DRAFT
International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome
2018

For public consultation and will be submitted to NHMRC for consideration of approval under section 14A of the NHMRC Act 1992.
Publication approval
This draft guideline is released for public consultation and will be submitted to the National Health and Medical Research Council (NHMRC) for consideration of approval under section 14A of the NHMRC Act 1992. Collaborator and partner organisations have agreed that the NHMRC will be the single approving body for the International Evidence-based Guidelines in the Assessment and Management of PCOS. These organisations have agreed to form special interest groups to review the guideline and provide feedback during the public consultation period consistent with best practice NHMRC guideline development processes.

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Disclaimer
The Centre for Excellence in PCOS research in partnership with the European Society of Human Reproduction and Embryology (ESHRE) and American Society of Reproductive Medicine (ASRM), and in collaboration with professional societies and consumer advocacy groups internationally, developed the current evidence-based guideline, to provide evidence-based recommendations to improve the quality of healthcare, health outcomes and quality of life of women with PCOS. This guideline represents the integration of the best evidence available at the time of preparation, multidisciplinary, international clinical perspectives and patient preferences. In the absence of scientific evidence in PCOS, evidence from the general population was considered and a consensus between the engaged stakeholders was obtained.

The aim of evidenced-based guidelines is to aid healthcare professionals and consumers in decisions about appropriate and effective care, although recommendations are generalised and application requires consideration of individual patient characteristics and preferences.

Adherence to these guidelines does not guarantee a successful or specific outcome in an individual or override the healthcare professional's clinical judgment or patient preference in diagnosis and treatment of individual patients. Ultimately, healthcare professionals must make their own clinical decisions on a case-by-case basis, using their clinical judgment, knowledge, and expertise, and taking into account the condition, circumstances, and perspectives of the individual patient, in consultation with that patient and/or the guardian or carer.

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2. Our partner organisations which co-funded the guideline:
   - American Society for Reproductive Medicine (ASRM)
   - European Society of Human Reproduction and Embryology (ESHRE)

3. Our collaborating societies and consumer groups:
   - Androgen Excess and Polycystic Ovary Syndrome Society (AEPCOS)
   - African Society for Paediatric and Adolescent Endocrinology (ASPAE)
   - Asia Pacific Paediatric Endocrine Society (APPES)
   - Asia Pacific Initiative on Reproduction (ASPIRE)
   - Australasian Paediatric Endocrine Group (APEG)
   - Australian Diabetes Society (ADS)
   - Australian Psychological Society
   - British Fertility Society (BFS)
   - Canadian Society of Endocrinology and Metabolism (CSEM)
   - Dietitians Association Australia
   - Endocrine Society (US Endo)
   - Endocrine Society Australia (ESA)
   - European Society of Endocrinology (ESE)
   - European Society for Paediatric Endocrinology (ESPE)
   - Exercise and Sports Science Australia (EESA)
   - Federation of Obstetric and Gynaecological Societies of India (FOGSI)
   - Fertility Society Australia (FSA)
   - International Society of Endocrinology (ISE)
   - International Federation of Fertility Societies (IFFS)
   - International Federation of Gynecology and Obstetrics (FIGO)
   - Italian Society of Gynaecology and Obstetrics
   - Japanese Society for Paediatric Endocrinology (JSPE)
   - Latin American Society for Paediatric Endocrinology (SLEP)
   - Nordic Federation of Societies of Obstetrics and Gynaecology (NFOG)
   - PCOS Challenge
   - PCOS Society of India
   - Paediatric Endocrine Society (PES)
   - Polycystic Ovary Association Australia (POSSA)
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   - Royal Australian College of General Practitioners (RACGP)
   - Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)
   - Royal College of Obstetricians and Gynaecologists (RCOG)
   - South African Society of Gynaecology and Obstetrics (SASOG)
   - Victorian Assisted Reproductive Technology Association (VARTA)

Other relevant organisations are welcome to partner in guideline translation once approved.
Contents

Publication approval .................................................................................................................................... 2
Publication history ....................................................................................................................................... 2
Disclaimer .................................................................................................................................................... 2
Copyright information ................................................................................................................................. 3
Acknowledgments ....................................................................................................................................... 4
Preface ................................................................................................................................................................. 8
Executive summary – Guideline process and recommendations ................................................................. 9
Context and background ................................................................................................................................ 10
PCOS diagnostic criteria ................................................................................................................................ 11
Recommendations ............................................................................................................................................. 13
Introduction ....................................................................................................................................................... 29
  Guideline purpose and aims .......................................................................................................................... 29
  Key principles .................................................................................................................................................. 29
  Patient population ......................................................................................................................................... 29
  Setting and audience .................................................................................................................................... 29
  Governance ................................................................................................................................................... 30
  Guideline Development groups (GDGs) ........................................................................................................ 30
  Prioritised clinical questions .......................................................................................................................... 30
CHAPTER ONE      Screening, diagnostic assessment, risk assessment and life-stage ...................................... 33
  1.1 Irregular cycles and ovulatory dysfunction ............................................................................................ 33
  1.2 Biochemical hyperandrogenism ............................................................................................................. 34
  1.3 Clinical hyperandrogenism ..................................................................................................................... 36
  1.4 Ultrasound and polycystic ovarian morphology (PCOM) ....................................................................... 38
  1.5 Anti-Müllerian Hormone (AMH) ............................................................................................................. 41
  1.6 Ethnic variation ....................................................................................................................................... 42
  1.7 Menopause life-stage .............................................................................................................................. 43
  1.8 Cardiovascular disease ........................................................................................................................... 44
  1.9 Gestational diabetes, impaired glucose tolerance and type 2 diabetes ................................................ 46
  1.10 Obstructive sleep apnea (OSA) ............................................................................................................. 49
  1.11 Endometrial cancer ............................................................................................................................... 50
CHAPTER TWO      Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing..... 52
  2.1 Quality of life .......................................................................................................................................... 52
2.2 Depressive and anxiety symptoms, screening and treatment ............................................................... 53
2.3 Psychosexual function ............................................................................................................................ 57
2.4 Body image ............................................................................................................................................. 58
2.5 Eating disorders and disordered eating ............................................................................................... 60
2.6 Information resources, models of care, cultural and linguistic considerations ...................................... 62

CHAPTER THREE       Lifestyle ............................................................................................................................. 65
3.1 Effectiveness of lifestyle interventions ................................................................................................. 65
3.2 Behavioural interventions .................................................................................................................... 67
3.3 Dietary interventions ............................................................................................................................ 68
3.4 Exercise interventions ........................................................................................................................... 70
3.5 Obesity and weight assessment ........................................................................................................... 72

CHAPTER FOUR Pharmacological treatment for non-fertility indications .................................................... 75
4.2 Combined Oral Contraceptive Pills (COCP) ............................................................................................. 75
4.4 Metformin ............................................................................................................................................... 81
4.5 Anti-obesity pharmacological agents ..................................................................................................... 85
4.6 Anti-androgen pharmacological agents ................................................................................................. 87
4.7 Inositol .................................................................................................................................................... 89

CHAPTER FIVE       Assessment and treatment of infertility .............................................................................. 91
5.1a Assessment of factors that may affect fertility, treatment response or pregnancy outcomes .......... 91
5.1b) Tubal patency testing .......................................................................................................................... 93
5.2 Ovulation induction principles ............................................................................................................. 94
5.3 Letrozole ................................................................................................................................................. 94
5.4 Clomiphene citrate and metformin ........................................................................................................ 96
5.5 Gonadotrophins ..................................................................................................................................... 99
5.6 Anti-obesity agents ............................................................................................................................... 101
5.7 Laparoscopic ovarian surgery ............................................................................................................... 102
5.8 Bariatric surgery ................................................................................................................................... 105
5.9a In-vitro fertilisation (IVF) .................................................................................................................... 106
5.9b GnRH protocol .................................................................................................................................... 108
5.9c Trigger type ......................................................................................................................................... 109
5.9d Choice of FSH .................................................................................................................................... 110
5.9e Exogenous LH ..................................................................................................................................... 111
5.9f Adjunct metformin ............................................................................................................................... 112
5.9g In-vitro maturation (IVM) .................................................................................................................. 113
CHAPTER SIX  Guideline development methods

Governance

Multidisciplinary international guideline development groups

Clinical question development and prioritisation

Outcome prioritisation using the GRADE method

Adaptation of existing evidence based guidelines

Evidence reviews to answer the clinical questions

Quality (certainty) of the body of evidence using GRADE evidence profiles

Formulation of recommendations using the GRADE evidence to decision framework

Public consultation

External review

Scheduled review and update of the guideline

Translation and implementation

References

Appendix I: Project board

Appendix II: International Advisory Panel

Appendix III: Guideline development groups

Guideline development technical team members

Appendix IV:

Appendix V: Abbreviations and acronyms

Appendix VI: Glossary

Appendix VII: Evidence-based guideline development pathway
Preface

This International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome, designed to provide clear information to assist clinical decision making and support optimal patient care, is the culmination of the work of over 3000 health professionals and consumers internationally. The vast majority gave of their time and expertise voluntarily. We fully appreciate the considerable contributions of the guideline development group members and particularly of the project board (Appendix I), international advisory board (Appendix II) and most importantly to the chairs, co-chairs and members of the international, multidisciplinary guideline development groups (Appendix III).

We acknowledge the tireless efforts, commitment, dedication and drive of the Project Director, Professor Helena Teede and Project Manager, Ms Linda Downes, the Senior Evidence Officer, Dr Marie Misso, the Project board chair Professor Robert Norman and the Guideline Evidence Team for their contribution. We acknowledge the enthusiasm and engagement of the over 1600 health professionals and 1500 women affected by PCOS, our partners ESHRE and ASRM and our collaborating societies and consumer advocacy and support organisations internationally. This engagement has guided prioritisation of clinical questions, identification of gaps and needs, clinical outcomes of importance, review of evidence and formulations of guidelines and consideration of implementation and translation issues.

Professor Helena Teede MBBS, PhD, FRACP, FAHMS.
Director NHMRC Centre of Excellence in PCOS and Guideline lead
Executive Director Monash Partners Academic Health Sciences Centre
Head Monash Centre for Health Research and Implementation – MCHRI,
Monash Public Health and Medicine, Monash University
Executive summary – Guideline process and recommendations

This international guideline addresses health professional and consumer priorities. It integrates the best available evidence with international, multidisciplinary clinical expertise and consumer preferences to provide health professionals, consumers and policy makers with guidance for timely diagnosis, accurate assessment and optimal treatment of polycystic ovary syndrome (PCOS). The guideline aims to promote accurate diagnosis, optimal consistent care, prevention of complications and improved patient experience and health outcomes for the one in ten women worldwide with PCOS.

Extensive international health professional and patient engagement informed the need, priorities and core outcomes for the guideline. International Society-nominated panels and co-opted experts included women with PCOS, paediatricians, endocrinologists, gynaecologists, primary care physicians, reproductive endocrinologists, psychiatrists, psychologists, dermatologists, dieticians, exercise physiologists, public health experts, researchers, and a project management, evidence synthesis and translation team developed the guideline.

Evidence-based guideline development followed international best practice, involving 60 systematic and narrative reviews and applying the full Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to reflect quality of evidence, and consider feasibility, acceptability, cost, implementation and ultimately the strength of recommendations.

Governance included an international advisory board from six continents, a project board, five guideline development groups with 8-10 members each, advisors and a translation committee. Special Interest groups of world experts were formulated to review and provide feedback on the guidelines. Guideline development groups and special interest groups/ experts were nominated by the partner and collaborator organisations. The Australian Centre for Research Excellence in PCOS, funded by the National Health and Medical Research Council (NHMRC), partnered with the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) to fund and complete the guideline. Four project board and 15 guideline development group face to face meetings occurred across Europe, USA and Australia over 15 months, and enabled training, guideline development and informed translation. Sixty prioritised clinical questions were addressed with 40 systematic and 20 narrative reviews, generating 170 recommendations and practice points. Feedback from our over 40 partner and collaborator special interest groups is now sought during consultation to inform the final guideline.

Summary of recommendations:

For the purposes of this guideline, we have unanimously endorsed the Rotterdam diagnostic criteria for PCOS (two from: clinical or biochemical hyperandrogenism, ovulatory dysfunction, or polycystic ovaries on ultrasound) in adult women. Caution should be applied in making a diagnosis in adolescents, with both hyperandrogenism and ovulatory dysfunction required and ultrasound not recommended. In adults, where irregular menstrual cycles and hyperandrogenism are present, an ovarian ultrasound is not necessary for diagnosis. Clinical hyperandrogenism requires well considered assessment using scoring tools and if present assessment of biochemical androgen status, which requires high quality assays, may not be required.
Ultrasound criteria have been modified, given advancing ultrasound technology and anti-Müllerian hormone levels were deemed not yet adequate for PCOS diagnosis. Weight, body mass index, cardiovascular risk factors and glucose status require assessment, whilst other potential complications require consideration including obstructive sleep apnea and endometrial cancer.

Care should be provided in partnership with women promote self-empowerment and include with education. Culturally and linguistically appropriate approaches are needed. Depressive and anxiety symptoms should be screened for whilst quality of life, body image, psychosexual dysfunction, eating disorders and disordered eating are increased in PCOS and require consideration. Health lifestyle is important to prevent weight gain and lifestyle intervention including behavioural, dietary and exercise components should be recommended to manage excess weight, with no optimal specific dietary recommendations in PCOS.

Combined oral contraceptive pills are first-line pharmacological management for menstrual irregularity and hyperandrogenism, with no specific preparations recommended and caution advised with higher dose preparations. Metformin is recommended in addition or alone, primarily for metabolic features, whilst the evidence for and role of anti-androgens and anti-obesity agents in PCOS are limited and inositol is currently considered experimental therapy.

Health should be optimised before and during pregnancy in PCOS to reduce complications. In women with PCOS, anovulatory infertility and no other fertility factors, letrozole is recommended as first-line pharmacological infertility treatment; with clomiphene and metformin also showing efficacy. Gonadotrophins are generally second line where oral ovulation induction has failed and laparoscopic surgery could be considered second line. Bariatric surgery and anti-obesity agents remain experimental for improving fertility. In-vitro fertilisation could be considered where first or second line ovulation induction therapies fail.

In PCOS, research is generally inadequate and of low to moderate quality and should be significantly expanded given that the condition affects one in ten women internationally. The guideline is supported by a well-informed translation program engaging all international partner and collaborator organisations and including novel resources such as a consumer targeted app that promotes personalised care in PCOS. The guideline and translation program will be rigorously evaluated.

Context and background

Polycystic ovary syndrome (PCOS) is a significant public health issue with reproductive, metabolic and psychological features. PCOS is one of the most common conditions in reproductive aged women affecting 8-13% of reproductive-aged women [2-5] with up to 70% of affected women remaining undiagnosed [4]. Presentation varies by ethnicity and in high risk populations such as Indigenous women, prevalence and complications are higher [5, 6]. Women with PCOS present with diverse features including psychological (anxiety, depression) [7-9], reproductive (irregular menstrual cycles, hirsutism, infertility and pregnancy complications) [10] and metabolic features (insulin resistance (IR), metabolic syndrome, prediabetes, type 2 diabetes (DM2) and cardiovascular risk factors) [11, 12].

Diagnosis and treatment of PCOS remain controversial with challenges defining individual components within the diagnostic criteria, significant clinical heterogeneity generating a range of phenotypes, ethnic differences and variation in clinical features across the life course. These factors contribute to variation in diagnosis and care across geographical regions and health professional groups [13]. This culminates in delayed diagnosis,
poor diagnosis experience and dissatisfaction with care reported by women internationally [14]. These challenges are exacerbated by a lack of recognition of the diverse features of PCOS, inadequate funding for quality research and a lack of comprehensive international evidence-based guidelines [15]. In this context, there was a compelling need for development and translation of an International Evidence-based Guideline for Assessment and Management of PCOS addressing psychological, metabolic and reproductive features of PCOS, promoting consistent evidence-based care and guiding and encouraging research in PCOS.

The extensive international guideline network across our partners and collaborators engaged in prioritisation of clinical questions and outcomes, identification of gaps in knowledge and care and into translation preferences and information needs for health professionals and consumers. This stakeholder engagement directly informed the guideline and translation program and involved over 3000 health professionals and consumers with PCOS. Our partners and collaborators contributed members to the guideline governance, development and translation committees. They formed special interest groups with considerable expertise in PCOS to provide feedback during the public consultation process and are engaged in translation and evaluation. Partners and collaborators have agreed that the NHMRC is the single approving body for the guideline, and we will seek individual endorsement of the final guideline after NHMRC approval.

Governance included international representation across the Advisory Committee, Project Board, Consumer reference group, Translation Committee and five multidisciplinary Guideline Development Groups comprising partner and collaborator nominated experts, practising clinicians and consumers (Appendix I-III). International best practice comprehensive methods for evidence review and guideline development were applied, aligned with the NHMRC and EHSRE requirements. A highly experienced team undertook evidence synthesis with a focus on study designs least susceptible to bias; a priori criteria for inclusion and appraisal of studies, stakeholder prioritised clinical questions and outcome measures, extraction of study data; quality appraisal and meta-analysis where appropriate. Recommendations were formulated using the considered judgement process in the GRADE framework [16] across the quality of available evidence, integrating clinical expertise and consumer preference, and considering the applicability, feasibility, equity, cost effectiveness, implementation and value for consumers and health professionals through the GRADE framework. Implementation issues and international health systems and settings were also considered.

### PCOS diagnostic criteria

The project board and international guideline development groups endorsed the overarching ESHRE and ASRM Rotterdam diagnostic criteria for PCOS [1] (Figure 1) aligned with prior evidence based Australian, UK, European, and US guidelines, and with the National Institute of Health (NIH) evidence based workshop [17-21].

**Figure 1: Rotterdam diagnostic criteria for PCOS**

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

and exclusion of other aetiologies of the above features [1]

We recommend that PCOS be diagnosed:
• In adolescents (<20 years of age) who are more than two years after onset of menarche, where both androgen excess and ovulatory dysfunction are present. Ultrasound is not recommended for diagnosis in this age group.

• In adult women if two of the three of androgen excess, ovulatory dysfunction, or polycystic ovarian morphology are present, with ultrasound required where either androgen excess or ovulatory dysfunction are not present.

• Where disorders of exclusion are ruled out including thyroid disease (thyroid stimulating hormone), hyperprolactinemia (prolactin level), and non-classic congenital adrenal hyperplasia (serum 17-OHP) in all women with further assessment guided by clinical judgement.

We acknowledge the challenges in defining individual diagnostic components of each of these criteria, especially in adolescence and at menopause where diagnostic features undergo natural evolution. These challenges are explored within the guideline.

Importantly, we recognise that PCOS is an insulin resistant, metabolic disorder, however measurement of insulin resistance currently lack accuracy and therefore cannot be incorporated into PCOS diagnostic criteria at this time.

We recognise that women with PCOS have greater prevalence and severity of psychological symptoms and poorer quality of life, and whilst assessment is important, these features are not included in current diagnostic criteria.

We also endorse the recommendation of the NIH evidence-based methodology workshop in PCOS [21], that specific phenotypes should be reported explicitly in all research and ideally identified in practice across:

A) Androgen Excess + Ovulatory Dysfunction + Polycystic Ovarian Morphology
B) Androgen Excess + Ovulatory Dysfunction
C) Androgen Excess + Polycystic Ovarian Morphology
D) Ovulatory Dysfunction + Polycystic Ovarian Morphology
Recommendations

Interpreting the guideline recommendations

Detailed methods for stakeholder engagement and guideline development can be found in Chapter six: Guideline development methods. In developing and interpreting the recommendations in this guideline, evidence has been evaluated alongside multidisciplinary health professional expertise and consumer perspectives. The latter two are transparently captured in the GRADE frameworks, alongside voting to reflect degree of consensus (see technical reports). To assist in interpreting the recommendations, these are presented by i) category, ii) terms used, iii) GRADE and iv) quality of evidence.

i) **Recommendation category** is either evidence-based or consensus. When sufficient evidence was available in PCOS, an evidence based recommendation was made, where there was insufficient evidence in PCOS, evidence in general or other relevant populations was considered and if appropriate and there was consensus, clinical consensus recommendations were made. Clinical practice points were included for implementation issues such as safety, side effects and risks (Table 2).

