
- Subclinical vascular disease
- Impaired glucose tolerance
- Family history of premature cardiovascular disease

At high risk:
- Metabolic syndrome
- Type 2 diabetes
- Overt vascular, renal or cardiovascular disease

**REPRODUCTIVE RISK**

- Infertility\textsuperscript{1,2}
- Adverse pregnancy outcomes including risk of miscarriage\textsuperscript{2}
- Endometrial hyperplasia/cancer\textsuperscript{2,3}
Management of PCOS represents a significant financial burden to healthcare systems\(^1\)

<table>
<thead>
<tr>
<th>Symptoms included in literature review</th>
<th>Prevalence amongst women with PCOS (%)</th>
<th>Annual cost in millions US$ (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial evaluation</td>
<td></td>
<td>99 (2.3)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual dysfunction/abnormal uterine bleeding</td>
<td>75</td>
<td>1350 (30.9)</td>
</tr>
<tr>
<td>Hirsutism*</td>
<td>70</td>
<td>622 (14.2)</td>
</tr>
<tr>
<td>Infertility</td>
<td>50</td>
<td>533 (17.2)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>7.2</td>
<td>1766 (40.4)</td>
</tr>
<tr>
<td><strong>Total cost</strong></td>
<td></td>
<td>4370 (100.0)</td>
</tr>
</tbody>
</table>

* Treatment of hirsutism includes both cosmetic and hormonal therapies but does not take into account management of psychological and QoL impact or women’s own expenditure on treatment

Diagnosis of PCOS and exclusion of other causes
The global AWARE group PCOS Checklist

Assessment and Diagnosis of Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is a common, heterogeneous disorder affecting 6% to 21% of women worldwide.¹ The global AWARE group is an independent panel of physicians with expertise in the treatment of androgen excess in women. Formation of the AWARE group and its ongoing work is supported by Bayer AG.

1. **ASK**
   - **Medical history**
     - Menstrual irregularity (intervals <21 days or >35 days, prolonged or heavy menstrual bleeding)²
     - Ovulatory dysfunction (irregular intervals, intervals of <21 or >35 days, or delayed ovulation)²
     - Previous treatment and/or self care (e.g., shaving, waxing)
   - Regular waxing or shaving can disguise the presence of hyperandrogenic skin symptoms such as hirsutism

2. **ASSESS**³,⁵
   - **Hyperandrogenic manifestations**
     - Clinical presence of skin symptoms such as acne, hirsutism, seborrhea and alopecia
     - Biochemical evidence of elevated androgens
   - **Physical examination**
     - Body mass index (BMI)
     - Waist/height ratio (WHR)
     - Blood pressure (BP)

3. **CONSIDER**⁶–¹⁰
   - **Psychosocial impact**
     - Emotional wellbeing
   - **Long term health risks**
     - Androgen excess, particularly if there is accompanying anovulation or PCOS may lead to increased risk of metabolic syndrome and endometrial hyperplasia or malignancy if left untreated³

4. **TEST**¹⁴,⁵
   - **Investigations to confirm a diagnosis of PCOS remain the same regardless of phenotype**
     - **Ultrasound**
       - To confirm PCOS
     - **Serum 17-hydroxyprogesterone (OHP)**
       - To exclude other hyperandrogenic conditions e.g., thyroid disease, non-classical congenital adrenal hyperplasia, adrenal or ovarian tumors, androgen insensitivity syndrome
     - **DHEA-S**
     - **Serum or urine human chorionic gonadotrophin (hCG)**
       - To evaluate amenorrhea and exclude pregnancy
     - **Anti-Mullerian hormone (AMH)**
       - 4th urinary free cortisol
     - **Sex hormone binding globulin (SHBG)**
   - **Serum free IGF-1**
     - Other tests which may be helpful e.g., AMH has an emerging role in predicting Ovarian Hyperstimulation Syndrome (OHSS) in IVF cycles or to consider the presence of granulosa cell tumors

**Metabolic assessment following confirmation of PCOS**
- Complete lipid profile, including total cholesterol, low-density lipoprotein (LDL)-cholesterol, non-HDL cholesterol and triglycerides
- Oral glucose tolerance test (OGTT)
- Blood pressure

**Defining PCOS**
The Rotterdam criteria define PCOS by the presence of two of the following: irregular menses, hyperandrogenism (either clinical or biochemical) and polycystic ovary morphology, after exclusion of other androgen excess related disorders and endocrine causes such as hyperprolactinemia.

