Pharmacological treatment of adolescent Polycystic Ovary Syndrome (PCOS) according to the 2018 International Evidence-Based Guidelines for the Assessment and Management of PCOS

Alexia Peña [1], Selma Witchel [2], Kathy Hoeger [3], Sharon Oberfield [4], Marie Misso [6], Maria Vogiatzi [5] and Helena Teede [6]

[1] University of Adelaide, Discipline of Paediatrics, North Adelaide, Australia

[2] Children's Hospital of Pittsburgh of University of Pittsburgh Medical Center, Pediatric Endocrinology

iversity of Rochester School of Medicine and Dentistry, Division Chief, Reproductive Endocrinology and Infertility.

[4] Columbia University Medical Center

[5] The Children's Hospital of Philadelphia.

[6] Monash Centre for Health Research and Implementation – MCHRI, Monash University

Background

Polycystic ovary syndrome (PCOS) is the most common endocrine condition affecting reproductive aged women[1-2]. Previous guidelines for assessment and management of PCOS have not followed rigorous best practice in development, failed to engage consumers and international multidisciplinary perspectives or were outdated[1-3] resulting in inconsistent guidelines for clinicians. The aim of international evidence-based PCOS guidelines was to promote accurate diagnosis, optimal consistent care, prevention of complications and improve patient health outcomes.

Methods

Extensive international health professional and patient engagement informed the priorities and core outcomes for the guidelines. International nominated panels including women with PCOS, multidisciplinary teams of health care professionals, researchers and an evidence synthesis and translation team developed the guidelines that were funded and led by NHMRC Australia (project number APP1078444). The evidence-based guideline development followed international best practice involving 60 systematic/narrative reviews and applying full Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to reflect quality of the evidence, and consider feasibility, acceptability, cost, implementation and the strength of recommendations[3].

Categories of the PCOS guideline recommendations and quality of evidence categories are summarised below (Table 1 and 2):

Table I Categories of recommendations in the PCOS guideline.

EBR	Evidence-based recommendations are made where evidence is sufficient to inform a recommendation made by the guideline development group.
CCR	Clinical consensus recommendations are made in the absence of adequate evidence on PCOS. These are informed by evidence in other populations and are made by the guideline development group, using rigorous and transparent processes.
CPP	Clinical practice points are made where evidence was not sought and are made where important clinical issues arose from discussion of evidence-based or clinical consensus recommendations.

Table II Quality (certainty) of evidence categories.*

High	⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	⊕⊕⊕O	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.
Low	⊕⊕OO	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very Low	⊕OOO	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Adapted from the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (GRADE working group).

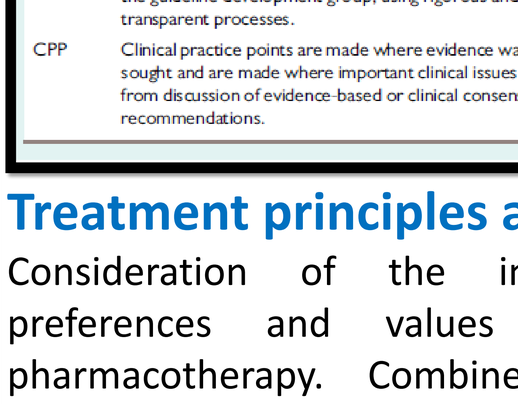
Treatment principles and recommendations

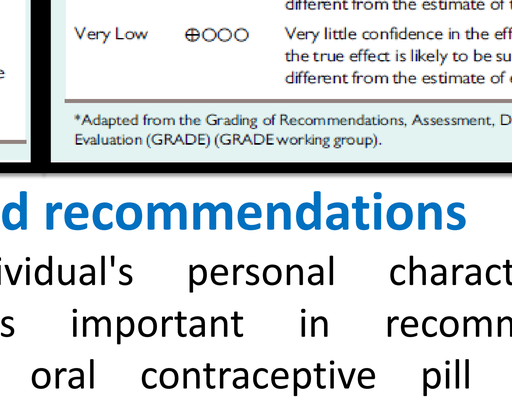
Consideration of the individual's personal characteristics, preferences and values is important in recommending pharmacotherapy. Combined oral contraceptive pill (COCP), metformin and other medications are generally off label for PCOS. However off label use is evidence-based and is allowed in many countries. Antiandrogens must be used with effective contraception. Holistic approaches are required and pharmacotherapy in PCOS should be considered alongside education, lifestyle (behavioural, diet and exercise) and other options including cosmetic therapy and counselling. Treatment recommendations are included in table 3.