Table 2: Recommendation categories generated by the evidence synthesis team and guideline development group

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EBR</td>
<td>Evidence sufficient to inform an Evidence-based recommendation (EBR)</td>
</tr>
<tr>
<td>CCR</td>
<td>In the absence of adequate evidence in PCOS, a clinical consensus recommendation (CCR) was made</td>
</tr>
<tr>
<td>CPP</td>
<td>Evidence not sought. A clinical practice point (CPP) was made where important issues arose from discussion of evidence-based or clinical consensus recommendations</td>
</tr>
</tbody>
</table>

ii) **The recommendation terms** include “should”, “could” and “should not” based on the nature of the recommendation, GRADE framework and quality of evidence and are independent descriptors intended to reflect the judgement of the multidisciplinary guideline development group which includes consumers. They refer to the practical application of the recommendation, balancing benefits and harms. Where the word “should” is used in the recommendations, the guideline development group judged that the benefits of the recommendation exceed the harms. Where the word “could” is used, either the quality of evidence was limited or the available studies did not clearly demonstrate advantage of one approach over another, or the balance of benefits to harm was unclear. Where the words “should not” are used, there is either a lack of appropriate evidence, or the harms outweigh the benefits.

iii) **GRADE of recommendations** were determined by the guideline development group based on comprehensive consideration of all elements of the GRADE framework [16]: desirable and undesirable effects, balance of effects, resource requirements and cost effectiveness, equity, acceptability, 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.

iv) **Quality of evidence** was according to: information about the number and design of studies addressing the outcome; judgments about the quality of the studies and/or synthesised evidence, across risk of bias, inconsistency, indirectness, imprecision and any other quality considerations: key statistical data; and
classification of importance of 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 (table 3) [16].

Table 3: Quality (certainty) of evidence categories (adapted from GRADE [16]):

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>⊕⊕⊕⊕</td>
<td>Confidence that the true effect lies close to that of the estimate of the effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>⊕⊕⊕</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>⊕⊕</td>
<td>Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</td>
</tr>
<tr>
<td>Very Low</td>
<td>⊕</td>
<td>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 the quality of evidence is a continuum; any discrete categorisation is therefore somewhat arbitrary, nevertheless, advantages of simplicity and transparency outweigh these limitations [16].

The Recommendations table (table 4) includes the category, terms, GRADE of the recommendation and the quality of the evidence. Within the body of the guideline we integrate a summary of the clinical need for the question, the clinical question, the evidence summary (systematic and/or narrative), the recommendation and practice points and a justification developed by the guideline development groups. The extensive full evidence tables and individual GRADE frameworks supporting each recommendation, can be found in the supplementary Technical reports, along with voting to reflect degree of consensus.
Table 4: Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>Category</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>Screening, diagnostic assessment, risk assessment and life-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td></td>
<td>Irregular cycles and ovulatory dysfunction</td>
<td>****</td>
<td></td>
</tr>
<tr>
<td>1.1.1</td>
<td>CR</td>
<td>In adolescents (&lt;20 years), two years after the onset of menarche, if a patient reports irregular menstrual cycles (&gt;35 or &lt;21 days) a diagnosis of PCOS should be considered and assessed according to the guidelines</td>
<td>****</td>
<td></td>
</tr>
<tr>
<td>1.1.2</td>
<td>CR</td>
<td>In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors</td>
<td>****</td>
<td></td>
</tr>
<tr>
<td>1.1.3</td>
<td>CPP</td>
<td>Irregular menstrual cycles (&gt;35 days of &lt;21 days) in adult women clinically reflect ovulatory dysfunction. However ovulatory dysfunction can still occur with regular cycles and biochemical progesterone levels can be assessed when PCOS is clinically suspected and cycles are regular</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.1.4</td>
<td>CPP</td>
<td>When commencing hormonal contraception in adolescents, in relation to PCOS assessment and diagnosis, the following should be considered: • after twelve months of irregular menstrual cycles (&gt;35 or &lt;21 days) following onset of menarche, baseline assessment of clinical and biochemical hyperandrogenism and cycle patterns can be completed before commencement of hormonal contraception • if baseline assessment is abnormal, potential increased risk of PCOS could be discussed with the patient and future reassessment recommended</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.2</td>
<td></td>
<td>Biochemical hyperandrogenism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2.1</td>
<td>EBR</td>
<td>Calculated bioavailable testosterone, calculated free testosterone or free androgen index should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS</td>
<td>****</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>1.2.2</td>
<td>EBR</td>
<td>High quality assays such as liquid chromatography–mass spectrometry (LCMS)/ mass spectrometry and extraction/chromatography immunoasays, should be used for the most accurate assessment of total or free testosterone in PCOS</td>
<td>***</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>1.2.3</td>
<td>EBR</td>
<td>Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however these provide limited additional information in the diagnosis of PCOS</td>
<td>***</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>1.2.4</td>
<td>CR</td>
<td>Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in assessment of biochemical hyperandrogenism in PCOS, as they demonstrate poor sensitivity, accuracy and precision</td>
<td>****</td>
<td>-</td>
</tr>
<tr>
<td>1.2.5</td>
<td>CPP</td>
<td>Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin- dependent androgen production</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.2.6</td>
<td>CPP</td>
<td>Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal should occur for three months or longer before measurement, and contraception should be managed alternatively during this time</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.2.7</td>
<td>CPP</td>
<td>Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS, and the phenotype where clinical signs of hyperandrogenism are unclear or absent, in particular hirsutism</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.2.8</td>
<td>CPP</td>
<td>Interpretation of androgen levels should be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values should ideally be determined by the</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Recommendations

| 1.2.9 | CPP | Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism, including neoplasia, and rare syndromes of severe insulin resistance, should be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism. |   |   |
| 1.3 | Clinical hyperandrogenism |
| 1.3.1 | CR | A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism | **** |   |
| 1.3.2 | CR | Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and reporting of unwanted excess hair growth or female pattern hair loss should be considered important in assessment and management, regardless of apparent clinical severity | **** |   |
| 1.3.3 | CR | Standardized visual scales are preferred when assessing hirsutism such as the modified Ferriman Gallway score (mFG) with a level >3 and more often >5 indicating hirsutism, acknowledging that self-treatment is common and can limit clinical assessment | **** |   |
| 1.3.4 | CR | The Ludwig visual score is preferred for assessing female pattern hair loss, whilst no universally accepted visual instruments are available for assessing acne | **** |   |
| 1.3.5 | CPP | The mFG cut-off scores for defining hirsutism are the same across ethnicities, yet the prevalence and degree of hirsutism severity varies by ethnicity |   |   |
| 1.3.6 | CPP | As ethnic variation in vellus hair density is notable, over-estimation of hirsutism may occur if vellus hair is confused with terminal hair; only terminal hairs should be considered in pathological hirsutism, with terminal hairs clinically growing >5 mm in length if untreated, varying in shape and texture and generally being pigmented |   |   |
| 1.4 | Ultrasound and polycystic ovarian morphology (PCOM) |
| 1.4.1 | CR | Ultrasound should not be used for the diagnosis of PCOS in adolescence, due to the high incidence of multi-follicular ovaries in this life stage | **** |   |
| 1.4.2 | CR | The threshold for PCOM should be revised regularly with advancing ultrasound technology and age specific cut off values for PCOM should be defined | **** |   |
| 1.4.3 | CR | The transvaginal ultrasound approach should be used in the diagnosis of PCOS if acceptable to the patient, with the exception of those not yet sexually active | **** |   |
| 1.4.4 | CR | Using ultrasound transducers with a frequency > 8MHz, the threshold for PCOM should be a follicle number per ovary of ≥ 18 and/or an ovarian volume > 10 ml, ensuring no corpora lutea, cysts or dominant follicles are present in one or both ovaries | **** |   |
| 1.4.5 | CPP | In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however ultrasound will identify the complete PCOS phenotype |   |   |
| 1.4.6 | CPP | Transabdominal ultrasound should primarily report ovarian volume with a threshold of ≥ 10ml, given the difficulty of accurately assessing follicle number with this approach |   |   |
| 1.4.7 | CPP | If using lower resolution ultrasound transducers with a frequency < 8MHz, the threshold for PCOM should be a follicle number per ovary of ≥ 12 and/or an ovarian volume ≥ 10ml |   |   |
| 1.4.8 | CPP | Clear protocols are recommended for reporting antral follicle count and ovarian volume on ultrasound. Minimum reporting standards should include: * Last menstrual period |   |   |
### Recommendations

**1.4.9 CPP** There is a need for training in careful and meticulous counting of antral follicle numbers per ovary, to improve reporting

**1.5 Anti- Müllerian Hormone (AMH)**

1.5.1 EBR 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

1.5.2 CPP 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 may become useful in the detection of PCOM in future

**1.6 Ethnic variation**

1.6.1 CR Health professionals should consider ethnic variation in the presentation and manifestations of PCOS, including differences in hirsutism and acanthosis nigricans and in metabolic sequelae including obesity and insulin resistance

**1.7 Menopause life stage**

1.7.1 CR Post-menopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism

1.7.2 CR A diagnosis of PCOS postmenopause could be considered if there is a past diagnosis of PCOS or a long term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive years

1.7.3 CPP Postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, should be investigated to rule out androgen-secreting tumours and ovarian hyperthecosis

**1.8 Cardiovascular disease risk**

1.8.1 CR All those with PCOS should be assessed for weight gain and excess weight at every visit, in consultation with and where acceptable to the individual woman (see obesity and weight assessment section)

1.8.2 CR Weight, height, BMI and ideally waist circumference should be measured and the following considered:
- BMI categories and waist circumference should follow World Health Organisation guidelines
- Consideration should be given for Asian and high risk ethnicity and for adolescent specific ranges

1.8.3 CR All women with PCOS should be assessed for individual cardiovascular risk factors and global CVD risk

1.8.4 CR If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD

1.8.5 CR All women with PCOS, regardless of age, should have a lipid profile (Total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and Triglyceride level at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidemia and global CVD risk

1.8.6 CR All women with PCOS, should have blood pressure measured annually or more frequently based on global CVD risk
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8.7 CPP</td>
<td></td>
<td>Consideration should be given to the significant differences in CVD risk across ethnicities, when determining frequency of risk assessment</td>
</tr>
<tr>
<td>1.9 CR</td>
<td></td>
<td>Gestational diabetes, impaired glucose tolerance and type 2 diabetes</td>
</tr>
<tr>
<td>1.9.1 CR</td>
<td></td>
<td>Health professionals and women with PCOS should be aware that, regardless of age, the prevalence of gestational diabetes, impaired glucose tolerance and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are significantly increased in PCOS, with risk independent of, yet exacerbated by obesity</td>
</tr>
<tr>
<td>1.9.2 CR</td>
<td></td>
<td>Glycaemic status should be assessed at baseline in all women with PCOS. Thereafter, assessment should be every one to three years, influenced by the presence of other diabetes risk factors</td>
</tr>
<tr>
<td>1.9.3 CR</td>
<td></td>
<td>An oral glucose tolerance test (OGTT), should be performed at baseline in high risk women with PCOS (including a BMI &gt;25 or in Asian &gt;23kg/m², history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of DM2, hypertension or high risk ethnicity). Fasting plasma glucose or HbA1c may be substituted in women with PCOS without other diabetes risk factors</td>
</tr>
<tr>
<td>1.9.4 CR</td>
<td></td>
<td>An OGTT should be offered in all women with PCOS who are planning pregnancy or seeking fertility treatment preconception or at antenatal booking and then at 28 weeks gestation, given the high risk of gestational and type 2 diabetes and the associated comorbidities in pregnancy</td>
</tr>
<tr>
<td>1.10 CR</td>
<td></td>
<td>Obstructive Sleep Apnea (OSA)</td>
</tr>
<tr>
<td>1.10.1 CR</td>
<td></td>
<td>Screening should only be considered for OSA in PCOS to identify and alleviate related symptoms, such as snoring, waking unrefreshed from sleep, daytime sleepiness, and the potential for fatigue to contribute to mood disorders. Screening should not be considered with the intention of improving cardiometabolic risk, with inadequate evidence for metabolic benefits of OSA treatment in PCOS and in general populations</td>
</tr>
<tr>
<td>1.10.2 CR</td>
<td></td>
<td>A simple screening questionnaire, preferably the Berlin tool, could be applied and if positive, referral to a specialist considered</td>
</tr>
<tr>
<td>1.10.3 CPP</td>
<td></td>
<td>A positive screen raises the likelihood of OSA, however it does not quantify symptom burden and alone does not justify treatment. If women with PCOS have OSA symptoms and a positive screen, they should ideally be referred to a specialist centre for further evaluation</td>
</tr>
<tr>
<td>1.11 CR</td>
<td></td>
<td>Endometrial cancer</td>
</tr>
<tr>
<td>1.11.1 CR</td>
<td></td>
<td>Health professionals and women with PCOS should be aware of a two to six fold increased risk of endometrial cancer, which often presents before menopause; however absolute risk of endometrial cancer remains relatively low</td>
</tr>
<tr>
<td>1.11.2 CPP</td>
<td></td>
<td>Health professionals should have a low threshold for investigation of endometrial cancer in women with PCOS or a history of PCOS, with investigation by transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or prolonged oligo amenorrhea and/or abnormal vaginal bleeding. However routine ultrasound screening of endometrial thickness in PCOS is not recommended</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing</td>
</tr>
<tr>
<td>2.1 CR</td>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td>2.1.1 CR</td>
<td></td>
<td>Health professionals and women should be aware of the adverse impact of PCOS on quality of life</td>
</tr>
<tr>
<td>2.1.2 CR</td>
<td></td>
<td>Health professionals should capture and consider women’s perceptions of their symptoms, impact on their quality of life and personal priorities for care to improve patient outcomes</td>
</tr>
<tr>
<td>Section</td>
<td>Code</td>
<td>Text</td>
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<tr>
<td>2.1.3</td>
<td>CPP</td>
<td>The PCOS quality of life tool (PCOSQ) or the modified PCOSQ may be useful clinically</td>
</tr>
<tr>
<td>2.2</td>
<td><strong>Depressive and anxiety symptoms, screening and treatment</strong></td>
<td></td>
</tr>
<tr>
<td>2.2.1</td>
<td>CR</td>
<td>Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents</td>
</tr>
<tr>
<td>2.2.2</td>
<td>CR</td>
<td>Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis and if the screen is positive, health professionals should further assess and/or refer for assessment</td>
</tr>
<tr>
<td>2.2.3</td>
<td>CR</td>
<td>If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered to women with PCOS, informed by regional clinical practice guidelines</td>
</tr>
<tr>
<td>2.2.4</td>
<td>CPP</td>
<td>The optimal interval for anxiety and depressive symptom screening is not known. A pragmatic approach could include repeat screening using clinical judgment, considering risk factors, comorbidities and life events</td>
</tr>
</tbody>
</table>
| 2.2.5 | CPP | Assessment of anxiety and/or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened using the following stepped approach:  
**Step 1:** Initial questions could include:  
- 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 |
| 2.2.6 | CPP | Where pharmacological treatment is offered in PCOS, the following should be considered:  
- Caution is needed to avoid inappropriate treatment with antidepressants or anxiolytics. Where, mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, treatment of depression or anxiety should be informed by clinical regional practice guidelines  
- Use of agents that exacerbate PCOS symptoms including exacerbating weight gain, should be limited |
| 2.3 | **Psychosexual function** |
| 2.3.1 | CR | All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider screening in adult women with PCOS |
| 2.3.2 | CR | If psychosexual dysfunction is suspected, further assessment, referral or treatment should follow as appropriate |
| 2.3.3 | CPP | Obesity and infertility are common in PCOS and need consideration as they independently exacerbate psychosexual dysfunction |
| 2.4 | **Body Image** |
| 2.4.1 | CR | Health professionals and women should be aware that features of PCOS can impact on body image |
| 2.4.2 | CPP | Negative body image, can be screened using the following stepped approach:  
**Step 1:** Initial questions could include:  
- Do you worry a lot about the way you look and wish you could think about it less? |
• On a typical day, do you spend more than 1 hour per day worrying about your appearance? (More than 1 hour a day is considered excessive)
• What specific concerns do you have about your appearance?
• What effect does it have on your life?
• Does it make it hard to do your work or be with your friends and family?

**Step 2:** If an issue is identified, health professionals could further assess by:
• Identifying any focus of concern of the patient and respond appropriately
• Assessing the level of depression and/or anxiety
• Identifying distortion of body image or disordered eating

### Eating disorders and disordered eating

<table>
<thead>
<tr>
<th>2.5.1</th>
<th>CR</th>
<th>All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5.2</td>
<td>CR</td>
<td>If eating disorders and disordered eating are suspected, further assessment, referral or treatment including psychological therapy could be offered, informed by regional clinical practice guidelines</td>
</tr>
</tbody>
</table>
| 2.5.3  | CPP | Eating disorders and disordered eating can be screened using the following stepped approach.  
**Step 1:** The SCOFF screening tool can be used or initial screening questions can include:  
• Does your weight affect the way you feel about yourself?  
• Are you satisfied with your eating patterns?  
**Step 2:** If the SCOFF tool or any of these questions are positive, further screening should involve:  
• Assessment of risk factors and symptoms using age, culturally and regionally appropriate tools  
• Referral to an appropriate health professional for further mental health assessment and diagnostic interview. If this is not the patient’s usual healthcare provider, inform the primary care physician |

### Information resources, models of care, cultural and linguistic considerations

<table>
<thead>
<tr>
<th>2.6.1</th>
<th>CR</th>
<th>Information and education resources for women with PCOS should be culturally appropriate, tailored and high-quality, should use a respectful and empathetic approach, and promote self-care and highlight peer support groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.6.2</td>
<td>CR</td>
<td>Information and education resources for healthcare professionals should promote the recommended diagnostic criteria, appropriate screening for comorbidities and effective lifestyle and pharmacological management</td>
</tr>
<tr>
<td>2.6.3</td>
<td>CR</td>
<td>PCOS information should be comprehensive, evidence-based and inclusive of the biospsychosocial dimensions of PCOS across the life-span</td>
</tr>
<tr>
<td>2.6.4</td>
<td>CR</td>
<td>Women’s needs, communication preferences, beliefs and culture should be considered and addressed through provision of culturally and linguistically appropriate resources and care</td>
</tr>
<tr>
<td>2.6.5</td>
<td>CPP</td>
<td>Interdisciplinary care should be offered to those with PCOS where appropriate and available</td>
</tr>
<tr>
<td>2.6.7</td>
<td>CPP</td>
<td>Care should be provided in partnership with women with PCOS</td>
</tr>
<tr>
<td>2.6.8</td>
<td>CPP</td>
<td>Guideline dissemination and translation including multimodal education tools and resources is important, with consultation and engagement with stakeholders internationally</td>
</tr>
</tbody>
</table>