- Hyperandrogenism (HA)
- Ovulatory dysfunction (OD)
- Polycystic ovary morphology (POM)

**Parameter** | **Phenotype**
--- | ---
Hyperandrogenism (HA) | A + + + +
Ovulatory dysfunction (OD) | + + − +
Polycystic ovary morphology (POM) | + + + +

Note: adapted from Conney et al, 2013

¹ Other sources: Endocrine Society Clinical Practice Guidelines, European Society of Human reproduction and Embryology, American Society of Reproductive Medicine, and American College of Obstetricians and Gynecologists.

Confirming a diagnosis of PCOS and establishing phenotype

1. Regular waxing or shaving can disguise the severity of hyperandrogenic skin symptoms such as hirsutism.

Women in parts of Asia more commonly present with menstrual irregularities than hyperandrogenic skin symptoms.

2. ASSESS
   - Hyperandrogenic manifestations
     - Clinical presence of skin symptoms such as acne, hirsutism, seborrhea and alopecia
     - Biochemical evidence of elevated androgens
   - Physical examination
     - Body mass index (BMI)
     - Waist/height ratio (WHR)
     - Blood pressure (BP)

3. CONSIDER
   - Psychosocial impact
     - Emotional wellbeing
     - Quality of life
   - Long term health risks
     - Androgen excess, particularly if there is accompanying anovulation or PCOS may lead to increased risk of metabolic syndrome and endometrial hyperplasia or malignancy if left untreated
     - Hyperandrogenic skin symptoms are associated with significant quality of life and psychological impairment

References:
Additional tests and investigations are needed to exclude other causes of androgen excess.

<table>
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<th>4. TEST</th>
<th>Investigations to confirm a diagnosis of PCOS remain the same regardless of phenotype</th>
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<tr>
<td><strong>Please note:</strong> Use of these laboratory tests will be guided by local protocols and/or cost constraints according to clinical practice and availability.</td>
<td></td>
</tr>
</tbody>
</table>
| • Ultrasound | To confirm PCOS  
NB absence of ovarian morphology does not exclude diagnosis |
| • Serum 17-hydroxyprogesterone (OHP)  
• 24h urinary free cortisol  
• DHEA-S | To exclude other hyperandrogenic conditions  
e.g. thyroid disease, non-classical congenital adrenal hyperplasia, adrenal or ovarian tumors, acromegaly, Cushing syndrome and late-onset androgenital syndromes (AGS) |
| • Serum or urine human chorionic gonadotrophin (HCG) | To evaluate amenorrhea and exclude pregnancy |
| • Anti-Mullerian hormone (AMH) 4h urinary free cortisol  
• Sex hormone binding globulin (SHBG)  
• Serum free IGF-1 | Other tests which may be helpful  
e.g. AMH has an emerging role in predicting Ovarian Hyperstimulation Syndrome (OHSS) in IVF cycles or to consider the presence of granulose cell tumors |

**Metabolic assessment (following confirmation of PCOS)**

- Complete lipid profile, including total cholesterol, low-density lipoprotein (LDL)-cholesterol, non-high-density lipoprotein (HDL)-cholesterol, HDL-cholesterol and triglycerides
- Oral glucose tolerance test (OGTT)
- Blood pressure
Treatment of PCOS and management of long term implications
Goals of treatment for PCOS$^{1-4}$

✓ Improve skin symptoms
✓ Restore menstrual function
✓ Resolve infertility
✓ Improve quality of life
✓ Protect from long-term health problems

Overview of treatments for PCOS

• **Lifestyle modification**\(^1\)
  – Maintaining a healthy diet, exercise and achievement of weight reduction

• **Topical or cosmetic options**\(^2\)
  – Targets androgenic skin symptoms such as hirsutism and acne

• **Pharmacological treatment**\(^2\)
  – Aimed at reducing the level of circulating androgens and controlling their effect at tissue level

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Selection of appropriate antiandrogen therapy in PCOS

<table>
<thead>
<tr>
<th>Progestogen</th>
<th>Mode of action</th>
</tr>
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<tbody>
<tr>
<td>CPA</td>
<td>Inhibits the activity of 5-alpha-reductase and androgen synthesis in the skin and decreases androgen blood concentration through an antigonadotrophic effect.</td>
</tr>
<tr>
<td>CMA</td>
<td>Inhibits the activity of 5-alpha reductase in the skin and reduces ovarian and adrenal androgen production via its antigonadotrophic effect.</td>
</tr>
<tr>
<td>DNG</td>
<td>Possesses strong progestational effects and moderate Antiandrogenic and antigonadotrophic effects.</td>
</tr>
<tr>
<td>DRSP</td>
<td>Blocks ovarian steroid production, reduces adrenal androgen synthesis and blocks peripheral androgen receptors in the skin.</td>
</tr>
</tbody>
</table>

