

Polycystic ovary syndrome (PCOS)

Educational Slide Kit

Module 4

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.

October 2018 PP-DIA-ALL-0046-1

- 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 <u>higher</u> 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



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

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

The importance of phenotypic definition of PCOS¹



	-			
Parameter	Phenotype A	Phenotype B	Phenotype C	Phenotype D
PCOS features	HA/OD/PCOM	HA/OD	НА/РСОМ	OD/PCOM
Hyperandrogenism (HA)	+	+	+	-
Ovulatory dysfunction (OD)	+	+	_	+
Polycystic ovarian morphology (PCOM)	+	-	+	+

Prevalence of different phenotypes varies widely¹



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

Country	Phenotyp e A	Phenotype B	Phenotype C	Phenotype D	Reference
Denmark n:447, PCOS: 86	4.7	4.7	72.1	18.6	Lauritsen, 2014
China n:15,924, PCOS:886	28.7	19.0	37.3	15.0	Li R, 2013
Australia n:728, PCOS:129.5	21.2	27.5	18.9	32.5	March, 2010
Mexico n:150, PCOS:10	70	20	0	10	Moran, 2010
Iran n:929, PCOS:136	12.9	22.4	49.4	15.3	Tehrani, 2014
Turkey n:392, PCOS:78	25.6	5.1	46.2	23.1	Yildiz, 2012
Table adapted from Lizneya 2016					

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^{*1}

* When assessed using the Rotterdam criteria²

Variability in prevalence data for PCOS is due to:²



- 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 dysfunction¹ PCOS causes 85% of cases of oligomenorrhea... ...and 30-40% of cases of amenorrhea **Common presenting symptoms of PCOS include:** Infertility² Hirsutism Menstrual cycle **Clinical elements** Acne abnormalities of the metabolic syndrome

Primary presentation of PCOS symptoms may vary with age¹⁻⁴





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

1. Sirmans SM & Pate KA. Clin Epidemiol 2014;6:1–13; 2. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 4. Lizneva D, et al. Fertil Steril 2016;106(1):6–15

Long-term impact of PCOS extends to metabolic and reproductive risks¹⁻⁴



1. Sirmans SM, Pate KA.. Clin Epidemiol 2014;6:1–13; 2. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 3. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565– 4592; 4. Haoula Z, et al. Human Reprod. 2012;27(5):1327-1331

The burden of PCOS on health and quality of life

PCOS has a negative impact on healthrelated quality of life¹⁻⁵



Graph adapted from Elsenbruch S, 2003

1. Elsenbruch S, et al. Quality-of-life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88(12):5801–7; 2. Sirmans SM & Pate KA. Clin Epidemiol. 2014;6:1–13; 3. Zafari Zangeneh F, et al. J Reprod Infertil. 2012;13(2):111–5; 4. Jones GL, et al. Hum Reprod Update. 2008;14:15–25; 5. Azziz R, et al. J Clin Endocrinol Metab. 2005;90:4650–8 Infertility contributes to quality of life impairment



- Women with PCOS are **3x** more worried about their fertility than women with normal androgen levels¹
- Women with PCOS and fertility problems experience a 50% reduction in health-related quality of life²

Women with PCOS have multiple long-term health implications¹⁻³





Management of PCOS represents a significant financial burden to healthcare systems¹

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

* 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



Confirming a diagnosis of PCOS and establishing phenotype¹⁻³





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



4. TEST^{4,5} Investigations to confirm a diagnosis of PCOS remain the same regardless of phenotype

Please note: Use of these laboratory tests will be guided by local protocols and/or cost constraints according to clinical practice and availability.

• 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 syndrome (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 (fo Complete lipid profile, inclu	bllowing confirmation of PCOS ding total cholesterol, low-density

- (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 PCOS¹⁻⁴

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



Overview of treatments for PCOS

Lifestyle modification¹

 Maintaining a healthy diet, exercise and achievement of weight reduction

Topical or cosmetic options²

 Targets androgenic skin symptoms such as hirsutism and acne

Pharmacological treatment²

 Aimed at reducing the level of circulating androgens and controlling their effect at tissue level





Selection of appropriate antiandrogen therapy in PCOS



Decreasing antiandrogenic effect

Progestogen	СРА	СМА	DNG	DRSP
	Inhibits the activity of	Inhibits the activity of		
	5-alpha-reductase and	5-alpha reductase in	Possesses strong	Blocks ovarian steroid
Mada	androgen synthesis in	the skin and reduces	progestational effects	production, reduces
wode	the skin and decreases	ovarian and adrenal	and moderate	adrenal androgen
of	androgen blood	androgen production	Antiandrogenic and	synthesis and blocks
action	concentration through	via its	antigonadotrophic	peripheral androgen
	an antigonadotrophic	antigonadotrophic	effects.	receptors in the skin.
	effect.	effect.		

- A combination of EE with a progestogen that possesses antiandrogenic activity is regarded as the most appropriate choice for treatment of PCOS¹
- 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^{1,2}



- Significant reduction in: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 contraception²
- Reduction in long-term risk of endometrial hyperplasia and endometrial cancer²



- Clinical studies confirm an effect of CPA/EE on lipid metabolism¹
 - 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

Cardiovascular safety with EE/progestogen combinations





ATE, Arterial thromboembolism; **COC**, Combined oral contraceptive; **DVT**, Deep vein thrombosis; **PE**, Pulmonary embolism; **OC**, Oral contraceptive; **VTE**, Venous thromboembolism; **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.