### Lifestyle

<table>
<thead>
<tr>
<th>3.1.1</th>
<th>EBR</th>
<th>Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural intervention) should be recommended in women with PCOS and excess weight for reductions in weight, central obesity and insulin resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.2</td>
<td>CR</td>
<td>Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all women with PCOS to achieve and</td>
</tr>
<tr>
<td>Section</td>
<td>Type</td>
<td>Description</td>
</tr>
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<tr>
<td>3.1.3</td>
<td>CPP</td>
<td>Achievable goals such as 5% to 10% weight loss in overweight women yields significant clinical improvements and is considered successful weight reduction within six months. Ongoing assessment and monitoring is important during weight loss and maintenance in all women with PCOS</td>
</tr>
<tr>
<td>3.1.4</td>
<td>CPP</td>
<td>SMART (Specific Measurable, Achievable, Realistic and Timely) goal setting and self-monitoring can enable achievement of realistic lifestyle goals</td>
</tr>
<tr>
<td>3.1.5</td>
<td>CPP</td>
<td>Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, should be considered and managed to optimise engagement and adherence to lifestyle interventions</td>
</tr>
<tr>
<td>3.1.6</td>
<td>CPP</td>
<td>Health professional interactions around healthy lifestyle including diet and exercise, should be respectful, patient-centred and should value women’s individualised healthy lifestyle preferences and cultural and ethnic differences. Health professionals should also consider personal sensitivities, marginalisation and potential weight-related stigma</td>
</tr>
<tr>
<td>3.1.7</td>
<td>CPP</td>
<td>Adolescent and ethnic-specific body mass index and waist circumference categories should be considered when optimising lifestyle and weight management</td>
</tr>
<tr>
<td>3.1.8</td>
<td>CPP</td>
<td>Healthy lifestyle may contribute to health and quality of life benefits in the absence of weight loss</td>
</tr>
<tr>
<td>3.1.9</td>
<td>CPP</td>
<td>Healthy lifestyle and optimal weight management is the joint responsibility of all health professionals, partnering with women with PCOS. Where complex issues arise, referral to suitably trained allied health professionals should be considered</td>
</tr>
<tr>
<td>3.1.10</td>
<td>CPP</td>
<td>Ethnic groups with PCOS who are at high cardiometabolic risk require greater consideration in terms of healthy lifestyle and lifestyle intervention</td>
</tr>
</tbody>
</table>

### 3.2 Behavioural Interventions

<table>
<thead>
<tr>
<th>Section</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1</td>
<td>CR</td>
<td>Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS</td>
</tr>
<tr>
<td>3.2.2</td>
<td>CPP</td>
<td>Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS</td>
</tr>
</tbody>
</table>

### 3.3 Dietary Intervention

<table>
<thead>
<tr>
<th>Section</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3.1</td>
<td>CR</td>
<td>A variety of balanced dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in women with PCOS and overweight and obesity, as per general population recommendations</td>
</tr>
<tr>
<td>3.3.2</td>
<td>CR</td>
<td>General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations</td>
</tr>
<tr>
<td>3.3.3</td>
<td>CPP</td>
<td>To achieve weight loss, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kJ/day) should be prescribed for women, also considering individual energy requirements, body weight and physical activity levels</td>
</tr>
<tr>
<td>3.3.4</td>
<td>CPP</td>
<td>In women with PCOS, there is no or limited evidence that any specific energy equivalent diet type is better than another, or that there is any differential response to weight management intervention, compared to women without PCOS</td>
</tr>
<tr>
<td>3.3.5</td>
<td>CPP</td>
<td>Tailoring of dietary changes to food preferences, allowing for a flexible and individual approach to reducing energy intake and avoiding unduly restrictive</td>
</tr>
</tbody>
</table>
and nutritionally unbalanced diets are important, as per general population recommendations

<table>
<thead>
<tr>
<th>3.4</th>
<th>Exercise Intervention</th>
</tr>
</thead>
</table>
| 3.4.1 CR | Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:  
- in adults from 18-64 years, a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both including muscle strengthening activities on 2 non-consecutive days/week  
- in adolescents at least 60 minutes of moderate to vigorous intensity physical activity/day including those that strengthen muscle and bone, at least 3 times weekly  
- activity be performed in at least 10 minutes bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days | *** |

| 3.4.2 CR | Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits including:  
- a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both AND  
- muscle strengthening activities such as resistance or flexibility activities on 2 non-consecutive days/week  
- minimised sedentary or sitting time | *** |

| 3.4.3 CPP | Physical activity includes leisure time physical activity, transportation such as walking or cycling, occupational work, household chores, games, sports or planned exercise, in the context of daily, family and community activities with 10,000 steps per day being ideal, including activities of daily living plus 30 minutes of structured physical activity or around 3000 steps. Structuring of recommended activities around women's and family preferences and cultural considerations is recommended | _ |

| 3.4.4 CPP | Realistic physical activity SMART goals could include progressively increasing physical activity 5% weekly up to and above recommendations | _ |

| 3.4.5 CPP | Self-monitoring including with fitness tracking devices and technologies could be used as an adjunct to support and promote active lifestyles and minimise sedentary behaviours | _ |

<table>
<thead>
<tr>
<th>3.5</th>
<th>Obesity and weight assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5.1 CR</td>
<td>Health professionals and women should be aware that women with PCOS have an increased risk of weight gain and obesity, presenting significant concerns for women, impacting on health and emotional wellbeing, with a clear need for prevention</td>
</tr>
</tbody>
</table>

| 3.5.2 CR | Assessment for excess weight and weight gain should be considered at every visit in women with PCOS, in consultation with and where acceptable to the individual woman | **** |

| 3.5.3 CR | Weight, height, BMI and where appropriate waist circumference should be assessed and the following considered:  
- BMI categories and waist circumference should follow World Health Organisation guidelines  
- Consideration should be given for Asian and high risk ethnicity and for adolescent specific ranges | *** |

| 3.5.4 CPP | When assessing weight, related stigma, negative body image and/or low self-esteem should be considered and assessment should be respectful and considerate. Beforehand, explanations on the purpose and how the information will be used and the opportunity for questions and preferences should be provided, permission sought and scales and tape measures | _ |
adequate. Implications of results should be explained and where this impacts on emotional wellbeing, support provided

| 3.5.5 | CPP | Prevention of weight gain, monitoring of weight and encouraging evidence based and socio-culturally appropriate healthy lifestyle is important in PCOS, particularly from adolescence | – | – |

### 4 Pharmacological treatment for non-fertility indications

#### 4.1 Pharmacological treatment principles in PCOS

- **4.1.1 CPP** Consideration of the individual’s personal characteristics, preferences and values is important in recommending pharmacological treatment

- **4.1.2 CPP** COCPs, metformin and other pharmacological treatments are generally off label in PCOS. However off label use is predominantly evidence-based and is allowed in many countries. Where is it allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment

- **4.1.3 CPP** Pharmacological therapy in PCOS should be considered in addition to lifestyle therapy

#### 4.2 Combined Oral Contraceptive Pills (COCPs)

- **4.2.1 EBR** The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and irregular menstrual cycles

- **4.2.2 EBR** The COCP alone should be considered in adolescents with a clear diagnosis of PCOS for management of clinical hyperandrogenism and irregular menstrual cycles

- **4.2.3 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

- **4.2.4 EBR** Specific types or dose of progestins, estrogens or combinations of COCP cannot currently be recommended with inadequate evidence in adults and adolescents with PCOS and practice should be informed by general population guidelines

- **4.2.5 CR** The 35ug ethinyl estradiol and cyproterone acetate preparations should not be considered first line in adults and adolescents with PCOS as per general population guidelines

- **4.2.6 CPP** When prescribing COCPs in adults and adolescents with PCOS:
  - various COCP preparations have similar efficacy in treating hirsutism
  - androgenic properties of progestins and venous thromboembolic risk should be considered
  - lower dose estrogen preparations, and natural estrogen preparations (such as 20-30mcg of ethinyl estradiol or equivalent), should be considered balancing efficacy, metabolic risk profile and side effects
  - the generally limited evidence on effects of COCP’s in PCOS should be appreciated with practice informed by general population guidelines
  - side-effects of the COCP should be the subject of individualised discussion
  - PCOS specific risk factors such as high BMI, hyperlipidemia and hypertension should be considered

#### 4.3 Combined Oral Contraceptive Pills in combination with metformin and/or anti-androgen pharmacological agents

- **4.3.1 EBR** In combination with the COCP, metformin should be considered in women with PCOS for management of metabolic features

- **4.3.2 EBR** In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI ≥25

- **4.3.3 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
### 4.3.4 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 ** оБо

### 4.3.5 CR
In combination with the COCP, antiandrogens could be considered for the treatment of female pattern hair loss in PCOS **

### 4.3.6 CPP
In PCOS, antiandrogens must be used with effective contraception, to avoid male foetal undervirilisation. Variable availability and regulatory status of these agents is notable and for some agents, potential liver toxicity requires caution

### 4.4 Metformin

#### 4.4.1 EBR
Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes *** оБо

#### 4.4.2 EBR
Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI≥25kg/m² for management of weight and metabolic outcomes *** оБо

#### 4.4.3 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 *** оБо

#### 4.4.4 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

#### 4.4.5 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

### 4.5 Anti-obesity pharmacological agents

#### 4.5.1 CR
Anti-obesity medications in addition to lifestyle, could be considered for the management of obesity in adults with PCOS after lifestyle intervention, as per general population recommendations

#### 4.5.2 CPP
Anti-obesity medications are currently costly, contraindications and side effects need to be considered and availability and regulatory status is variable

### 4.6 Anti-androgen pharmacological agents

#### 4.6.1 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 alopecia *** оБо

### 4.7 Inositol

#### 4.7.1 EBR
Inositol (in any form) should currently be considered an experimental therapy in women with PCOS, with the evidence on efficacy too uncertain to advocate this therapy *

#### 4.7.2 CPP
Women taking inositol and other alternative therapies are encouraged to advise their health professional

### 5 Assessment and treatment of infertility

#### 5.1 Assessment of factors that may affect fertility, treatment response or pregnancy outcomes

#### 5.1.1 CPP
Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health should be optimised
in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population
Refer to Lifestyle, Emotional Wellbeing and Diabetes risk sections

| 5.1.2 | CPP | Monitoring during pregnancy is important in women with PCOS, given increased risk of adverse maternal and offspring outcomes | – | – |
| 5.1.3 | CR  | In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing of tubal patency testing should be discussed on an individual basis | *** | – |
| 5.1.4 | CR  | Tubal patency testing should be considered prior to ovulation induction in women with PCOS where there is suspected tubal infertility | *** | – |

5.2 Ovulation Induction Principles

| 5.2.1 | CPP | The use of ovulation induction agents, including letrozole, metformin and clomid is still off label in many countries. Where off label use of ovulation induction agents is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects | – | – |
| 5.2.2 | CPP | Pregnancy should be excluded prior to ovulation induction | – | – |
| 5.2.3 | CPP | Unsuccessful, prolonged (>12 treatment cycles) use of ovulation induction agents should be avoided, due to poor success rates | – | – |

5.3 Letrozole

| 5.3.1 | EBR | Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates | **** | ⊗⊗⊗ ⊗ |
| 5.3.2 | CPP | Where letrozole is not available or use is not permitted, health professionals should use other ovulation induction agents | – | – |
| 5.3.3 | CPP | Health professionals and women should be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate | – | – |

5.4 Clomiphene citrate and Metformin

| 5.4.1 | EBR | Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates | *** | ⊗⊗⊗ ⊗ |
| 5.4.2 | EBR | Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents | *** | ⊗⊗⊗ ⊗ |
| 5.4.3 | EBR | Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese (BMI ≥30 kg/m²) with anovulatory infertility and no other infertility factors | *** | ⊗⊗⊗ ⊗ |
| 5.4.4 | EBR | If metformin is being used for ovulation induction in women with PCOS who are obese (BMI ≥30kg/m²) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates | *** | ⊗⊗⊗ ⊗ |
| 5.4.5 | EBR | Clomiphene citrate could be combined with metformin, rather than persisting with clomiphene citrate alone, in women with PCOS who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates | *** | ⊗⊗⊗ ⊗ |
| 5.4.6 | CPP | The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered | – | – |

5.5 Gonadotrophins

<p>| 5.5.1 | EBR | Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors | *** | ⊗⊗⊗ ⊗ |</p>
<table>
<thead>
<tr>
<th>Section</th>
<th>Source</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5.2</td>
<td>EBR</td>
<td>Gonadotrophins could be considered as first line treatment, in the presence of ultrasound monitoring, following counselling on cost and potential risk of multiple pregnancy, in women with PCOS with anovulatory infertility and no other infertility factors</td>
</tr>
<tr>
<td>5.5.3</td>
<td>EBR</td>
<td>Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate combined with metformin therapy for ovulation induction, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates</td>
</tr>
<tr>
<td>5.5.4</td>
<td>EBR</td>
<td>Gonadotrophins with the addition of metformin, could be used rather than gonadotrophin alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates</td>
</tr>
<tr>
<td>5.5.5</td>
<td>EBR</td>
<td>Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, following counselling on benefits and risks of each therapy</td>
</tr>
<tr>
<td>5.5.6</td>
<td>CPP</td>
<td>Where gonadotrophins are prescribed, the following should be considered:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• cost and availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• expertise required for use in ovulation induction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• degree of intensive ultrasound monitoring required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• lack of difference in clinical efficacy of available gonadotrophin preparations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• low dose gonadotrophin protocols optimize monofollicular development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• risk and implications of potential multiple pregnancy</td>
</tr>
<tr>
<td>5.5.7</td>
<td>CPP</td>
<td>Gonadotrophin induced ovulation should only be triggered when there is two or less follicles in total of over 14mm in diameter and should be cancelled if there are more than two follicles of this size, with the patient advised to avoid unprotected intercourse</td>
</tr>
<tr>
<td>5.6</td>
<td>CR</td>
<td>Pharmacological anti-obesity agents should be considered an experimental therapy in women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy</td>
</tr>
<tr>
<td>5.7</td>
<td>EBR</td>
<td>Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors</td>
</tr>
<tr>
<td>5.7.2</td>
<td>CR</td>
<td>Laparoscopic ovarian surgery could potentially be first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors</td>
</tr>
<tr>
<td>5.7.3</td>
<td>CPP</td>
<td>Risks should be explained to all women with PCOS considering laparoscopic ovarian surgery</td>
</tr>
<tr>
<td>5.7.4</td>
<td>CPP</td>
<td>Where laparoscopic ovarian surgery is to be recommended, the following should be considered:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• comparative cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• expertise required for use in ovulation induction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• intra-operative and post-operative risks are higher in women who are overweight and obese</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• there may be a small associated risk of lower ovarian reserve or loss of ovarian function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• periadnexal adhesion formation may be an associated risk</td>
</tr>
<tr>
<td>5.8</td>
<td></td>
<td>Bariatric Surgery</td>
</tr>
</tbody>
</table>
5.8.1 CR | Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy | * | _

5.8.2 CPP | If bariatric surgery is to be prescribed, the following should be considered:
- comparative cost
- the need for a structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health to continue post-operatively
- perinatal risks such as small for gestational age, premature delivery, possibly increased infant mortality
- potential benefits such as reduced incidence of large for gestational age fetus and gestational diabetes
- recommendations for pregnancy avoidance during periods of rapid weight loss and for at least 12 months after bariatric surgery with appropriate contraception

If pregnancy occurs, the following should be considered:
- awareness and preventative management of pre-and post-operative nutritional deficiencies is important, ideally in a specialist interdisciplinary care setting
- monitoring of fetal growth during pregnancy | _ | _

5.9

**In-vitro fertilisation (IVF)**

5.9.1 CR | In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory infertility could be offered IVF if first or second line ovulation induction therapies have failed | *** | _

5.9.2 CPP | In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used multiple pregnancies can be minimised. | _ | _

5.9.3 CPP | Women with PCOS undergoing IVF ± ICSI therapy should be counselled prior to starting treatment including on:
- availability, cost and convenience
- increased risk of ovarian hyperstimulation syndrome
- options to reduce the ovarian hyperstimulation | _ | _

5.9.4 CPP | Urinary or recombinant follicle stimulation hormone can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI, with insufficient evidence to recommend specific FSH preparations | _ | _

5.9.5 CPP | Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI | _ | _

5.9.6 EBR | A gonadotrophin releasing hormone antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle, over a gonadotrophin releasing hormone agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose and incidence of ovarian hyperstimulation syndrome (OHSS) | *** | ⊕⊕⊕

5.9.7 CPP | Human chorionic gonadotrophins should be used at the lowest doses to trigger final oocyte maturation in women with PCOS undergoing an IVF ± ICSI cycle to reduce the incidence of OHSS | _ | _

5.9.8 CPP | Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned | _ | _

5.9.9 CPP | In IVF ± ICSI cycles using the gonadotrophin releasing hormone antagonist protocol in women with PCOS, consideration should be given to an elective freeze of all embryos | _ | _
<table>
<thead>
<tr>
<th>5.9.10</th>
<th>EBR</th>
<th>Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing a IVF ± ICSI therapy with a gonadotrophin releasing hormone agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS</th>
<th>**</th>
<th>(⊕⊕⊕)</th>
</tr>
</thead>
</table>
| 5.9.11 | CPP | In a gonadotrophin releasing hormone agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF ± ICSI treatment, the following could be considered:  
- metformin commencement at the start of gonadotrophin releasing hormone agonist treatment  
- metformin use at a dose of between 1000mg to 2550mg daily  
- metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated)  
- metformin side-effects (link to above metformin section) | _ | _ |
| 5.9.12 | CPP | In IVF ± ICSI cycles, women with PCOS could be counselled on potential benefits of adjunct metformin in a gonadotrophin releasing hormone antagonist protocol to reduce ovarian hyperstimulation syndrome (link to metformin therapy considerations) | _ | _ |
| 5.9.13 | CR | In units with sufficient expertise, IVM could be offered to achieve pregnancy and livebirth rates approaching those of standard IVF ± ICSI treatment without the risk of OHSS for women with PCOS, where an embryo is generated, then vitrified and thawed and transferred in a subsequent cycle | ** | _ |
| 5.9.14 | CPP | The term in vitro maturation (IVM) treatment cycle should be applied to “the maturation in vitro of immature cumulus oocyte complexes collected from antral follicles” (encompassing both stimulated and unstimulated cycles, but without the use of a human gonadotrophin trigger). | _ | _ |
Introduction

Guideline purpose and aims

The purpose of this international evidence-based guideline is to integrate the best available evidence with multidisciplinary expertise and consumer preferences to provide health professionals, consumers and policy makers with transparent evidence-based guidance on timely diagnosis, accurate assessment and optimal treatment of PCOS, to reduce variation in care, optimise prevention of complications and improve health outcomes.

These guidelines aim to ensure that women with PCOS receive optimal, evidence-based care by:

- engaging multidisciplinary international expert representation in PCOS care nominated by partner and collaborator societies;
- including international consumer and primary care representatives;
- following rigorous AGREEII-compliant evidence-based guideline processes;
- developing an international comprehensive guideline on diagnosis, assessment and management of PCOS;
- providing a single source of international evidence-based recommendations to guide clinical practice and reduce variation worldwide with the opportunity for adaptation in relevant health systems as needed;
- providing a basis for improving patient outcomes;
- identifying knowledge gaps and promoting research and translation into practice and policy
- co-developing resources to upskill health professionals and empower consumers including a mobile app and online resources
- delivering an international translation program with in-depth evaluation

Key principles

- Principles that underpinned the development and interpretation of all evidence-based guidelines are:
- The need for consumers and health professionals to recognise the life course implications of PCOS
- Partnership between health professionals and women in managing PCOS
- Individual differences, preferences and modulating or exacerbating factors are understood
- Metabolic, reproductive and psychological features of PCOS are all considered
- Education, optimal lifestyle and emotional wellbeing are important in PCOS
- Indigenous and high risk ethnic populations are considered

Patient population

This guideline is relevant to the assessment and management of adolescents, reproductive age and postmenopausal women who have PCOS, including women with PCOS who are infertile.

Setting and audience

These guidelines are designed to apply in a broad range of health care settings and to a broad audience including:

- Patients
- General practitioners/primary care physicians
- Obstetricians and Gynaecologists
- Endocrinologists
• Dermatologists
• Allied health professionals - Psychologists, Dietitians, Exercise Physiologists, Physiotherapists,
• Community care practitioners
• Indigenous health care workers
• Nurses
• Policy makers
• Community support groups (ie. POSAA)
• General public
• Students

When translating these guideline into practice, issues such as cost, accessibility, availability and ethnic considerations are required.

Governance

A formal international governance process (Figure 2) was established as outlined in figure 2.