- A combination of EE with a progestogen that possesses antiandrogenic activity is regarded as the most appropriate choice for treatment of PCOS\(^1\)
- Antiandrogenic potential of EE/progestogen combinations varies according to the dose and type of progestogens used\(^2,3,4\)

CPA/EE offers effective treatment of androgen levels, hyperandrogenic skin symptoms and menstrual dysfunction\textsuperscript{1,2}

- Significant reduction in:\textsuperscript{1}
  - Acne lesion count and severity at 6 months
  - Hirsutism score (mF-G) and use of cosmetic treatments at 6 months
  - Sebum production at 9 months

- Additional benefits of menstrual regularity and effective contraception\textsuperscript{2}

- Reduction in long-term risk of endometrial hyperplasia and endometrial cancer\textsuperscript{2}

Clinical studies confirm an effect of CPA/EE on lipid metabolism\(^1\):
- Changes are generally within normal limits and of little clinical relevance

Improvement of biochemical hyperandrogenism with CPA/EE leads to a reduction in long-term risks of PCOS:\(^2\):
- Arterial diseases such as myocardial infarction
- Metabolic syndrome
- Onset of new diabetes

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Cardiovascular safety with EE/progestogen combinations

Use of estrogen/progestogen combinations is associated with an increased risk for VTE (DVT or PE)\textsuperscript{1,2}

The use of CPA/EE carries an increased risk of VTE/ATE compared with no use or LNG/EE use

- Highest during the 1\textsuperscript{st} year of use
- Highest when restarting or switching from another OC\textsuperscript{*}

However, the risk of VTE during COC use remains lower than that during pregnancy and childbirth\textsuperscript{3,4}

\textbf{ATE}, Arterial thromboembolism; \textbf{COC}, Combined oral contraceptive; \textbf{DVT}, Deep vein thrombosis; \textbf{PE}, Pulmonary embolism; \textbf{OC}, Oral contraceptive; \textbf{VTE}, Venous thromboembolism; \textbf{CPA/EE}, 0.035mg ethinylestradiol/2mg cyproterone acetate

Cardiovascular safety with EE/progestogen combinations (continued)

Due to its labeled indication, CPA/EE may channel use towards women with an inherently higher cardiovascular risk\(^1,2\)

Observational studies of VTE risk with CPA/EE compared to LNG-containing and other COCs (low-estrogen <0.05mg) yield varying findings

Some studies reported a greater VTE risk, comparable to so-called 3rd generation COCs\(^3-5\)

Other studies showed no differences in VTE risk\(^1,6,7\)

Studies that addressed the issue of confounding or duration of use concluded that the VTE risk is not significantly higher\(^1,7\)

COC, Combined oral contraceptive; LNG, Levonorgestrel; PCOS, Polycystic ovary syndrome; VTE, Venous thromboembolism; CPA/EE, 0.035mg ethinylestradiol/2mg cyproterone acetate.

Factors to consider before prescribing combined hormonal treatment

- The WHO MEC provides guidance on contraindications when prescribing combined hormonal treatment\(^1\)

1. WHO MEC, 5\(^{th}\) Ed. 2015.
AWARE group recommendations for safe and effective prescribing in PCOS
Position papers, consensus statements and guidelines are available to guide the management of PCOS¹-⁵

- Providing physicians with:
  - Overview of important clinical issues¹-⁴
  - Summary of best practice¹-⁵
  - Guidance on the management of long-term consequences⁵

Conclusions

- PCOS is a common cause of **menstrual dysfunction**\(^1\)
- Other common presenting symptoms include **hyperandrogenic skin symptoms**\(^1\) (seborrhea, acne hirsutism, or alopecia), **infertility**\(^2\) and clinical elements of the **metabolic syndrome**\(^1,3,4,5\)
- PCOS has a **negative impact** on health-related **quality of life**\(^1,6,7,8,9\) associated with multiple long-term health risks\(^1,3,4\)
- PCOS can be treated both with **pharmacological methods** and **lifestyle modification**\(^10-11\)
- **WHO MEC** provides guidance on contraindications when prescribing combined hormonal treatment\(^12\)

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Find The Global AWARE Group educational materials on the European Menopause & Andropause Society website

https://www.emas-online.org/nonemaseducationalmaterials/

FREE resources to download

The AWARE group is a panel of independent physicians with an expert interest in androgen excess in women. Formation of the AWARE group and its ongoing work is supported and funded by Bayer AG.