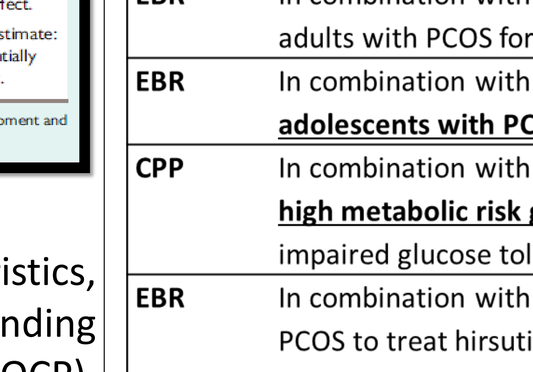
These guidelines are subject to extensive translation including a personalised patient app and certified online health professional training programs (figure 1).

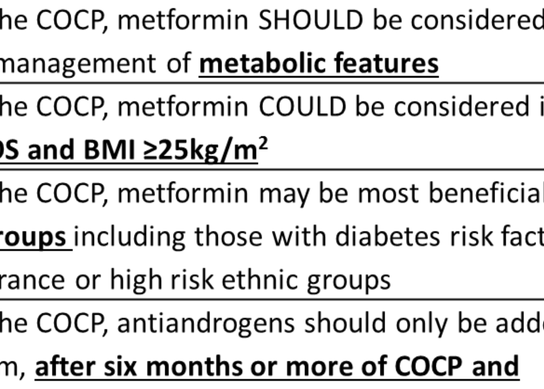
Table 3	Recommendations	Grade	Quality
	Combined oral contraceptive pill (COCP)		
EBR	COCP alone should be recommended in adults for clinical hyperandrogenism and irregular menstrual cycles	****	⊕⊕oo
EBR	COCP alone should be considered in **adolescents with a clear diagnosis of PCOS for management of clinical hyperandrogenism and irregular menstrual cycles**	***	⊕⊕oo
EBR	The COCP could be considered **in adolescents who are deemed "at risk" but not yet diagnosed with PCOS** for management of clinical hyperandrogenism and irregular menstrual cycles	***	⊕⊕oo
EBR	**Specific types or dose of progestins, estrogens or combinations of COCP cannot currently be recommended** with inadequate evidence in PCOS. Practice should be informed by general population guidelines	***	⊕⊕oo
	Metformin		
EBR	Metformin in addition to lifestyle, could be recommended in adult women with PCOS**, for the treatment of weight, hormonal and metabolic outcomes**	***	⊕⊕oo
EBR	Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI ≥25kg/m^2 for management of weight and metabolic outcomes	***	⊕⊕oo
EBR	Metformin in additional to lifestyle could be considered in **adolescents with a clear diagnosis of PCOS or with symptoms of PCOS before the diagnosis is made**	***	⊕⊕oo
CPP	Metformin may offer greater benefit in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high risk ethnic groups		
CPP	Where metformin is prescribed the following should be considered: • **adverse effects**, including gastrointestinal side-effects that are generally dose dependent and self-limiting, should be the subject of individualised discussion • **starting at a low dose, with 500mg increments** one-two weekly and extended release preparations may minimize side effects • metformin use **appears safe long-term**, based on use in other populations, however ongoing requirement should be considered and use may be associated with low vitamin B12 levels • use is **generally off label** and health professionals should inform women and discuss the evidence, possible concerns and side effects		
	COCP in combination with metformin and/or anti-androgen pharmacological agents		
EBR	In combination with the COCP, metformin SHOULD be considered in adults with PCOS for management of **metabolic features**	****	⊕⊕oo
EBR	In combination with the COCP, metformin COULD be considered in **adolescents with PCOS and BMI ≥25kg/m^2**	****	⊕⊕oo
CPP	In combination with the COCP, metformin may be most beneficial in **high metabolic risk groups** including those with diabetes risk factors, impaired glucose tolerance or high risk ethnic groups		
EBR	In combination with the COCP, antiandrogens should only be added in PCOS to treat hirsutism, **after six months or more of COCP and cosmetic therapy** have failed to adequately improve symptoms	**	⊕⊕oo
CR	In combination with the COCP, antiandrogens could be considered for the treatment of female pattern hair loss in PCOS	**	
	Anti-androgens		
EBR	**Where COCPs are contraindicated or poorly tolerated**, in the presence of other effective forms of contraception, anti-androgens could be considered to treat hirsutism and androgen-related alopecia	***	⊕ooo
CPP	**Specific types or doses of antiandrogens** cannot currently be recommended with inadequate evidence in PCOS		
CPP	Variable availability and regulatory status of these agents is notable and for some agents, potential liver toxicity requires caution		
	Inositol		
EBR	Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research	*	⊕ooo

Figure 1. Resources for Women with PCOS (Guidelines and other resources available: https://www.monash.edu/medicine/sphpm/mchri/pcos)









References:

1. Teede HJ et al, Med J Aust 2011.
2. Legro RS et al, J Clin Endocrinol Metab 2013.
3. Teede HJ et al, Hum Reprod 2018.