Figure 2: Governance (to be added to final guideline)

Guideline Development groups (GDGs)

Guideline development groups were formed based on skills (clinical and academic interests), expertise, geographical spread and were nominated by partner or collaborator organisations. The groups encompassed the broad range of expertise involved in the care of women with PCOS as well as primary care and consumers. Over 100 members were engaged across the governance, guideline development and translation committee. Whilst this does not encompass all leaders internationally with expertise in PCOS, these were engaged in the consultation process through online surveys and in providing feedback into the guideline through special interest groups formed across the partner and collaborator organisations. Given primary funding was from the Australian Government, diverse Australian collaborating organisations were engaged, however all continents have engaged throughout the process.

Prioritised clinical questions

Prioritisation of clinical questions for the guideline was informed by an International Delphi exercise on priorities for PCOS care. Clinical questions were identified and addressed across five guideline development groups (GDG).

• GDG 1 – Screening, diagnostic assessment, risk assessment and life-stage
• GDG 2 - Prevalence, screening, diagnostic assessment and management of emotional wellbeing
• GDG 3 – Lifestyle management and models of care
• GDG 4 – Medical treatment
• GDG 5 – Screening, diagnostic assessment and management of infertility

Specific questions are detailed in the methods section on clinical questions and prioritisation.

What the guideline does not address

This guideline does not seek to provide full safety and usage information on pharmacological and surgical interventions. The pharmacological and surgical interventions recommended in the guideline should not be applied without consideration of the patient’s clinical profile and preferences. We recommended that the
Introduction

The reader consults relevant regional bodies for prescribing information including indications, drug dosage, method and route of administration, contraindications, supervision and monitoring, product characteristics and adverse effects. This guideline did not include a formal analysis of cost effectiveness or economic feasibility, however the potential impact of cost on recommendations was considered in GRADE process.

Guideline development methods

The methods used to develop this guideline are aligned with International best practice, AGREE II criteria and the comprehensive criteria of the Australian government NHMRC and ESHRE for approval of evidence-based guidelines. The steps are summarised in Figure 3, with details found in Chapter 6: Methods.

Figure 3: Guideline development process

Funding

The Australian National Health and Medical Research Council funded guideline development through the NHMRC Centre for Research Excellence in Polycystic Ovary Syndrome (APP1078444), administered through Monash University and University of Adelaide, Australia. Guideline partners, European Society of Human Reproduction and Embryology (ESHRE) and American Society for Reproductive Medicine (ASRM) co-funded guideline development activities.

Editorial independence and Disclosures of interest

This guideline is editorially independent. The primary funders, NHMRC, were not involved in the development of the guideline and have not influenced the scope. They set standards for guideline development and based on independent peer review approved the guideline process. ESHRE and ASRM nominated experts in PCOS who participated in the project board and guideline development groups. ESHRE and ASRM formed special interest groups to provide feedback on the guideline during public consultation and all feedback will be reviewed by the project board and guideline development groups, blinded by the
organisation providing the feedback. All members of committees and GDGs publically disclosed all relevant interests and these were reviewed at each meeting and considered when making recommendations.

**Guideline Translation**

A comprehensive, international translation and dissemination program will disseminate, translate and amplify the impact of the International Evidence-based Guideline on the Assessment and Management of Polycystic Ovary Syndrome.

The aims of the translation program are to:
- Build capability of health professionals to deliver high-quality, evidence-based assessment and management of PCOS;
- Augment the health literacy of PCOS health consumers, optimising diagnosis and improving health outcomes;
- Promote best-practice evidence-based PCOS care

The guiding principles of the comprehensive international translation and dissemination program are:
- Components are informed by the needs and preferences of women with PCOS;
- Resources are co-created with, and attuned to, the needs of end-users; and,
- Dissemination strategies are multi-faceted, multi-modal and refined to the communication channels of end-users

Central to the translation and dissemination program is active engagement of over 40 partner and collaborator organisations (see acknowledgements) and leading engaged health experts who will leverage their extensive reach and influence to promote guideline uptake. Leading consumer groups internationally and translation organisations are strongly engaged and committed to translation and impact. The program is supported by a comprehensive evaluation framework, measuring international impacts and outcomes.
CHAPTER ONE

Screening, diagnostic assessment, risk assessment and life-stage

1.1 Irregular cycles and ovulatory dysfunction

_In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?_

Clinical need for the question

Ovulatory dysfunction is a key diagnostic feature of PCOS with irregular menstrual cycles (>35 days or <21 days) in adult women clinically reflecting ovulatory dysfunction in the Rotterdam criteria. Ovulatory dysfunction can occur with regular cycles, with hormonal assessment needed when PCOS is clinically suspected and cycles are regular. Irregular cycles and ovulatory dysfunction are also a normal component of the pubertal and menopausal transitions and defining abnormality at these life stages remains challenging.

The greatest controversy in this diagnostic criteria is in adolescents. Physiological maturation of the hypothalamic, pituitary ovarian axis occurs over years and ovulation and cycles in adolescents do not match those of reproductive aged women. When irregular cycles reflect reproductive maturity and when they may indicate PCOS is unclear challenging accurate diagnosis and potentially resulting in over diagnosis. Likewise women internationally report under diagnosis and delayed diagnosis, associated with dissatisfaction in diagnosis experience, with related anxiety and limited opportunity for education, prevention of complications and treatment of symptoms [14]. Adolescents may also be commenced on the combined oral contraceptive pill prior to assessment and diagnosis, potentially delaying diagnosis. Hence this clinical question was prioritised.

Summary of systematic review evidence

We did not identify any evidence in our patient population to answer the question.

Summary of narrative review evidence

Given the limited evidence identified on systematic review, a narrative review was completed (see technical report) and is summarised here. Physiologically, during the first year post-menarche, hormonal responses do not match adult patterns. During the second year about one half of the menstrual cycles range from 21-45 days in length, however progesterone levels are low [22]. The average adult menstrual cycle is 28 days ranging from 24 - 35 days [23]. The majority of irregular cycles may be ovulatory two years post-menarche (3-6), with 80% of cycles being within 21 - 45 days [24-27]. By the third post-menarcheal year, 95% of cycles fall into this range. Regular ovulatory cycle onset is also related to age at menarche [28]. In those who begin menses before 12 years, between 12 and 13 years, and after 13 years of age, 50% of cycles are ovulatory by one year, three years, and 4.5 years, respectively [28]. At age 15 more than 50% of girls who are oligo-amenorrheic remain so at age 18 (10). Overall, irregular cycles (>35 or <21 days) that continue for more than two years post menarche are likely to have oligo-anovulation, based on general population data, with consideration needed for age of menarche.
### Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1</td>
<td>CR</td>
<td>In adolescents (&lt;20 years), two years after the onset of menarche, if a patient reports irregular menstrual cycles (&gt;35 or &lt;21 days) a diagnosis of PCOS should be considered and assessed according to the guidelines</td>
<td>****</td>
<td></td>
</tr>
<tr>
<td>1.1.2</td>
<td>CR</td>
<td>In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors</td>
<td>****</td>
<td></td>
</tr>
<tr>
<td>1.1.3</td>
<td>CPP</td>
<td>Irregular menstrual cycles (&gt;35 days or &lt;21 days) in adult women clinically reflect ovulatory dysfunction. However ovulatory dysfunction can still occur with regular cycles and biochemical progesterone levels can be assessed when PCOS is clinically suspected and cycles are regular</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1.1.4 | CPP        | When commencing hormonal contraception in adolescents, in relation to PCOS assessment and diagnosis, the following should be considered:  
• after twelve months of irregular menstrual cycles (>35 or <21 days) following onset of menarche, baseline assessment of clinical and biochemical hyperandrogenism and cycle patterns can be completed before commencement of hormonal contraception  
• if baseline assessment is abnormal, potential increased risk of PCOS could be discussed with the patient and future reassessment recommended |       |        |

### Justification

Whilst no evidence was found to specifically address this question in PCOS, recommendations are informed by the best available evidence on normal adolescent menstrual patterns and ovulatory function and by previous available guidelines, multidisciplinary expertise and consumer perspectives. The group considered the potential for both over diagnosis and delayed diagnosis when assessing this diagnostic feature in PCOS, the need for individual consideration around timing and value of diagnosis and the potential desirable and undesirable impacts of making a diagnosis. It was also recognised that many adolescents may be commenced on pharmacological therapy for irregular cycles without a diagnostic assessment for PCOS and this was addressed in the recommendations and practice points.

### 1.2 Biochemical hyperandrogenism

**In women with suspected PCOS, what is the most effective measure to diagnose PCOS-related biochemical hyperandrogenism?**

**Clinical need for the question**

Hyperandrogenism is a key diagnostic feature of PCOS affecting between 60% -100% with the condition with both clinical (hirsutism, female pattern hair loss and acne) and biochemical hyperandrogenism. Both are challenging to assess and vary by methods of assessment, ethnicity and confounding factors including excess weight and life stage. Assessment of biochemical hyperandrogenism is hampered by a lack of clarity on which androgens to measure, what assays to use, how to define normal ranges, overlaps between values...
obtained in controls and PCOS, and access and cost issues for high quality assays. Calculated bioavailable testosterone and calculated free testosterone using the formula of Vermuelen et al is commonly used [29] as is free androgen index (FAI = 100 x (total testosterone/SHBG). Direct testosterone assays are widely used, however deficiencies in the accuracy of these assays limit their use, in a setting where standardised testosterone measurements that are accurate, reliable and comparable over time are essential [30, 31]. Given the controversy, methodological challenges, options, uncertainty in clinical practice and role of biochemical hyperandrogenism in the diagnosis of PCOS, this question was prioritised.

Summary of systematic review evidence

Seven studies of moderate to high risk of bias reported the diagnostic accuracy of different hormone markers to detect PCOS [32-38]; and another study of moderate risk of bias compared the diagnostic accuracy of different types of assays to detect PCOS [39]. There was insufficient evidence to make clear recommendations on the optimal hormone and method to measure biochemical diagnosis of PCOS, although data indicates that, as a single measure, free testosterone measure, free testosterone provide the most optimal accuracy to detect biochemical hyperandrogenism followed, in no specific order, total testosterone, DHEAS, and androstenedione.

Summary of narrative review evidence

Given the limited evidence identified on systematic review, a narrative review was completed (see technical report). In summary, with few exceptions [15] methods for directly assessing total circulating testosterone levels (e.g. direct radioimmunoassays or chemiluminescence immunoassays) are of insufficient precision, sensitivity and specificity to be used for the accurate assessment of total testosterone levels in women and female adolescents, including those with PCOS. There are also currently no reliable direct assays for total or free testosterone. However laboratories can provide calculated bioavailable testosterone, calculated free testosterone, or free androgen index (FAI). Androstenedione and dehydroepiandrosterone sulfate have a more limited role and can increase the probability of detecting hyperandrogenemia, yet they are arguably more useful in exclusion of other causes of hyperandrogenism. Dehydroepiandrosterone sulfate is predominantly an adrenal androgen and mild elevation may be seen with PCOS, with significant elevations and/or virilisation requiring investigation for possible androgen secreting adrenal tumour. Androstenedione, is elevated in 21-hydroxylase deficient non-classical congenital adrenal hyperplasia. Testosterone secretion may be increased during mid-cycle and assessment of androgen status should preferably be during the early follicular phase in cycling women, whilst diurnal variation means morning levels may be most predictive [14].

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.1</td>
<td>EBR</td>
<td>Calculated bioavailable testosterone, calculated free testosterone or free androgen index should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS</td>
<td>****</td>
<td>⊕⊕○○</td>
</tr>
<tr>
<td>1.2.2</td>
<td>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>
<td>***</td>
<td>⊕⊕○○</td>
</tr>
<tr>
<td>1.2.3</td>
<td>EBR</td>
<td>Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated; however these provide limited additional information in the diagnosis of PCOS</td>
<td>***</td>
<td>☀️☀️☀️</td>
</tr>
<tr>
<td>1.2.4</td>
<td>CR</td>
<td>Direct free testosterone assays, such as radiometric or enzyme-linked assays, preferably should not be used in assessment of biochemical hyper-androgenism in PCOS, as they demonstrate poor sensitivity, accuracy and precision</td>
<td>****</td>
<td>—</td>
</tr>
<tr>
<td>1.2.5</td>
<td>CPP</td>
<td>Reliable assessment of biochemical hyperandrogenism is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.2.6</td>
<td>CPP</td>
<td>Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal should occur for three months or longer before measurement, and contraception should be managed alternatively during this time</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.2.7</td>
<td>CPP</td>
<td>Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS, and the phenotype where clinical signs of hyperandrogenism are unclear or absent, in particular hirsutism</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.2.8</td>
<td>CPP</td>
<td>Interpretation of androgen levels should be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values should ideally be determined by the range of values in a well phenotyped healthy control population or by cluster analysis of a large general population</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.2.9</td>
<td>CPP</td>
<td>Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism, including neoplasia, and rare syndromes of severe insulin resistance, should be considered. History of symptom onset and progression is critical in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in biochemical hyperandrogenism.</td>
<td>—</td>
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</tr>
</tbody>
</table>

**Justification**

Total testosterone alone can identify 20-30% of women with PCOS as having biochemical hyperandrogenism, while measures of unbound or free testosterone will identify 50-60%. High quality assays provide a more accurate diagnosis and the additional associated cost was deemed important and justified after considering all elements of the GRADE framework. Access issues were acknowledged and considered with an accurate diagnosis valued over increased costs. Given the challenges in assessing biochemical hyperandrogenism, whilst androgen measures are useful to detect biochemical hyperandrogenism where PCOS is suspected, these are likely to be most useful in diagnosis of PCOS in adolescents and women who demonstrate minimal to no features of clinical hyperandrogenism (e.g. hirsutism). Clarity around standardised assessment for biochemical hyperandrogenism is likely to be valued.

### 1.3 Clinical hyperandrogenism

*In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS-related hyperandrogenism?*

**Clinical need for the question**
Signs and symptoms of severe androgen excess can result in virilisation (e.g. male pattern balding, severe hirsutism, and clitoromegaly) and masculinisation. Virilisation is rare. Clinical evidence of mild to moderate androgen excess is more common including hirsutism, acne, and female pattern hair loss. The interrelationships of these clinical features remains unclear, they varies by ethnicity, and require clinician training, vigilance and skill to assess. These features impact considerably on quality of life in women with PCOS and treatment burden including cosmetic therapies can be significant. Given the fundamental role of hyperandrogenism in diagnosis, and the adverse impact of on quality of life, this question was prioritised.

Summary of systematic review evidence

We did not identify any evidence in our patient population to answer the question.

Summary of narrative review evidence

A narrative review provided in the technical report, notes the most recognisable clinical sign of hyperandrogenism as terminal hairs in a male-like pattern in women or hirsutism. Elevated androgens are detected in the vast majority (>70%) of women with hirsutism and few do not demonstrate other features of PCOS (<5%) [40]. The most common visual assessment tool is the modified Ferriman-Gallwey (m-FG) [41, 42] to assess terminal hairs (hairs that would grow >5 mm in length if left unmolested, are usually pigmented, and are medullated). m-FG assesses nine primarily masculine body areas for terminal hair: upper lip, chin and neck, upper chest (excluding the nipples), upper abdomen (above the umbilicus), lower abdomen (also known as male escutcheon), thighs (front and/or back), upper back, lower back, and upper arms [42, 43]. Each area is visually scored from zero (no terminal hair visible) to four (terminal hair consistent with a well-developed male). A photographic atlas assists scoring [42].

Defining ‘abnormal’ is controversial. The m-FG cut-off score can be based on percentile with a score >6-8 consistent with the 95th percentile of unselected women [41, 43, 44]) or by cluster analysis which suggests an m-FG scores of >3 in White and Black women [45], and >5 in Mongoloid Asian (Han Chinese) women [46], represents true abnormality. There may be differences in the degree and prevalence of hirsutism between ethnic groups, yet cut-offs for defining ‘hirsutism’ appear similar. Overall, >50% of women with mFG scores of 3-5 have elevated androgens and/or PCOS [47], and >70-90% of women with scores >5 [42, 44]. Referral bias needs to be considered in reported populations [48, 49]. Hirsutism adversely impacts quality of life [50] and most women readily treat hirsutism complicating assessment, hence health professionals should be prepared to assess any woman who complains of excess hair [47, 51].

Acne is associated with biochemical hyperandrogenism [52, 53], yet the predictive value of acne alone is unclear [40, 52] and there is no accepted assessment tool [40]. Most studies of women with female pattern hair loss (FPHL), characterized by diffuse sagittal scalp alopecia, reveal a relatively low prevalence of hyperandrogenemia [40, 54] and the predictive value of female pattern hair loss alone remains unclear. Hair loss on the scalp is usually assessed visually using the Ludwig scale [40].

**Recommendations**

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/ CR/ CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
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<tbody>
<tr>
<td>1.3.1</td>
<td>CR</td>
<td>A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism</td>
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</tr>
</tbody>
</table>
1.3.2 CR  Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and reporting of unwanted excess hair growth or female pattern hair loss should be considered important in assessment and management, regardless of apparent clinical severity

1.3.3 CR  Standardized visual scales are preferred when assessing hirsutism such as the modified Ferriman Gallway score (mFG) with a level >3 and more often >5 indicating hirsutism, acknowledging that self-treatment is common and can limit clinical assessment

1.3.4 CR  The Ludwig visual score is preferred for assessing female pattern hair loss, whilst no universally accepted visual instruments are available for assessing acne

1.3.5 CPP  The mFG cut-off scores for defining hirsutism are the same across ethnicities, yet the prevalence and degree of hirsutism severity varies by ethnicity

1.3.6 CPP  As ethnic variation in vellus hair density is notable, over-estimation of hirsutism may occur if vellus and terminal hairs are not distinguished. The desirable effects (an accurate and sensitive diagnosis) outweigh the undesirable effects (over-estimation of hirsutism). Assessing for clinical hyperandrogenism is low cost, relative to biochemical assessments for hyperandrogenism, and a standardised assessment for clinical hyperandrogenism is likely to be valued.

Justification

Both patients and clinicians value an accurate diagnosis of PCOS, clinical hyperandrogenism is an important determinant of quality of life and simple treatments are readily available. While subjective and visual, the m-FG score for facial and terminal hair growth is the principal instrument for clinical assessment of hirsutism. It hirsutism can be over-estimated if vellus and terminal hairs are not distinguished. The desirable effects (an accurate and sensitive diagnosis) outweigh the undesirable effects (over-estimation of hirsutism). Assessing for clinical hyperandrogenism is low cost, relative to biochemical assessments for hyperandrogenism, and a standardised assessment for clinical hyperandrogenism is likely to be valued.

1.4 Ultrasound and polycystic ovarian morphology (PCOM)

When is ultrasound indicated to diagnose PCOS?

What are the most effective ultrasound criteria to diagnose PCOS?

Clinical need for the questions

Polycystic ovarian morphology (PCOM) was incorporated into the diagnosis of PCOS in 2003 in the Rotterdam criteria, as a common feature associated with clinical and endocrine features of the condition [1]. This introduced arguably milder phenotypes into PCOS with limited data on natural history, prompting calls for phenotype identification and more research [21]. The definition of PCOM in the Rotterdam criteria is 12 or more follicles measuring 2 - 9mm throughout the entire ovary or an ovarian volume ≥10cm³. This was based on a single report on sensitivity and specificity in PCOS compared to controls. Factors that mandate revision of this diagnostic criteria include inadequate initial evidence, advances in ultrasound technology with greater resolution, variable operator skill level, lack of standard reporting, ill-defined cut-offs between normal ovaries and PCOM, the impact of approach (e.g. transvaginal), body habits and age. Natural changes occur in antral follicle count during the pubertal and menopausal transitions and up to 70% of adolescents have PCOM on current criteria [55]. The term “cystic” is a misnomer referring to arrested follicles (not cysts) and identification of PCOM alone can lead to over diagnosis. Diagnosis of PCOS mandates not only PCOM,
but associated features of hyperandrogenism and/or ovulatory dysfunction. This clinical question was prioritised, with recognition that a reproducible technique and standard reporting to reliably estimate antral follicle count (AFC) and define PCOM is critical in the accurate diagnosis of PCOS.