1. Seaman HE, et al. Pharmacoepidemiol Drug Saf 2004;13(7):427–436; 2. Bird ST, et al. J Thromb Haemost 2013;11(6):1059–1068; 3. Vasilakis-Scaramozza C et al. Lancet 2001;358(9291):1427–9; 4. Seaman HE, et al. Hum Reprod 2003;18(3):522–6; 5. Lidegaard Ø, et al. Acta Obstet Gynecol Scand 2013;92(10):1135–1142; 6. Lidegaard Ø, et al. J Obstet Gynaecol Can 2003;25(7):575–7; 7. EURAS 2007

Factors to consider before prescribing combined hormonal treatment



 The WHO MEC provides guidance on contraindications when prescribing combined hormonal treatment¹



AWARE group recommendations for safe and effective prescribing in PCOS



BEFINING POOS 2.AS5E951 -4. TEST^A is only clean in an ing a stage. Parlimente en subira 520 que s Hyperson design hars-a The Global ALC: N Aware Group hing dynamics of the hereb optic requirements (F. P. 1 1 Appropriate Care For Women With Andragen Excess () a.a 🕜 1. ASK School Follow In give a man ball of a mail y the Safety defender 'n opter enveld apound - 7 o 17 betra enderved 🕎 5. EXPLAIN in a sector de la sector Periodi interferenzi des entre e effective des Prophysical generation de la composition What to explain?

Assessment and Diagnosis of Polycystic Ovary Syndrome (PCO5)

he Global Wate Group

- The importance of lifestyle management including regular exercise and healthy eating behaviour
- The pathophysiology of symptoms in simple, patient-focused language
- How the treatments work
- The need for a follow-up plan

Why?

- Lifestyle modification is important for all women affected by PCOS: moderate weight loss (5 to 10%) in women with PCOS can improve insulin resistance as well as androgenic and reproductive outcomes⁴
- Increasing patient knowledge helps to empower patients¹¹
- Explaining how treatments work can help patients understand the importance of correct and consistent treatment, especially in long term conditions¹²
- Skin symptoms such as acre and hirsutism often require long-term treatment¹³
- PCOS is associated with long-term metabolic and reproductive health risks?

 $\Omega_{\rm e}$ with Qintendial CFA. Quarter over notate, CFA, at large due notate, $\Omega M \Omega_{\rm e}$ d is equal

Essentials for safe and effective prescribing in the management of PCOS

😯 6. MANAGE

What to manage?

- Symptoms of clinical hyperandrogenism i.e. hirsutism, acne, seborrhea or alopecia
- Symptoms of biochemical hyperandrogenism such as endometrial or metabolic complications
- Use established treatment combinations for androgen excess and follow clinical guidelines and relevant criteria for use.
- Patients must be carefully screened before using any estrogen/
- progestogen combinations, and pregnancy must be excluded • Further guidance on contraundications is available in the, 'WHO MEC for contraceptive use''t

Why?

- Effective treatment can help to improve the significant quality of life and psychological impairment associated with hyperandrogenic skin symptoms^{14,15}
- To help reduce the risk of both reproductive and metabolic/ cardiovascular consequences associated with long term androgen excess disorders^{3,11}
- EE in combination with progestogens with antiandrogenic potential (CPA, CMA, DNG or DRSP) are preferred treatment options^{16/7}
- CPA combined with EE is indicated for the treatment of moderate to severe acre related androgen sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age¹⁸¹⁸

🔁 7. REFER IF

What to refer?

- Abnormal findings (ovaries or endometrium) with clinical ultrasound
- Evidence of metabolic disorders

Why?

- Further imaging procedures may be needed
- For effective assessment and treatment

April 2017 LUM 04070410412217.0017 Position papers, consensus statements and guidelines are available to guide the management of PCOS¹⁻⁵



1. Goodman NF, et al. Endocrinol Pract. 2015;21(12):1415–26; 2. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 4. Conway G, et al. Eur J Endocrinol. 2014;171:1–29; 5. RCOG. Green-top Guideline No. 33. November 2014

Conclusions



- PCOS is a common cause of menstrual dysfunction¹
- Other common presenting symptoms include hyperandrogenic skin symptoms¹ (seborrhea, acne hirsutism, or alopecia), infertility² 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 modification¹⁰⁻¹¹
- WHO MEC provides guidance on contraindications when prescribing combined hormonal treatment¹²

^{1.} Sirmans SM & Pate KA. Clin Epidemiol 2014;6:1–13; 2. Androgen Excess and PCOS Society Education Committee.2016 Accessed at: http://www.ae-society.org/pdf/handouts/pcos.pdf; 3. Fauser BCJM, et al. Fertil Steril 2012;97:28–38; 4. Legro RS, et al. J Clin Endocrinol Metab 2013;98:4565–4592; 5. Haoula Z, Salman M, Atiomo W. Human Reprod. 2012;27(5):1327-1331; 6. Elsenbruch S, et al. J Clin Endocrinol Metab 2003;88(12):5801–7; 7. Zafari Zangeneh F, et al. J Reprod Infertil. 2012;13(2):111–5; 8. Jones GL, et al. Hum Reprod Update. 2008;14:15–25; 9. Azziz R, et al. J Clin Endocrinol Metab. 2005;90:4650–8; 10. Moran LJ, et al. Cochrane Database Syst Rev 2011;16(2):CD007506; 11. Goodman NF, et al. Endocrin Pract 2015;21(11):1291– 1300; 12. WHO MEC, 5th ed. 2015

- 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^{1,2}



2. How often is amenorrhea related to PCOS?

- A. 10 30% of cases
- B. 30 40% of cases¹
- 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 C¹

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^{1,2}

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

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



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.