Summary of systematic review evidence

A systematic review was completed to address the second clinical question on the most effective ultrasound criteria to diagnose PCOS. Fifteen studies of moderate to high risk of bias reported the diagnostic accuracy of different ovarian morphology parameters to detect PCOS [32, 37, 56-68]. Two of the fifteen studies were in adolescents [61, 68]. The index tests addressed in these studies included various measures and thresholds of ovarian volume and follicle number. None of the studies pre-specified thresholds. Some studies have reported diagnostic accuracy data using multiple thresholds. Due to the heterogeneity in threshold/cut off values for each index test, meta-analyses (for pooled sensitivity and specificity estimates) could not be performed. However, forest plots were created and imputation of sensitivity and specificity data performed to derive true and false positives and true and false negatives to provide greater detail on accuracy outlined in the technical report. This approach enabled a rigorous evaluation of available evidence, acknowledging the overall poor quality of the studies. For follicle number per ovary (FNPO) there were 11 studies with 2961 adult participants suggesting optimal sensitivity and specificity at ≥19 AFC. For ovarian volume, 12 studies with 2096 participants showed significant heterogeneity with a lack of clarity on the optimal size with both 5-8cm³ and 9-10cm³ emerging. There is insufficient evidence to suggest use of other ultrasound parameters including ovarian area; maximum number follicles in a single sonographic plane (FSSP); peripheral distribution of ovarian follicles; bright ovarian stroma; combination of age, follicle number, log ovarian volume, and testosterone; or combination of follicular size and ovarian volume for diagnosis of PCOS.

Summary of narrative review evidence

A narrative review was completed to address the first question, supplemented with additional relevant evidence from the above systematic search. The ovary has a full complement of follicles and oocytes, arrested at meiosis, during fetal life. These mature in childhood with ovulation noted after puberty and continuing until menopause [69]. Ovarian volumes change over time with increased antral follicles and stroma. There are no large studies across the lifespan to validate normal ovarian development. Ovarian size increases from age 9-11 and maximum volume is reached at age 20 [70-74]. The correlation between menstrual function and ovarian morphology is not straightforward in adolescence with the majority of adolescents having PCOM consistent with Rotterdam criteria, and the few longitudinal studies suggest that 2-4 years post menarche, PCOM is common and not associated with reproductive dysfunction [75, 76]. Therefore adult PCOM criteria are likely inaccurate for ultrasound diagnosis of PCOS in adolescence with substantive overlap between follicle counts in normal adolescents and those with other features of PCOS.

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
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<tbody>
<tr>
<td>1.4.1</td>
<td>CR</td>
<td>Ultrasound should not be used for the diagnosis of PCOS in adolescence, due to the high incidence of multi-follicular ovaries in this life stage</td>
<td>****</td>
<td>–</td>
</tr>
<tr>
<td>1.4.2</td>
<td>CR</td>
<td>The threshold for PCOM should be revised regularly with advancing ultrasound technology and age specific cut off values for PCOM should be defined</td>
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<tr>
<td><strong>1.4.3 CR</strong></td>
<td>The transvaginal ultrasound approach should be used in the diagnosis of PCOS if acceptable to the patient, with the exception of those not yet sexually active</td>
<td>****</td>
<td></td>
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<tr>
<td><strong>1.4.4 CR</strong></td>
<td>Using ultrasound transducers with a frequency &gt; 8MHz, the threshold for PCOM should be a follicle number per ovary of ≥ 18 and/or an ovarian volume &gt; 10 ml, ensuring no corpora lutea, cysts or dominant follicles are present in one or both ovaries</td>
<td>***</td>
<td></td>
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</tr>
<tr>
<td><strong>1.4.5 CPP</strong></td>
<td>In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis; however ultrasound will identify the complete PCOS phenotype</td>
<td></td>
<td></td>
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<tr>
<td><strong>1.4.6 CPP</strong></td>
<td>Transabdominal ultrasound should primarily report ovarian volume with a threshold of ≥ 10 ml, given the difficulty of accurately assessing follicle number with this approach</td>
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<tr>
<td><strong>1.4.7 CPP</strong></td>
<td>If using lower resolution ultrasound transducers with a frequency &lt; 8 MHz, the threshold for PCOM should be a follicle number per ovary of ≥ 12 and/or an ovarian volume ≥ 10 ml</td>
<td></td>
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</tbody>
</table>
| **1.4.8 CPP** | Clear protocols are recommended for reporting antral follicle count and ovarian volume on ultrasound. Minimum reporting standards should include:  
• Last menstrual period  
• Transducer frequency  
• Approach/route assessed  
• Total follicle number per ovary measuring 2-9 mm  
• Three dimensions of each ovary and the volume  
• Reporting of endometrial thickness and appearance is preferred – 3 layer endometrial assessment may be useful and can exclude endometrial pathology  
• Other ovarian and uterine pathology, including ovarian cysts, corpus luteum, dominant follicles > equal 10 mm |   |
| **1.4.9 CPP** | There is a need for training in careful and meticulous counting of antral follicle numbers per ovary, to improve reporting |   |

**Justification**

It was recognised that the data in adolescents is inadequate, peak ovarian maturity has not yet been reached and defining PCOM at this life stage (<20 years) is not currently possible with the high incidence of multifollicular ovaries. There was recognition of the risk of over diagnosis in adolescents where ultrasound criteria were included in this age group and the limitations in performing transvaginal ultrasounds in those not yet sexually active. These recommendations were deemed to make the use of ultrasound inappropriate for diagnosis of PCOS in adolescents at this time. Ultrasound may be indicated for other reasons in adolescents, this recommendation is limited to the role of ultrasound in PCOS diagnosis.

Ultrasound is not required for diagnosis in adults with features of hyperandrogenism and ovulatory dysfunction, who already meet PCOS diagnostic criteria. It is recognised that omission of ultrasound does limit full phenotyping. The recommendation to use Follicle Number per Ovary (FNPO) as the key diagnostic criteria for PCOM in adults was reconfirmed by the updated evidence review. Technology advancements in the last decade support an increase in FNPO in diagnosis. Rigorous evaluation of the evidence and multidisciplinary expertise informed modified FNPO recommendations and reaffirmed secondary ovarian volume assessment in diagnosis. Limitations in the evidence were recognised, however it was stronger than the evidence informing the original Rotterdam recommendations. These recommendations recognise the
optimal ultrasound approach, technological ultrasound advances and variability in availability of newer technologies and aim to improve training and standardise reporting. They are likely to improve the reliability of assessing and reporting FNPO, provide for more accurate reporting of PCOM in the diagnosis of PCOS and limit use and costs of a somewhat invasive test where it is not appropriate.

1.5 Anti-Müllerian Hormone (AMH)

What are the most effective ultrasound criteria to diagnose PCOS?
What are the most effective ultrasound criteria to diagnose PCOM?

Clinical need for the questions

Given the challenges with ultrasound in diagnosis of PCOS, including in adolescent populations, serum AMH has been proposed as an alternative marker of ovulatory dysfunction in PCOS. AMH is a polypeptide of the TGFβ family solely secreted by granulosa cells of the preantral and small antral ovarian follicles. Serum AMH levels are significantly higher in women with PCOS compared with normal ovulatory women [77, 78]. Strong correlations have been demonstrated between circulating AMH levels and antral follicle count on ultrasound in PCOS. AMH may also provide insight into the pathogenesis of PCOS and the different phenotypes.

However, current literature reveals significant heterogeneity and the diagnostic value of serum AMH remains far from clear.

Summary of systematic review evidence

Twenty-nine studies of moderate to high risk of bias were identified by our search to address diagnostic accuracy of AMH for PCOS and/or PCOM [59, 79-106]. One of these was a systematic review [87] and included nine of the studies identified here, however it also included studies that did not meet the inclusion criteria for this evidence review and it was missing additional more recently studies identified by the search: therefore it cannot be used. Four of the 28 primary studies addressed the diagnostic accuracy of AMH for PCOS and PCOM [84, 85, 91, 97]; and one for PCOM only [102]. Six studies included adolescents and one of these addressed PCOS and PCOM [85]. The remaining 21 studies included adult participants for diagnosis of PCOS, with three addressing PCOS and PCOM [84, 91, 97], and the remaining 18 addressing PCOS [59, 62, 79-82, 86, 90, 92-96, 98, 101, 103, 104, 106]. In adolescents, one was in overweight and obese participants [88] and one had unclear BMI [105]. In adults, one [80] included lean and obese participants; and five [59, 79, 84, 90, 106] included overweight and obese participants. Here we generated receiver operating characteristic (ROC) curves by plotting the true positive rate against the false positive rate at various threshold settings, based on published literature. The area under the ROC curve in adolescents for PCOS was around 0.5-0.88 and the threshold from 25-44pmol/L. In adults, the area under the ROC curve was about 0.66-0.994 and the threshold from 10-57pmol/L. In PCOM detection, in adolescents, one study showed an area under the ROC curve of about 0.87 and the threshold 50pmol/L. In adults, the ROC was about 0.67-0.92 and the threshold 20-30pmol/L.

Although serum AMH levels in adolescent and adult women with both PCOM and PCOS are significantly higher than those without these features in all studies, there is considerable overlap. A specific threshold of AMH in PCOS and PCOM is therefore very challenging. Heterogeneity between studies relates to assays, life stage and phenotypes studied. Another key contributor is the lack of well-defined populations including variable ultrasound criteria to establish PCOM and the criteria used to define controls.
### Recommendations

<table>
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<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>1.5.1</td>
<td>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>
<td>***</td>
<td>⊕⊕⊕</td>
</tr>
<tr>
<td>1.5.2</td>
<td>CPP</td>
<td>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 may become useful in the detection of PCOM in future</td>
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</table>

### Justification

Whilst an AMH assay to reflect ovarian morphology and diagnose PCOS offers convenience and lower costs, current assays and available evidence do not adequately support these roles for AMH at the current time. It is acknowledged that both ultrasound and AMH levels present challenges in PCOS diagnosis. It is also acknowledged that assays are improving and this recommendation may evolve over time.

### 1.6 Ethnic variation

**In women with suspected PCOS is there evidence of ethnic and geographic variations in prevalence and presentation?**

#### Clinical need for the question

PCOS was originally described in Caucasians and subsequently has shown to be prevalent across the world. Whilst there are many studies that explore PCOS within different ethnic groups, few compare across groups. Some studies consider within country populations by ethnicity, yet do not consider differences in diet, lifestyle and occupation. None the less, studies suggest differences in prevalence and clinical features across ethnic groups and greater clarity is needed to inform considerations and adaptation of guideline recommendations in the diagnosis and treatment of PCOS.

#### Summary of narrative review evidence

A systematic review was not conducted to answer this question which was reviewed narratively based on clinical expertise. In summary, an identified systematic review on prevalence and phenotypic features revealed some differences internationally [5] between ethnic and geographic regions. The highest prevalence has been reported among Australian aboriginal women and South Asians migrating to developed countries, both populations with increased BMI [5, 107]. Ovulation appears not to differ, whilst androgen levels appear similar. Ultrasound ovarian features are difficult to compare, compromised by the differences in technology, diagnostic features and operator skill, yet no clear differences have emerged. For hirsutism there are clear ethnic differences, with Middle Eastern and South Asian women having far greater hirsutism than those of Eastern Asian origin. Acanthosis is more common in women of South East Asian background, reflecting increased insulin resistance. For metabolic features, BMI differs between ethnic groups, primarily dependent on lifestyle and environmental factors. Insulin resistance, diabetes risk and lipid profiles do appear to vary, potentially influenced by genetic factors and visceral adiposity. Genetic data shows both similarities and differences. Psychological features have not been well studied, however on quality of life
Studies, cultural rather than ethnic factors appear to impact, including cultural perspectives on infertility [108]. In terms of treatment responses, IVF may be less successful in women with of Asian ethnicity but there is no similar data for ovulation induction.

**Recommendations**

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<th>No.</th>
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<th>Quality</th>
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<tbody>
<tr>
<td>1.6.1</td>
<td>CR</td>
<td>Health professionals should consider ethnic variation in the presentation and manifestations of PCOS, including differences in hirsutism and acanthosis nigricans and in metabolic sequelae including obesity and insulin resistance</td>
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</table>

**Justification**

Ethnic differences appear to relate primarily to skin manifestations and metabolic features of PCOS. These may affect interpretation and application of relevant guideline recommendations and need to be considered by health professionals when assessing the individual woman.

**1.7 Menopause life-stage**

*What is the post-menopausal phenotype of PCOS and how elevated should androgens be to indicate PCOS?*

**Clinical need for the question**

Menopause is a natural life stage occurring around the age of 51 years. The diagnosis of PCOS by Rotterdam criteria requires two of three criteria including oligo- and/or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries by ultrasound [1]. However, these three criteria for diagnosis change naturally with age impacting on phenotype and presenting challenges in diagnosis. Postmenopausal phenotypes of PCOS are poorly defined, with limited longitudinal natural history studies. Uncertainty in assessment and diagnosis at this life stage leads to confusion for health professionals and women on long term health risks and screening recommendations.

**Summary of narrative review evidence**

A systematic review was not conducted to answer this question, which was reviewed narratively based on clinical expertise. With aging, changes occur in all three diagnostic criteria. Menstrual cycles become more regular in PCOS [109-111]. Ovarian volume and follicle number decrease longitudinally in PCOS and control women. Using cross-sectional data, ovarian volume and follicle number decrease in both groups, but the decrease in ovarian volume is less pronounced in women with PCOS than in controls. Age-based criteria to define PCOM have been proposed using a combination of age, log ovarian volume, follicle number, and testosterone to distinguish PCOS from non-PCOS [57]. Androgen levels in PCOS decrease with age toward menopause [112-114] in longitudinal and cross-sectional studies [115]. Testosterone FAI, and calculated free testosterone are higher in women with PCOS aged 18–44 years compared to controls [115]. Regarding menstrual cycles, the average age of menopause in PCOS is not known. A two-year delay in the age of menopause has been estimated using AMH levels [116] and PCOS has been independently associated with later menopause [117]. There is no established phenotype for PCOS after menopause. In postmenopausal
women, ovulation ceases. Hirsutism is greater in PCOS than in controls in postmenopausal women [118] but little is known about acne and female pattern hair loss in these women. Postmenopausal women with PCOS have higher 17-hydroxyprogesterone, androstenedione, DHEAS, total Testosterone and FAI than women without PCOS [115, 118, 119]. However, androgen assays are unreliable in women especially with the lower levels generally observed postmenopause [120]. Post-menopausal women with PCOS have abnormal glucose metabolism [121] and higher triglycerides than controls [122]. Other methods to identify PCOS in postmenopausal women have been proposed. For PCOS diagnosis in menopause previous history of oligo-ovulation, PCOM and current features of hyperandrogenism [123, 124] can be considered as had insulin resistance [125].

**Recommendations**

<table>
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<tr>
<th>No.</th>
<th>EBR/ CR/ CPP</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1.7.1</td>
<td>CR</td>
<td>Post-menopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism</td>
<td>***</td>
<td>-</td>
</tr>
<tr>
<td>1.7.2</td>
<td>CR</td>
<td>A diagnosis of PCOS postmenopause could be considered if there is a past diagnosis of PCOS or a long term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive years</td>
<td>***</td>
<td>-</td>
</tr>
<tr>
<td>1.7.3</td>
<td>CPP</td>
<td>Postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, should be investigated to rule out androgen-secreting tumours and ovarian hyperthecosis</td>
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</table>

**Justification**

A conditional consensus recommendation was made around assessment of persistence of PCOS in those with a past diagnosis of PCOS or the relevant diagnostic features, or in women with persistent hyperandrogenism. The importance of excluding other diagnoses in cases of significant hyperandrogenism was recognised. These recommendations align with past guidelines with a key emphasis placed on research to provide clarity on post-menopausal PCOS phenotypes and persistence of PCOS post-menopause. Undesirable effects are unclear and it is important to note that reliance on history may overestimate the presence of oligo/amenorrhoea. Labelling of patients with a diagnosis may have adverse consequences (psychological etc).

**1.8 Cardiovascular disease**

*Are women with PCOS at increased risk for CVD?*

*In women with PCOS, what is the most effective tool/method to assess risk of CVD?*

**Clinical need for the questions**

CVD remains one of the leading causes of death in women and any condition further increasing CVD risk, will have significant public health impact. However CVD primarily affects postmenopausal women in the later decades of life. Longitudinal studies of well-defined cohorts with and without PCOS are limited. Existing cohorts have poorly defined PCOS status and focus on younger women, or on CVD risk factors rather than clinical events. This makes the determination of CVD risk in PCOS very challenging. It is acknowledged that metabolic syndrome and CVD risk factors are clearly increased in PCOS, however given the limited current
data on clinical events, overall CVD risk and optimal screening for additional risk factors remains highly controversial.

Summary of systematic review evidence

Two systematic reviews [126, 127] and eight observational studies [128-135] were identified by the search to address risk of CVD in women with PCOS. Seven of the observational studies were addressed across the two systematic reviews, however the systematic reviews included studies in the analysis that do not meet the PICO for this evidence review, therefore the data from the systematic reviews cannot be used here. The risk of bias/methodological quality assessments from the systematic reviews have been used. Studies were retrospective (six) and prospective cohort (one) studies reporting CVD-related event rates in women with and without PCOS over time.

Meta-analysis was conducted for outcomes with two or more studies. There was no statistical difference between PCOS and non-PCOS groups in terms of myocardial infarction (3 studies, 1633 participants, I² 0%); stroke (4 studies, 3012 participants, I² 14%; CVD-related death (2 studies, 779 participants, I² 0%); and coronary artery/heart disease (2 studies, 2152 participants, I² 80%). One study each addressed angina (no difference), large vessel disease (p value not reported), coronary artery calcification (p value not reported).

One study presented odds ratios and suggest that when a group of women with PCOS are compared to a UK-wide population, the risk of myocardial infarction (but not angina) was increased in women with PCOS over 45 years (stratified into 15-44, 45-54, 55-64 and >65). When they compared the same women with PCOS to a local community population, the risk of myocardial infarction and angina was increased in women with PCOS. However, when all age groups were combined, there was no difference in risk between women with and without PCOS, for either myocardial infarction or angina, regardless of where the control population was sourced. Given the methodological and reporting limitations and small sample sizes of these observational studies, all findings should be interpreted with caution.

On screening tools/ methods for CVD, we did not identify any evidence in women with PCOS to answer the question regarding the most effective method/tool to assess risk of CVD. The summary of the narrative review evidence is provided here including an international position statement on CVD risk assessment in PCOS [136] and existing guidelines on absolute or global CVD risk assessment [137], obesity [138], lipids [139, 140] and hypertension [141] for the general population. The concept of overall or global CVD risk was also considered important and relevant in women with PCOS.

Recommendations

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<tr>
<th>No.</th>
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<tbody>
<tr>
<td>1.8.1</td>
<td>CR</td>
<td>All those with PCOS should be assessed for weight gain and excess weight at every visit, in consultation with and where acceptable to the individual woman (see Obesity and weight assessment section)</td>
<td>****</td>
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<tr>
<td>1.8.2</td>
<td>CR</td>
<td>Weight, height, BMI and ideally waist circumference should be measured and the following considered: • BMI categories and waist circumference should follow World Health Organisation guidelines • Consideration should be given for Asian and high risk ethnicity and for adolescent specific ranges</td>
<td>****</td>
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<tr>
<td>1.8.3</td>
<td>CR</td>
<td>All women with PCOS should be assessed for individual cardiovascular risk factors and global CVD risk</td>
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</table>
### Justification

Assessment of CVD risk in PCOS needs to encompass assessment of well-established risk factors, including those specifically increased in PCOS: weight, BMI, waist circumference, lipid profiles, blood pressure, glucose levels and physical activity. The presence of PCOS as an independent CVD risk factor is yet to be confirmed pending quality studies to determine whether these elevated CVD risk factors convert to the anticipated risk of CVD in the longer term. However, in the presence of well-established CVD risk factors and inadequate longitudinal CVD data, it was deemed that women with PCOS require screening.

### 1.9 Gestational diabetes, impaired glucose tolerance and type 2 diabetes

**Are women with PCOS at increased risk for impaired glucose tolerance, gestational diabetes and type 2 diabetes mellitus?**

**In women with PCOS, what is the most effective tool/method to assess risk of type 2 diabetes?**

### Clinical need for the questions

Glucose is a continuous variable. Cut off levels for GDM, IGT and DM2 remain controversial and somewhat arbitrary. Clinical sequelae inform the arbitrary cut offs for these conditions; in pregnancy any elevation of blood glucose increases morbidity for mother and baby; in IGT long term health risks including CVD are increased and in DM2, both micro and macrovascular risks are increased. In the general population, optimal screening protocols for these conditions vary and the most reliable tests for screening and diagnosis [oral glucose tolerance tests (OGTT), fasting glucose or HbA1c] remain controversial. These controversies extend to PCOS, where increased risks of GDM, IGT and DM2 [10] have been demonstrated on meta-analyses, independent of BMI. Controversy around the optimal screening test is significant in PCOS, with proposed benefits of identifying IGT on an OGTT, requiring balance with increased inconvenience, cost and poor implementation despite recommendations in past guidelines.

### Hyperglycemic conditions

#### Summary of narrative review evidence

A systematic review was not conducted to answer the first question and was reviewed narratively based on clinical expertise and prior systematic reviews and meta-analyses. In summary, meta-analyses indicate increased IGT, GDM and DM2 risks, independent of obesity. Women with PCOS had increased prevalence of

| 1.8.4 CR | If screening reveals CVD risk factors including obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance and lack of physical activity, women with PCOS should be considered at increased risk of CVD | **** | – |
| 1.8.5 CR | All women with PCOS, regardless of age, should have a lipid profile (Total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and Triglyceride level at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidemia and global CVD risk | **** | – |
| 1.8.6 CR | All women with PCOS, should have blood pressure measured annually or more frequently based on global CVD risk | **** | – |
| 1.8.7 CPP | Consideration should be given to the significant differences in CVD risk across ethnicities, when determining frequency of risk assessment | – | – |
Consistently, DM2 was four times higher in a recent Danish registry study and was diagnosed four years earlier in PCOS [143]. The prevalence differs by ethnicity and is higher in more obese study populations [143]. HbA1c, fasting glucose, 2h glucose, measures of insulin resistance, triglycerides, sex hormone binding globulin and BMI at baseline may be the best predictors for development of DM2 [143]. When models were corrected for age and BMI, fasting glucose, 2h glucose on OGTT and triglycerides were the best predictors.

**Screening**

**Summary of systematic review evidence**

One low quality systematic review with high risk of bias was identified by our search [144] that asked the question: How can women with PCOS be identified for risk of DM2 screening? The authors of the systematic review found no studies addressing the question and in the absence of evidence, the authors suggest that oligomenorrhoea, along with clinical or biochemical hyperandrogenism, obesity or a family history of risk of DM2 may be indicators of risk of DM2. The systematic review was deemed insufficient evidence on which to base a recommendation. Therefore clinical consensus recommendations have been made based on the systematic review, an international position statement on CVD risk assessment in PCOS [136] and national guidelines for case detection and diagnosis of type 2 diabetes [145].

**Summary of narrative review evidence**

Whilst guidelines consistently recommend screening for DM2 in PCOS, whether to target high risk subgroups, which test to use (fasting glucose, OGTT or HbA1c) and optimal frequency, vary between guidelines [146] and remain controversial. Some recommend screening all women with PCOS [19], whereas others consider additional risk factors including ethnicity, BMI, previous GDM or a family history of DM2. Most recommend the OGTT, whilst frequency of testing is variable. The specific impact of ethnicity (65% of the world’s population are of high risk Asian ethnicity) and excess weight on DM2 risk in PCOS, presents challenges. In a low risk ethnic group, lean women did not develop DM2 by 46 years, with risk increased in the majority who were overweight or obese [147]. Yet, in a recent abstract, 47% of Asian women with PCOS had IGT or DM2 by 41 years, despite limited obesity. The concept of absolute versus relative risk is important as in low risk populations (Caucasian, healthy weight), a four-fold increased risk from PCOS equates to a low incidence of DM2, yet in high risk South East Asians or obese women, PCOS dramatically impacts on DM2 incidence.

General guidelines recommend testing for prediabetes and DM2 in adolescents and adults at any age who are overweight or obese (BMI over 25 kg/m2 or 23 kg/m2 in Asians), with additional risk factors (e.g. PCOS) [148]. Given the increased risks associated with hyperglycaemia in reproductive aged women (outlined below), the high prevalence of additional risk factors in PCOS and the increased risks with PCOS, baseline screening was recommended in all adults with PCOS, and adolescents who are overweight or from a high risk ethnic group.

The optimal screening test remains unclear in the general population and in PCOS, with fasting glucose, OGTT or HbA1c now acceptable for diagnosis of DM2. The OGTT has higher cost and greater inconvenience, yet can define IGT and influence practice around lifestyle intervention and metformin use, with clear evidence of DM2 prevention in general populations [149], not yet demonstrated based on fasting glucose or HbA1c criteria [148]. HbA1c also brings cost, interference with other conditions and variation across
ethnicities. The guideline development group deemed that on balance, the type of screening should be influenced by clinical judgement on overall risk, resources, access, preference and consideration of where results for IGT will influence practice on prevention of DM2. The high background risk of GDM and the increase in PCOS were considered, along with morbidity in pregnancy based on OGTT (fasting, one hour and two hour levels are all independently associated with adverse outcomes) [150]. Population recommendations are to screen at antenatal booking and at 24-28 weeks in women with risk factors for DM2 [148], with many guidelines recommending universal screening at 24-28 weeks. In this context the guideline development group recommended an OGTT preconception or at booking and at 24-28 weeks, acknowledging the need for further research.

In terms of frequency of screening, a minimum of three yearly is recommended in the general population, considering other risk factors. This was considered reasonable in PCOS, with increased frequency with other risk factors.

Recommendations

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<tbody>
<tr>
<td>1.9.1</td>
<td>CR</td>
<td>Health professionals and women with PCOS should be aware that, regardless of age, the prevalence of gestational diabetes, impaired glucose tolerance and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are significantly increased in PCOS, with risk independent of, yet exacerbated by obesity</td>
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<tr>
<td>1.9.2</td>
<td>CR</td>
<td>Glycaemic status should be assessed at baseline in all women with PCOS. Thereafter, assessment should be every one to three years, influenced by the presence of other diabetes risk factors</td>
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<tr>
<td>1.9.3</td>
<td>CR</td>
<td>An oral glucose tolerance test (OGTT), should be performed at baseline in high risk women with PCOS (including a BMI &gt;25 or in Asian &gt;23kg/m², history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of type 2 diabetes, hypertension or high risk ethnicity). Fasting plasma glucose or HbA1c may be substituted in women with PCOS with no other diabetes risk factors, however these may be less ideal for detecting impaired glucose tolerance, as a key predictor for diabetes</td>
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<tr>
<td>1.9.4</td>
<td>CR</td>
<td>An OGTT should be offered in all women with PCOS who are planning pregnancy or seeking fertility treatment preconception and if negative at &lt;20 weeks and at 28 weeks gestation, given their high risk of hyperglycaemia and the associated comorbidities in pregnancy</td>
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</table>

Justification

DM2 risk factors significantly increase background population risk and prevalence of GDM and DM2, which are further increased in PCOS, independent of BMI, age and ethnicity, representing a significant health and cost burden. The guideline development group unanimously agreed that screening was warranted in all adults with PCOS and in adolescents with additional risk factors at baseline. Optimal tests remain unclear and fasting glucose, HbA1c or OGTT can be used. An OGTT brings higher cost and inconvenience, yet where background risk is high, or where diagnosis of IGT will change practice (lifestyle intervention or metformin use) an OGTT is recommended, at minimum at baseline. Frequency of testing should be a minimum of 3 yearly informed by additional risk factors. These recommendations are less intensive than many prior guidelines. Where past guidelines were followed costs and inconvenience may now be reduced. The majority of guideline development group members voted in favour of the final recommendations (see technical report).
1.10 Obstructive sleep apnea (OSA)

Are women with PCOS at increased risk for sleep apnoea and what is the method/tool most effective to screen for sleep apnea in PCOS?

Clinical need for the question

Obstructive sleep apnoea is characterised by repetitive occlusions of the upper airway during sleep with futile ventilatory efforts, oxygen desaturations, sleep arousal and the resumption of ventilation, fragmenting sleep and causing daytime sleepiness. OSA appears more common in PCOS and in obesity, a common corollary of PCOS. OSA prevalence among general adult populations varies across cohorts and is between nine and 38% [151], with half being minimally symptomatic. Unlike conditions such as hypertension and diabetes where clinical sequelae are measurable at a particular cut off point that inform treatment decisions, there is no established cut off point at which OSA warrants treatment. Treatment process describes a personalised care plan that factors in symptomatology and disruptive impact of associated snoring. Although not well quantified, the potential long term health sequelae still remain an important consideration in the treatment decision and treatment is usually offered routinely to severe cases [152]. Addressing the public health implications of OSA are challenged by the magnitude of its prevalence, the complexity of the diagnostic process as well as the suboptimal effectiveness of device based treatments such as continuous positive airway pressure (CPAP).

Summary of narrative review evidence

A systematic review was not conducted to answer this question and was reviewed narratively based on clinical expertise. Randomised controlled trials demonstrate benefits for symptoms, quality of life, mood and productivity [153]. Observational trials link OSA to adverse cardiovascular outcomes and death [154] and surrogate outcomes may improve with treatment [155]. Relationships to diabetes and glycaemic response to treatment remain controversial [156-160], whilst large RCTs have failed to show CVD benefits of OSA treatment [153, 161, 162]. Clinically, OSA screening is currently warranted in those with symptoms, where treatment benefit has been demonstrated in the general population [163]. In PCOS several studies demonstrate high rates of OSA [164-167] and with matched controls [164], the high prevalence of OSA was not explained by obesity. Hyperandrogenism may contribute to OSA [168] and there are link to metabolic syndrome [169, 170], although treatment studies in PCOS are very limited [169].

Despite poor quality evidence and the current lack of rationale for screening and treatment of OSA based on metabolic risk, screening for OSA has been advocated in PCOS [171]. In the setting of current evidence, clinical screening for those women with symptoms is justified consistent with recommendations in the general population, with validated tools available [172, 173] including the Berlin Questionnaire which does not include age criteria and may be more applicable here (Appendix IV), although none of these are validated in young women with and without PCOS. A positive screen cannot guide treatment and further experiences assessment is required through a detailed history. Overall the most compelling case for treating OSA relates to the improving symptoms of non-restorative sleep, daytime fatigue and sleepiness.

Recommendations
### Justification

Screening and identification of women with symptomatic OSA who may benefit from treatment appears warranted. Wide scale screening on the basis of unproven metabolic benefits of OSA treatment is not currently warranted. The resource implications of selective screening in symptomatic women may both reduce or increase resources (clinician time) depending on current practice. Availability of ambulatory or in laboratory polysomnography in conjunction with clinical follow-up of the results and treatment planning may not be universal.

### 1.11 Endometrial cancer

**Are women with PCOS at increased risk of endometrial cancer and what is the method/tool most effective to screen for endometrial cancer in PCOS?**

#### Clinical need for the question

PCOS has been associated with increased risk of endometrial cancer, yet the interplay is complex with interrelated comorbidities including obesity, and with potential influence from PCOS treatments. Pathophysiology is related to unopposed estrogen in the setting of anovulation and prevention is feasible. Overall given the prevalence and interrelated comorbidities between endometrial cancer and PCOS, this question was prioritised.

#### Summary of narrative review evidence

A systematic review was not conducted to answer this question and it was reviewed narratively based on clinical expertise and is summarised here. The risk of endometrial cancer has been shown to be three times higher than women with PCOS [174], with most adenocarcinomas (>95%) including Type I and Type II cancers [175, 176], with type I increased in PCOS [177, 178]. The increased prevalence of endometrial cancer in PCOS [179], is related to prolonged endometrial exposure to unopposed estrogen in anovulation. Additionally, endometrium in PCOS may exhibit progesterone resistance [180]. Associations between PCOS and endometrial cancer are complex and co-morbid conditions such as obesity, infertility, DM2 and metabolic syndrome are relevant, whilst PCOS treatment options may influence cancer risk [178, 180].
Three meta-analyses, with overlapping studies, report increased risk of endometrial cancer in PCOS [181-183]. All include estimates from analyses that did not take into account BMI, relevant in both PCOS and endometrial cancer [174] with studies limited by few exposed cases. Where BMI was considered, associations with PCOS and endometrial cancer are less consistent [178]. A cohort study reported an increased risk of endometrial cancer in PCOS compared to age-matched controls with OR of 5.3 (95% CI = 1.5–18.6) without adjustment for BMI and 6.1 (95% CI = 1.0–36.9) with adjustment [184], yet others report contrasting results on BMI [177]. Another group reported a higher OR in premenopausal women [185]. Differences relate to variable adjustment for confounders and study population [178], with endometrial thickness and age significant predictors [186, 187].

Regarding PCOS treatments, metformin has no association or a protective association with endometrial cancer [178]. Clomiphene studies are limited by power, but a small non-significant increased risk of endometrial cancer has been shown [188]. Letrozole, yet to be explored in relation to endometrial cancer, is used as an adjuvant treatment for hormone receptor positive postmenopausal breast cancer and may decrease hormonal related cancer risk [178]. Oral contraceptives reduce risk for endometrial cancer in general populations and effects may be enduring.

Routine screening for endometrial hyperplasia or cancer in PCOS is not warranted although endometrial surveillance by transvaginal ultrasound or endometrial biopsy is indicated for those women with PCOS who have thickened endometrium, prolonged amenorrhea, unopposed estrogen exposure or abnormal vaginal bleeding, based upon clinical suspicion [180].

### Recommendations

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<tbody>
<tr>
<td>1.11.1</td>
<td>CR</td>
<td>Health professionals and women with PCOS should be aware of a two to six fold increased risk of endometrial cancer, which often presents before menopause; however absolute risk of endometrial cancer remains relatively low</td>
<td>***</td>
<td>–</td>
</tr>
<tr>
<td>1.11.2</td>
<td>CPP</td>
<td>Health professionals should have a low threshold for investigation of endometrial cancer in women with PCOS or a history of PCOS, with investigation by transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or prolonged oligo amenorrhea and/or abnormal vaginal bleeding. However routine ultrasound screening of endometrial thickness in PCOS is not recommended</td>
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</table>

### Justification

Associations between PCOS and endometrial cancer are complex, with many potential confounders. Women with PCOS appear to have an increased risk of endometrial cancer consistent with anovulation and increased prevalence of obesity. Routine screening for endometrial cancer in PCOS is not recommended, however vigilance and awareness of increased risk is important.
CHAPTER TWO

Prevalence, screening, diagnostic assessment and treatment of emotional well-being

The guideline development members involved here and the prioritised clinical questions overlapped with an international task force nominated by the Androgen Excess and PCOS (AEPCOS) Society to develop a Position Statement on Depression, Anxiety, Quality of Life and Eating Disorders in PCOS [108]. This task force completed relevant systematic and narrative reviews, which informed this guideline development group. Here we expand the AEPCOS task force to include additional members and expertise from primary care. We consider additional questions and completed a full GRADE framework evaluation.

2.1 Quality of life

In women with PCOS, what is the prevalence and severity of reduced QoL and should QoL be assessed as part of standard care?

In women with PCOS, what dimensions of QoL are most affected?

In women with PCOS, what is the most effective tool/method to assess quality of life?

Clinical need for the questions

Health Related Quality of life (HRQoL) is a well-recognised and important health outcome, especially in chronic disease and relates to patient reported physical, social and emotional effects of a condition and its associated treatments [108]. Assessment is self-reported and can be measured through a variety of tools. Generic tools include the Short Form -36 (SF-36) and WHO tools, yet these are not ideal for PCOS with a significant focus on mobility, impact on work, pain, environment and propensity to infective illnesses. They do not consider key dimensions of PCOS such as infertility and hirsutism and PCOS specific tools are now available. The PCOSQ has 26 items across emotions, body hair, weight, infertility and menstrual abnormalities and the modified MPCOSQ adds acne [108, 189]. These tools have been adapted and tested in different ethnic populations. The role of these tools in clinical care remains unclear and the key dimensions affecting QoL are controversial.

Summary of systematic review evidence

Meta-analysis of five studies using SF-36 and three studies using the WHO tool in adult women, all of which were low quality and low certainty, suggest that women with PCOS have lower quality of life compared to women without PCOS. Statistical heterogeneity was present in meta-analysis for six out of the ten domains in SF-36 and in one out of four domains in the WHO tool. These generic QoL tools are poorly tailored and include features unrelated to PCOS such as immobility, pain, risk of infections and environment with limited relevance in PCOS. However they are the only tools that can compare HRQoL across women with and without PCOS, with studies demonstrating reduced HRQoL scores in PCOS, compared to controls and normative population data, as summarised in the AEPCOS position statement [108].

Summary of narrative review evidence
PCOS specific tools have been developed, validated and applied across ethnic groups. The commonly used tools for screening women with PCOS are the PCOSQ scale with domains to assess emotions, body hair, weight, infertility difficulties and menstrual problems and the modified version (MPCOSQ) which includes an acne domain [190, 191]. In PCOS, HRQoL occurs in the context of the multitude of clinical features and is affected by anxiety, poor body image and low self-esteem, depressive symptoms, delayed diagnosis and inadequate education and information provision by health professionals [192]. A meta-analysis and recent update have showed that key domains were hirsutism, menstruation and infertility, yet this varied by population studied, life stage and cultural factors [108] and heterogeneity is to be expected.

In clinical care, the key consideration was determined by the guideline development group to be the self-reported priority of specific PCOS dimensions in an individual woman at a given life stage. Addressing patient reported and prioritised outcomes is important in improving QoL and optimising health in chronic conditions. If patient reported priorities and outcomes were recognised as fundamental in care, this was seen as a substantive step forward in addressing key gaps in care and dissatisfaction expressed by women with PCOS. It is important to consider QoL in PCOS research and may be useful to consider them for application in clinical care, with the caveat that clinically meaningful differences in scores need to be determined.

**Recommendations**

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<tbody>
<tr>
<td>2.1.1</td>
<td>CR</td>
<td>Health professionals and women should be aware of the adverse impact of PCOS on quality of life</td>
<td>****</td>
<td>_</td>
</tr>
<tr>
<td>2.1.2</td>
<td>CR</td>
<td>Health professionals should capture and consider women’s perceptions of their symptoms, impact on their quality of life and personal priorities for care to improve patient outcomes</td>
<td>****</td>
<td>_</td>
</tr>
<tr>
<td>2.1.3</td>
<td>CPP</td>
<td>The PCOS quality of life tool (PCOSQ) or the modified PCOSQ may be useful</td>
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</table>

**Justification**

HRQoL is reduced in PCOS. This diverse condition varies across the lifespan, phenotypes and is influenced by cultural factors which all impact on HRQoL. Key gaps in patient satisfaction have been demonstrated along with limited capture of patient priorities to guide management. There is a need to determine clinical meaningful differences in QoL scores and to validate the tools for change over time, based on a range of evidence sources. However the expert group including patient perspectives considered it important to formally measure QoL with condition specific tools in research settings. In the clinical setting, the role of formal screening is less clear. Rather health professionals should be armed with awareness of the impact of PCOS on QoL and should capture patient priorities to deliver meaningful outcomes when partnering with women with PCOS in their care. If preferred, the MPCOSQ could be considered to assess the domains which have greatest impact on QoL and could guide treatment.

### 2.2 Depressive and anxiety symptoms, screening and treatment

In women with PCOS, what is the prevalence and severity of depressive and anxiety symptoms and should they be screened?
In women with PCOS, what is the most effective tool/method to assess depression and/or anxiety?

Clinical need for the questions

The prevalence and severity of depressive and anxiety symptoms are increased in PCOS. Psychological conditions impact on QoL and are likely to influence engagement in lifestyle interventions and self-management in PCOS. Effective, readily available screening tools are available for clinical practice, yet uptake and recognition of psychological symptoms in PCOS appears limited internationally. A large international survey has shown that most women report psychological issues are under recognised [14] and less than 5% are satisfied with emotional support and counselling. Given the prevalence and severity of depressive and anxiety symptoms and the dissatisfaction expressed by women in this area, these clinical questions were prioritised.

Summary of systematic review evidence

A systematic review was not completed for the first question and the review for the second question did not identify any evidence in women with PCOS to answer this question.

Summary of narrative review evidence

These areas were reviewed narratively, based on clinical expertise.

**Depression:** Depressive symptoms and depression are more common in PCOS [108], with daily fatigue, sleep disturbances and diminished interest prominent [193]. A meta-analysis of 10 studies reported increased depressive symptom scores in 44% with PCOS versus 17% in controls (OR: 4.03, 95% CI: 2.96-5.5, p<0.01) [194], which persisted in BMI matched studies. A meta-analysis of 910 women with PCOS and 1347 controls reported higher depression scores in PCOS [195], although these may not have been clinically significant. A meta-analysis of 26 studies including 4716 participants from 14 countries [196], noted scores were not in a clinically significant range in half of studies, and others were consistent with mild depression. A recent meta-analysis of 23 studies with rigorous inclusion criteria including physician diagnosis of PCOS [197], showed increased moderate/severe depressive symptoms (OR4.18, 95% CI: 2.68-6.52) with a prevalence of depression of 36.6% in PCOS (IQR: 22.3, 50.0%) and 14.2% in controls (IQR: 10.7, 22.2%), independent of obesity and seen in both clinic and community recruits. Limitations included relatively small sample sizes and limited formal diagnosis of depression on clinical assessment. Also a large population-based registry study [198] showing an increased adjusted risk of depression in PCOS and a large hospital database study documented depression in PCOS (9.8%) compared to those without a recorded diagnosis of PCOS (4.6%) [199]. Overall, women with PCOS have a higher prevalence of depressive symptoms and depression, independent of obesity.

**Anxiety:** Anxiety symptoms are increased in PCOS [108]. Meta-analyses of six studies and another of 11 studies reported higher anxiety scores in PCOS compared to controls [195, 196]. Another of four studies reported a sevenfold increase in abnormal anxiety scores in PCOS [200], however, heterogeneity existed in all meta-analysis. A recent rigorous meta-analysis of 10 studies [197] showed increased moderate/severe anxiety symptoms in PCOS (OR: 5.38; 95% CI: 2.28, 12.67), with a prevalence of 41.9% (IQR: 13.6, 22.2%), independent of obesity and seen in both clinic and community recruits. A large population-based study of 24,385 women with PCOS matched for sex, age and country of birth to ten controls, showed increased anxiety disorder (OR 1.37, CI: 1.32, 1.43) [198]. A large hospital database showed anxiety in PCOS at 14%, compared to 5.9% of those
without a diagnosis of PCOS [199]. Collectively these studies indicate increased anxiety symptoms and anxiety disorders in women with PCOS, across diverse ethnic groups.

The cause of depressive and anxiety symptoms in PCOS are not fully elucidated [108] as are the effects of PCOS treatments. While acne, hirsutism, infertility and increased BMI have been linked to increased mood and distress, the evidence is inconsistent [201-204]. Further potential contributors to depression and anxiety in PCOS include the chronic [205-209], complex and frustrating nature of PCOS [210, 211]. Chronic conditions can cause related emotional distress, and treatment of the underlying condition may improve these, although few PCOS studies have explored this. In PCOS consideration should be given to the individual underlying concerns for each woman, to optimise impact on emotional wellbeing.

**Screening for depressive and anxiety symptoms:**

Given the lack of evidence to address this question in PCOS on systematic review, key relevant sources of evidence-based information were sourced for the general population, and with multidisciplinary guideline development group expertise and consumer perspectives, informed the recommendations. These included:

- The treatment of depression in adults with chronic physical health problems, NICE, 2009 [212].
- Common mental health problems: identification and pathways to care, NICE, 2011 [213].
- Antenatal and postnatal mental health: clinical management and service guidance, NICE, 2014 [214].
- Screening for Depression in Children and Adolescents: US Preventive Services Task Force Recommendations 2016 [216].
- Screening for and Treatment of Suicide Risk Relevant to Primary Care: A Systematic Review for the US Preventive Services Task Force, 2014 [217].
- Royal Australian NZ College of Psychiatrists Clinical Practice Guidelines for Mood Disorders 2015 [218].
- Principles of Practice in Mental Health Assessment with Aboriginal Australians. In Working Together: Aboriginal and Torres Strait Islander mental health and wellbeing principles and practice, 2014 [219].

National US and UK guidelines recommend routine screening for common mental health disorders for all adults and adolescents, particularly with chronic physical health problems and in the perinatal period [212-216]. The US guidelines conclude moderate benefit of depression screening in the general adult population [215]. Australian guidelines for the general population do not recommend routine screening, except during the perinatal period [218, 220].
Overall in PCOS, where prevalence and severity is higher, the guideline development group deemed that it was the responsibility of all health professionals partnering with women with PCOS to understand the increased prevalence of depressive and anxiety symptoms and the impact of PCOS on psychological health and routine screening for depressive and anxiety symptoms was recommended. Reciprocally screening may increase distress with another potentially stigmatising diagnosis. Evidence in diabetes suggests that depression and anxiety are over-estimated by screening questionnaires and that diabetes-specific distress explains considerable variance in these symptom scores. This would suggest a need to be sensitive to the distress associated with PCOS, and emphasises the need to avoid over diagnosis of anxiety and depression. While the optimal timing and interval for screening is unknown a pragmatic approach may be to screen all women and adolescents at the time of PCOS diagnosis. Frequency of screening is unclear and some assessment at the time of regular physical health checks for PCOS may be warranted. Use clinical judgement considering an individual woman’s risk factors to inform if additional screening appears warranted along with screening during the antenatal and postnatal periods aligned with recommendations in the general population.

Recommendations

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<tbody>
<tr>
<td>2.2.1</td>
<td>CR</td>
<td>Health professionals should be aware that in PCOS, there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents</td>
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<tr>
<td>2.2.2</td>
<td>CR</td>
<td>Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis and if the screen is positive, health professionals should further assess and/or refer for assessment</td>
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<tr>
<td>2.2.3</td>
<td>CR</td>
<td>If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered to women with PCOS, informed by regional clinical practice guidelines</td>
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<tr>
<td>2.2.4</td>
<td>CPP</td>
<td>The optimal interval for anxiety and depressive symptom screening is not known. A pragmatic approach could include repeat screening using clinical judgment, considering risk factors, comorbidities and life events</td>
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| 2.2.5| CPP        | Assessment of anxiety and or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened 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 | _     | _       |
| 2.2.6| CPP        | Where pharmacological treatment is offered in PCOS, the following should be considered:  
  • Caution is needed to avoid inappropriate treatment with antidepressants or anxiolytics. Where, mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, treatment of depression or anxiety should be informed by clinical regional practice guidelines | _     | _       |
Justification

Women with PCOS are at increased risk of depressive and anxiety symptoms compared to women without PCOS. Moderate to severe symptoms and clinically diagnosed disorders are increased. These symptoms may be related to the distress associated with PCOS. In the context of PCOS, identification of psychological features and mental health disorders is crucial to address gaps in care identified by affected women, to improve wellbeing and QoL, facilitate appropriate referral and care and optimise engagement with lifestyle and preventive strategies. However over diagnosis of depression and anxiety should also be avoided. Life stage, culture and preferred language should be considered. It is not always usual practice to screen women with PCOS for depressive and/or anxiety symptoms and this will change practice. Time, resources and access issues were considered, yet on balance screening is recommended, aligned with international, broadly validated screening approaches in general populations.

2.3 Psychosexual function

In women with PCOS what is the prevalence and severity of psychosexual dysfunction and should they be screened?

In women with PCOS, what is the most effective tool/method to assess psychosexual dysfunction?

Clinical need for the questions

Psychosexual dysfunction refers to sexual problems or difficulties that have a psychological origin based in cognitions and/or emotions such as depression, low self-esteem and negative body image [221] and both risk factors for and prevalence of psychosexual dysfunction appear increased in PCOS. This may be an important issue for the individual woman and may impact on QoL and relationships. Hence clinicians should be aware of potential psychosexual dysfunction in PCOS and screening and assessment should be considered. In this setting guidance on the most effective way to assess psychosexual dysfunction is needed.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions and they were reviewed narratively based on clinical expertise. The prevalence of psychosexual dysfunction varies from 13.3% to 62.5% in PCOS [222-225]. It appears that women with PCOS suffer from greater psychosexual dysfunction than women in the general population in most studies [203, 226-232]. Whilst there is limited quality research in this area, studies [203, 228, 229] do show a correlation between PCOS and reduced QoL, sexual satisfaction and feminine identity. This remains controversial with some studies suggesting the prevalence of psychosexual dysfunction in PCOS group is similar to the general population [224, 225]. A recent systematic review by guideline development group members, identified 18 relevant studies using validated sexual function questionnaires and Visual Analogue Scales (VASs). Small yet significant differences were detected in sexual function subscales, arousal, lubrication, satisfaction and orgasm were all impaired in PCOS compared to women without PCOS. Large effect sizes were evident for body hair impact, social impact of appearance, sexual attractiveness and satisfaction with sex life was impaired, whereas the importance of sex was similar.
to that of non-PCOS women. Physical PCOS symptoms such as hirsutism, obesity, menstrual irregularity and infertility may cause loss of feminine identity and a feeling of being unattractive which may impact on sexuality [203, 228, 230]. Women with PCOS also report less sexual satisfaction and lower sexual self-worth than women without PCOS and sexual dysfunction impacts more on relationships in women with PCOS [227]. In considering screening tools the female sexual function index (FSFI) [224] and Arizona Sexual Experience Scale (ASEX) [225] are commonly used to evaluate psychosexual dysfunction.

Recommendation

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<tr>
<td>2.3.1</td>
<td>CR</td>
<td>All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider screening in adult women with PCOS</td>
<td>****</td>
<td>_</td>
</tr>
<tr>
<td>2.3.2</td>
<td>CR</td>
<td>If psychosexual dysfunction is suspected, further assessment, referral or treatment should follow as appropriate</td>
<td>****</td>
<td>_</td>
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<tr>
<td>2.3.3</td>
<td>CPP</td>
<td>Obesity and infertility are common in PCOS and need consideration as they independently exacerbate psychosexual dysfunction</td>
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Justification

As prevalence and severity of psychosexual dysfunction appears increased in women with PCOS, screening and assessment should be considered in sexually active women to facilitate appropriate intervention aiming to optimise sexual function, limit the social impact of PCOS and improve QoL. It is not usual practice to screen and assess women with PCOS for psychosexual dysfunction. Sensitivities and cultural challenges around psychosexual dysfunction from the woman’s and health professional perspectives may present barriers to implementation. However the international, multi-disciplinary guideline development group, including consumers, agreed that despite implementation challenges, the recommendation was warranted on the basis of prevalence data from a recent systematic review and on potential impact.

2.4 Body image

_In women with PCOS, what is the prevalence and severity of body image distress and should they be screened?_

_In women with PCOS, what is the most effective tool/method to assess body image distress?_

Clinical need for the questions

Body image is complex and is influenced by many factors. Body image is defined here as the way a woman may feel, think about and view their body including their appearance. Relevant physical (excess weight and hirsutism), psychological (self-esteem) and sociocultural factors influence body image. Assessment of body image considers body dissatisfaction, disordered eating, body size estimation and weight. Most women from the general population are dissatisfied with their body, yet negative body image appears more prevalent in PCOS and impacts on thoughts and feelings of health, appearance, QoL, mood and physical fitness. In this context, body image should be considered in PCOS. Recommendations for screening and assessment that
are easy to use and widely applicable are needed and if identified, addressing negative body and associated mood disorders is important to improve emotional wellbeing and QoL in PCOS.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions, therefore the literature was reviewed narratively based on clinical expertise. There is no study investigating body study showed women with PCOS, compared with controls, had a negative body image on the validated Multidimensional Body-Self Relations Questionnaire [192]. Evidence is conflicting however with some case-control studies not finding differences in body image satisfaction and self-esteem, compared to women without PCOS [233-235]. Women with PCOS feel less physically attractive, healthy or physically fit and are less satisfied with their body size and appearance [236], and this negative body image predicts both depression and anxiety [237]. Infertile women with PCOS have lower body satisfaction, than non-infertile women with PCOS [238]. Hirsute women experienced lower self-esteem than non-hirsute women [238]. Overall, PCOS features, in particular hirsutism and increased weight, impact negatively on body image and QoL [239, 240], and negative body image is strongly associated with depression in women with PCOS [241, 242], even after controlling for weight [242, 243]. We did not identify any evidence in women with PCOS to address the question on screening tools and therefore a clinical consensus recommendation has been made based on the expertise of the multidisciplinary guideline development group and key relevant sources of evidence-based information for the general population. Assessment of body image includes measures of body dissatisfaction and disordered eating [244], body size estimation [245] and weight [246, 247]. The NICE Guideline 31 – Obsessive Compulsive Disorder: Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder [248] and the Australian Medical Association Position Statement: Body Image and Health 2002 [249] informed the recommendations provided.

Recommendation

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<tr>
<td>2.4.1</td>
<td>CR</td>
<td>Health professionals and women should be aware that features of PCOS can impact on body image</td>
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</table>
| 2.4.2 | CPP | Negative body image, can be screened using the following stepped approach: **Step 1**: Initial questions could include:  
• Do you worry a lot about the way you look and wish you could think about it less?  
• On a typical day, do you spend more than 1 hour per day worrying about your appearance? (More than 1 hour a day is considered excessive)  
• What specific concerns do you have about your appearance?  
• What effect does it have on your life?  
• Does it make it hard to do your work or be with your friends and family? **Step 2**: If an issue is identified, health professionals could further assess by:  
• Identifying any focus of concern of the patient and respond appropriately  
• Assessing the level of depression and/or anxiety  
• Identifying distortion of body image or disordered eating | _ | _ |
Justification

Given that negative body image in PCOS appears to be increased and may result in increased depression and poorer HRQoL, body image in women with PCOS should be considered as part of a comprehensive assessment and management plan. Recommendations for screening and assessment that are easy to use and widely applicable are needed. Detection of negative body image provides the opportunity to address both psychological aspects such as self-esteem and self-acceptance as well as working on the physical aspects of the condition such as hirsutism, overweight and acne if appropriate. It was acknowledged that it is not usual practice to screen PCOS women for negative body image and an individualised approach focusing on individual priorities is needed. Screening may have resource implications including length of consultation. Available body image scales can reduce time required in assessment and should also be considered in all clinical, health services and population health research in PCOS.

2.5 Eating disorders and disordered eating

*In women with PCOS what is the prevalence and severity of disordered eating, and should they be screened?*

*In women with PCOS, what is the most effective tool/method to assess disordered eating?*

Clinical need for the questions

Diagnosable eating disorders include Anorexia Nervosa; Bulimia Nervosa, Binge-Eating Disorder, Other Specified Feeding or Eating Disorder and Unspecified Feeding or Eating Disorders that do not meet the full criteria for any of the eating disorder diagnoses. Disordered eating refers to eating and weight related symptoms and can include behavioural (e.g. binging, excessive restriction), cognitive (e.g. excessive dietary restraint, negative body image) and emotional factors. Disordered eating affects health and wellbeing and capacity to participate in and contribute to society. Many of those affected are not identified in primary care. Risk factors and prevalence appears increased in PCOS [108]. Increased awareness of these conditions and effective assessment when clinically suspected is important as it should increase recognition and management of eating disorders and disordered eating, thereby improving the psychological functioning and overall QoL in women with PCOS and reducing associated health risks.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions, which were reviewed narratively based on clinical expertise. The prevalence of disordered eating is far higher than the prevalence of eating disorders; many women who do not meet full criteria for an eating disorder experience disordered eating and associated distress [250] including binge eating, purging, and strict dieting or fasting. There is a lack of good evidence regarding the prevalence of eating disorders and disordered eating in women with PCOS, although available data suggests a higher prevalence than in the general community, on clinical interview [251] of any eating disorder (21% vs 4%) but not bulimia nervosa (12% vs 4%). A registry study of women with PCOS (n=24 385) and matched controls reported increased bulimia nervosa, but not anorexia nervosa [252]. Surveys in PCOS show mixed results across the different disorders [253-255], but overall suggest an increased prevalence of eating disorders and disordered eating. Women with PCOS also have more identified risk factors for eating disorders [256] across obesity, depression, anxiety, self-esteem and poor body image [254, 255, 257].
The apparent higher prevalence of eating disorders and disordered eating in women with PCOS, and the negative biopsychosocial consequences of eating disorders and disordered eating highlight the need to raise awareness of these conditions. The NICE recommendations for Eating Disorders: Recognition and Treatment [258] suggest clinicians think about the possibility of an eating disorder in individuals with a range of symptoms relevant to PCOS. Many women with eating disorders are undiagnosed and unaware that they have an eating disorder or that their eating and weight related thoughts and behaviours are unusual and/or cause distress. Unfortunately there are not standardised, widely implemented processes for screening and assessment and the breadth and complexity of these conditions makes simple screening and assessment difficult. This review highlighted the limited, and low quality evidence regarding eating disorder screening tools and it was concluded that none of the tools are effective for identifying eating disorders when used in isolation. Instead the clinician should use their judgement based on a full diagnostic interview. The SCOFF tool is the most commonly used screening tool in adults, takes only a few minutes to administer [258] and is an option. Along with more sensitive tools it is outlined in translation resources (under development). The risk of false positives (and hence inappropriate treatment) was noted with these tools [258] and they cannot replace clinical interview.

**Recommendation**

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<tr>
<td>2.5.1</td>
<td>CR</td>
<td>All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS</td>
<td>(**)</td>
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<tr>
<td>2.5.2</td>
<td>CR</td>
<td>If eating disorders and disordered eating are suspected, further assessment, referral or treatment including psychological therapy could be offered, informed by regional clinical practice guidelines</td>
<td>(**)</td>
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</table>
| 2.5.3 | CPP | Eating disorders and disordered eating can be screened using the following stepped approach.  
Step 1: The SCOFF screening tool can be used or initial screening questions can include:  
• Does your weight affect the way you feel about yourself?  
• Are you satisfied with your eating patterns?  
Step 2: If the SCOFF tool or any of these questions are positive, further screening should involve:  
• Assessment of risk factors and symptoms using age, culturally and regionally appropriate tools  
• Referral to an appropriate health professional for further mental health assessment and diagnostic interview. If this is not the patient’s usual healthcare provider, inform the primary care physician | _ | _ |

**Justification**

The increased risk factors for and apparent increased prevalence of eating disorders and disordered eating in women with PCOS, and the negative biopsychosocial consequences of these disorders, highlight the need for greater awareness in women with PCOS. Many women with eating disorders are undiagnosed and unaware of the presence of an eating disorder. Likewise, many women with disordered eating are unaware that their eating and weight related thoughts and behaviours are unusual and/or causing distress. Therefore, raised awareness and consideration of assessment and diagnosis are important. It was acknowledged that
screening is challenging given the breath and complexity of these conditions and false positives with current tools are noted. Resource and time implications were also considered.

2.6 Information resources, models of care, cultural and linguistic considerations

**What is the effectiveness of different models of care compared to usual care?**

**What are the information, resource and education needs of women and healthcare providers regarding PCOS?**

**Access to culturally and linguistically diverse appropriate care.**

Clinical need for the questions

PCOS can involve diverse clinical features that change across the life course. For models of care, women affected by PCOS may consult multiple health professionals such as a general practitioner/primary care physician, gynaecologist, endocrinologist, infertility specialist, dietitian, dermatologist, psychologist and/or an exercise physiologist. Multidisciplinary care is increasing required in chronic disease management, with improvements in health related outcomes [259], yet presenting increased complexity, compartmentalisation and communication challenges. An interdisciplinary care model involves “the collaboration between a woman with PCOS and a care team who have shared goals for total wellbeing” and is founded on patient centred care principles and is well suited to the PCOS context.

In PCOS there is a well demonstrated gaps and compelling need for and improved information provision [14, 260, 261]. Women internationally report inadequate information, delayed diagnosis and variation in care is reported. Provision of information also improves satisfaction with care and patient experience. Culturally and linguistically appropriate care and information are also a key consideration in PCOS. PCOS is a common disorder worldwide and given the significant psychosocial impacts of PCOS, and the cultural differences in perception of features such as hirsutism, infertility and other complications, cultural awareness is important. The majority of consumer information is in English presenting language barriers for immigrant populations and for women living in countries where English is not the first language. Given current dissatisfaction in care and information provision noted by women internationally, the evidence that health professionals do not adequately address the diverse features of PCOS and the cultural and linguistic considerations in PCOS care, these clinical questions were prioritised.

**Summary of systematic review evidence**

We did not identify any evidence in our patient population to answer the question about models of care.

**Summary of narrative review evidence**

Narrative reviews were completed to address all three questions. Four studies described models of care across barriers, enablers and satisfaction of patients and health professionals and benefits of information and socio-emotional support. Evaluation of a multidisciplinary PCOS service showed successful evidence-based care, emotional screening and lifestyle management [262] and was greatly valued by patients and health professionals. Barriers included staffing limitations and turnover, lack of administrative support, funding challenges and system issues [262]. Support groups have been explored [263, 264] including online peer-support in the UK [263]. Connecting with people who understand, access to information and advice,
building confidence in interaction with health care professionals, help with treatment related decision-making and improvement in adjustment and management were reported. Disempowering experiences included “reading about the negative experiences of others” and “feeling like an outsider”. A nurse–led UK peer support group increased participation, reduced isolation and improved empowerment, provided relevant information and positively affected self-management [264]. A Canadian educational program [265] increased motivation to implement preventive strategies, enhanced satisfaction with health care professional engagement and empowered women to participate in self-management.

A systematic search was completed on i) women’s experiences of PCOS care and PCOS information ii) women’s perceived needs for PCOS care and information, iii) health care providers’ delivery of PCOS care and information, iv) health care providers’ perceived needs for PCOS information, education programs, or professional development. Comprehensive, accurate, personalised information is important in PCOS as a chronic condition requiring self-management [261], enables informed decisions, optimises prevention and is associated with better quality of life [14, 266]. Women often see multiple health professionals before diagnosis [14, 260, 267, 268], flag symptoms multiple times [269, 270] and experience delays in diagnosis [14, 260, 267, 270]. Receiving a diagnosis is important to women [270]; yet may lead to anxiety and frustration without adequate information [267-269]. Reproductive and metabolic features are concerns [14, 271], psychological features are under-appreciated [269], and women report that primary concerns go unrecognised [267]. Specific and practical information is needed, yet often not provided, or does not meet needs [14, 260, 268-270, 272, 273]. Women’s initial source of information is their healthcare provider [269-271], yet if inadequate, inaccurate or conflicting, frustration is reported [14, 272]. The internet is accessed yet quality is often poor [269, 270, 272] or conflicted by commercial interests [272], impacting patient experience [267]. Overall, PCOS information needs to be comprehensive, evidence-based and inclusive of the bio-psycho-social dimensions of the condition and care needs to prioritise women’s personal concerns [14, 267, 268, 274, 275]. Women with PCOS are best supported by a range of information resources: respectful and empathetic healthcare providers, websites, leaflets and support groups [270, 276, 277]. Health professional research suggests variation in care by specialty including across rates of undiagnosed PCOS [278] and investigations [279]. Women with PCOS infrequently report seeing a dietitian or receiving dietary advice [280]. Educational programs improve knowledge and confidence in PCOS among doctors [281], with greater activity needed to address gaps identified by women with PCOS.

Regarding culturally and linguistically competent medical care in PCOS there are few relevant studies. Adaptation of educational resources and longer consultation times may be required [282] and family rather than individual consultations may be relevant. Cultural barriers can include low health literacy, high level of tolerance to problems and unwillingness to see a male physician [282]. Many of the studies in information and care needs and preferences in PCOS are limited to English speaking women and do not explore cultural issues.

Recommendations

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<tr>
<td>2.6.1</td>
<td>CR</td>
<td>Information and education resources for women with PCOS should be culturally appropriate, tailored and high-quality, should use a respectful and empathetic approach, and promote self-care and highlight peer support groups</td>
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</table>
2.6.2 CR Information and education resources for healthcare professionals should promote the recommended diagnostic criteria, appropriate screening for comorbidities and effective lifestyle and pharmacological management

2.6.3 CR PCOS information should be comprehensive, evidence-based and inclusive of the biopsychosocial dimensions of PCOS across the life-span

2.6.4 CR Women’s needs, communication preferences, beliefs and culture should be considered and addressed through provision of culturally and linguistically appropriate resources and care

2.6.5 CPP Interdisciplinary care should be offered to those with PCOS where appropriate and available

2.6.7 CPP Care should be provided in partnership with women with PCOS

2.6.8 CPP Guideline dissemination and translation including multimodal education tools and resources is important, with consultation and engagement with stakeholders internationally

Evidence specific to PCOS models of care remains limited, especially for adolescents transitioning from paediatric to adult care. However, existing evidence suggests integrated multidisciplinary services, support groups and nurse-led education can address identified gaps, increase understanding of PCOS and improve lifestyle change whether online or nurse-led. New models of care should follow best practice and be co-designed with both women and health professionals.

Key gaps in information provision need to be addressed through a range of information resources: health professionals, websites, written information and support groups with more comprehensive, evidence-based information that covers diverse PCOS features and prioritises women’s personal concerns. Needs differ by individual and life stage and diagnosis is a time of greater need. Cultural influences need to be considered in PCOS in the context of both care and information needs. Culturally appropriate care involves more than linguistic considerations and is just as important for women who speak English but are not of the cultural majority.
CHAPTER THREE

Lifestyle

3.1 Effectiveness of lifestyle interventions

In women with PCOS, are lifestyle interventions (combined compared to minimal or nothing) effective for improving weight loss, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

Rates of weight gain and prevalence of excess weight are increased in adolescents and women with PCOS. The potent combination of excess weight and PCOS is adversely affecting reproductive, metabolic and psychological health, presenting a major public health challenge mandating both prevention and treatment. Insulin resistance is independently exacerbated by excess weight [283], increasing prevalence and severity of metabolic, reproductive and psychological features of PCOS [12, 284-286]. Benefits from lifestyle intervention and weight loss have been demonstrated in women with PCOS [287-290] and healthy lifestyle is important in preventing excess weight gain in PCOS and can offer benefits even without weight loss [291-295]. Women with PCOS internationally report that excess weight causes significant distress and concern and that there is inadequate information and support around lifestyle change [14]. Weight was also a highly ranked, prioritised outcome by both health professionals and women during the guideline development process. Overall, in women with PCOS and excess weight, lifestyle interventions which reduced weight by as little as 5% of total body weight have been shown to have health metabolic, reproductive and psychological benefits [287-290, 296-314]. Given the uncertainty on effectiveness and optimal components of lifestyle intervention in PCOS, underpinned by the generally small and uncontrolled trials, variable outcomes and populations, this clinical question was prioritised.

Summary of systematic review evidence

One high quality systematic review with a low risk of bias was identified to answer this question. The systematic review appraised six randomised controlled trials (RCTs) (low to moderate quality and moderate to high risk of bias) for the effectiveness of lifestyle treatment compared to minimal treatment in improving reproductive, metabolic, anthropometric and QoL factors in women with PCOS [315]. Due to the inconsistencies and methodological weaknesses of included studies, caution is recommended when interpreting the combined meta-analyses and results of the systematic review. There were three studies that used exercise and three that used combined lifestyle modification programmes (including diet, exercise and behaviour), with the outcome measurements reported at various times (12, 16, 24, and 48 weeks). Lifestyle intervention was better than minimal treatment for total testosterone (mean difference (MD) -0.27 nmol/L [-0.46 to -0.09] p=0.004), hirsutism by Ferriman-Gallwey score (MD -1.19 [-2.35 to -0.03] p=0.04), weight (MD -3.47 kg [-4.94 to -2.00] p<0.00001), waist circumference (MD -1.95 cm [-3.34 to -0.57] p=0.006), waist-hip-ratio (MD -0.04 [-0.07 to -0.00] p=0.02), fasting insulin (MD -2.02 µU/mL [-3.28 to -0.77] p=0.002) and oral glucose tolerance test insulin (standardised mean difference -1.32 [-1.73 to -0.92] p<0.00001) and percent weight change (MD -7.00% [-10.1 to -3.90] p<0.00001). There was no difference between the two interventions for BMI, FAI, SHBG, glucose or lipids. QoL, patient satisfaction and acne were not reported. None of the studies addressed fertility outcomes such as pregnancy, live birth and miscarriage. While some
studies reported on menstrual regularity and ovulation, the findings were reported in a variety of ways and it was not possible to estimate the overall effects of lifestyle on these outcomes.

### Recommendations

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<tr>
<td>3.1.1</td>
<td>EBR</td>
<td>Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural intervention) should be recommended in women with PCOS and excess weight for reductions in weight, central obesity and insulin resistance.</td>
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<td>3.1.2</td>
<td>CR</td>
<td>Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all women with PCOS to achieve and maintain healthy weight, improve hormonal outcomes, general health, and quality of life across the life course.</td>
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<td>3.1.3</td>
<td>CPP</td>
<td>Achievable goals such as 5% to 10% weight loss in overweight women yields significant clinical improvements and is considered successful weight reduction within six months. Ongoing assessment and monitoring is important during weight loss and maintenance in all women with PCOS.</td>
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<tr>
<td>3.1.4</td>
<td>CPP</td>
<td>SMART (Specific Measurable, Achievable, Realistic and Timely) goal setting and self-monitoring can enable achievement of realistic lifestyle goals.</td>
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<tr>
<td>3.1.5</td>
<td>CPP</td>
<td>Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, should be considered and managed to optimise engagement and adherence to lifestyle interventions.</td>
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<tr>
<td>3.1.6</td>
<td>CPP</td>
<td>Health professional interactions around healthy lifestyle including diet and exercise, should be respectful, patient-centred and should value women’s individualised healthy lifestyle preferences and cultural and ethnic differences. Health professionals should also consider personal sensitivities, marginalisation and potential weight-related stigma.</td>
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<td>3.1.7</td>
<td>CPP</td>
<td>Adolescent and ethnic-specific body mass index and waist circumference categories should be considered when optimising lifestyle and weight management.</td>
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<td>3.1.8</td>
<td>CPP</td>
<td>Healthy lifestyle may contribute to health and quality of life benefits in the absence of weight loss.</td>
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<td>3.1.9</td>
<td>CPP</td>
<td>Healthy lifestyle and optimal weight management is the joint responsibility of all health professionals, partnering with women with PCOS. Where complex issues arise, referral to suitably trained allied health professionals should be considered.</td>
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<td>3.1.10</td>
<td>CPP</td>
<td>Ethnic groups with PCOS who are at high cardiometabolic risk require greater consideration in terms of healthy lifestyle and lifestyle intervention.</td>
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</table>

### Justification

Given the high prevalence and important adverse impact of excess weight in PCOS and the apparent efficacy in PCOS and in general populations, lifestyle management was deemed important in this high risk group. The recommendations and practice points were informed by general population guidelines, the evidence identified in PCOS and by multidisciplinary health professional and consumer input. They are intended to reduce variation in practice, improve lifestyle advice and support for women with PCOS, and target both prevention of weight gain and where appropriate weight loss. The recommendations also consider important psychosocial, cultural and ethnic aspects in relation to lifestyle interventions and were informed by evidence generated for other clinical questions under emotional wellbeing and under specific lifestyle interventions. These recommendations may increase consultation times, referral to allied health professionals and associated healthcare costs, however long term benefits are anticipated to reduce the
health and economic burden of PCOS. Engagement of health practitioners and financial barriers for patients may present implementation issues.

3.2 Behavioural interventions

In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

With weight gain increasing in women, and even higher rates of weight gain shown in PCOS, preventive strategies are needed [316, 317]. Previous lifestyle intervention studies in PCOS have involved short-term dietary interventions with or without an exercise component. Dietary intervention studies have shown benefit with weight loss [318], however retention and sustainability prove challenging, suggesting a need for additional strategies. Behavioural and cognitive behavioural intervention approaches target behaviours, their antecedents and consequences and cognitions that maintain positive energy balance and promote weight gain [319] and are common in weight management. Behaviour therapy results in significantly greater weight loss than placebo, and behaviour/cognitive behaviour therapy combined with diet and exercise has efficacy. Given the need to improve adherence and impact of lifestyle interventions in PCOS, this question was prioritised.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

A multidisciplinary model of care with a dietitian, health psychologist, gynaecologist and endocrinologist in adolescents with PCOS, showed that a ‘behavioural intervention’ enhanced weight loss when combined with dietary consultation, compared to receiving neither or dietary advice only [320]. The intervention was not well defined or replicable and metabolic, reproductive and psychosocial outcomes were not assessed. Two RCT’s included behavioural lifestyle components, yet had minimal detail on the theoretical framework or behavioural components. These compared comprehensive lifestyle intervention (diet, behaviour and physical activity) over 24 weeks with placebo [321, 322] with variable but limited benefits.

In this context recommendations on behavioural lifestyle interventions in women with PCOS, are informed by data from general populations. A comprehensive systematic review of lifestyle interventions in populations at risk of DM2 or CVD, summarised key success factors in lifestyle interventions [323]. Behavioural change techniques in combination with diet and exercise interventions increased weight loss over diet and/or physical activity alone [323]. Self-management has positive impacts [323] and family support improves outcomes, [323]. Mode of delivery and trained intervention facilitator, setting and intensity didn’t impact outcomes [323]. Overall, this underpins international guidelines recommending integration of: 1/ established behaviour change techniques 2/ self-management/ self-monitoring and 3/ social support to preventative and treatment lifestyle interventions [323, e.g., 324]. Combining behavioural/cognitive behavioural weight loss components with
intensive interventions including very low calorie diets and weight loss medications also improves weight loss than these interventions alone [325-328].

Guidelines highlight the need for resources (e.g., written, audio-visual) and the potential for e-health to supplement face-to-face support with strategies including; goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slowing the rate of eating, reinforcing changes, and relapse prevention. Continued contact after treatment (face-to-face or telephone) also improves weight-loss maintenance. More intensive behavioural interventions induce greater weight loss [329]. In the general population, behavioural and cognitive behavioural interventions have strong empirical support and are recommended in international guidelines in on the treatment of excess weight [e.g., 324, 330].

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.1</td>
<td>CR</td>
<td>Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, stimulus control, problem solving, assertiveness training, slower eating, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS</td>
<td>****</td>
<td>–</td>
</tr>
<tr>
<td>3.2.2</td>
<td>CPP</td>
<td>Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Justification

In other high cardiometabolic risk populations, behavioural change strategies and/or behavioural/cognitive interventions in combination with diet and exercise improves weight loss over diet and/or physical activity alone. Emphasis on self-management components enhances weight loss and healthy lifestyle behaviour change and are incorporated into advice on lifestyle interventions for the general population. Skill levels among health professionals may vary presenting implementation challenges.

3.3 Dietary interventions

*In women with PCOS, are diet interventions (compared to no diet or different diets) effective for improving weight loss, metabolic, fertility, and emotional wellbeing outcomes?*

Clinical need for the question

Specific dietary composition in lifestyle interventions remains controversial. Given the general recommendations to reduce caloric (energy) intake, rather than modifying macronutrient composition, the widespread promotion of specific dietary composition in PCOS and the limited comparative research on efficacy of specific dietary macronutrient approaches in PCOS, this clinical question was prioritised.

Summary of systematic review evidence
Four articles reporting three studies were identified to answer this question. One RCT with a moderate risk of bias investigated the changes in anthropometric, metabolic and non-fertility outcomes by comparing a high protein diet to a high carbohydrate diet [331]; one RCT with a low risk of bias investigating the changes in anthropometric and metabolic outcomes by comparing a DASH diet with a control diet [332, 333]; and one RCT with a high risk of bias investigating the changes in anthropometric and metabolic outcomes by comparing a high protein diet with a normal protein diet [334]. There was no difference for the majority of the anthropometric, metabolic, fertility, non-fertility, QoL and emotional wellbeing outcomes, however, regardless of the type of diet, the overall finding was that a diet aimed at reducing weight was of benefit to women with PCOS.

Summary of narrative review evidence

Given the limitations in evidence in PCOS, evidence was also sought from the general population. Here recommendations for dietary lifestyle intervention components in management of excess weight includes a low-fat high fibre (~30% of energy, saturated fat ~10%, <300 mg cholesterol daily), moderate protein (~15%) and high carbohydrate diet (~55%) in conjunction with moderate regular exercise [138, 335, 336]. It is notable that dietary intervention studies have shown benefit with weight loss of 5-15% [318]. In both general populations and in PCOS, modifying diet macronutrient composition including the amount or type of carbohydrate, protein or fat, is promoted as having either more favourable hormonal or metabolic effects or being more effective in achieving and sustaining long-term weight loss. However, a systematic review in the general population reported similar or less weight loss and compliance for a low fat diet compared to other approaches [337, 338], and a large RCT reported similar changes in weight for a range of reduced energy diets with different macronutrient content over two years [339].

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3.1</td>
<td>CR</td>
<td>A variety of balanced dietary approaches could be recommended to reduce dietary energy intake and induce weight loss in women with PCOS and overweight and obesity, as per general population recommendations</td>
<td>****</td>
<td>–</td>
</tr>
<tr>
<td>3.3.2</td>
<td>CR</td>
<td>General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations</td>
<td>****</td>
<td>–</td>
</tr>
<tr>
<td>3.3.3</td>
<td>CPP</td>
<td>To achieve weight loss, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kj/day) should be prescribed for women, also considering individual energy requirements, body weight and physical activity levels</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3.3.4</td>
<td>CPP</td>
<td>In women with PCOS, there is no or limited evidence that any specific energy equivalent diet type is better than another, or that there is any differential response to weight management intervention, compared to women without PCOS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3.3.5</td>
<td>CPP</td>
<td>Tailoring of dietary changes to food preferences, allowing for a flexible and individual approach to reducing energy intake and avoiding unduly restrictive and nutritionally unbalanced diets are important, as per general population recommendations</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Justification

Given that consumer targeted information about PCOS purport the benefit of specific macronutrient composition, this recommendation is important to ensure that women and health professionals are informed on the evidence on dietary composition and efficacy. Emphasis should be on individual preferences and cultural needs of each woman and on an overall balanced and healthy dietary composition to achieve.
energy intake reduction for weight loss. Education for both women and health professionals is needed in this area. Specific cost and resource implications were considered but recommendations were approved on balance, informed by recommendations in the general population and benefits in PCOS.

3.4 Exercise interventions

_In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?_

Clinical need for the question

Whilst not formally included in the diagnostic criteria, insulin resistance, is involved in the aetiology and clinical features of PCOS [340, 341]. Exercise ameliorates insulin resistance and offers a potentially effective intervention in PCOS, with some evidence of clinical benefit. In general populations, physical activity (any bodily movement produced by skeletal muscles that requires energy expenditure) and structured exercise (activity requiring physical effort, carried out to sustain or improve health and fitness), deliver clear health benefits, whilst sedentary behaviours (activities during waking hours in a seated or reclined position with energy expenditure less than 1.5 times resting metabolic rate) have adverse health impacts. Despite the potential for benefit, women with PCOS report receiving limited lifestyle advice and specific efficacy of different types and intensity of exercise is unclear and was prioritised in PCOS and its associated co-morbidities.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

Physical activity and formal exercise interventions are classified as aerobic/endurance (focusing on aerobic capacity/fitness), resistance activities (targeting muscle mass and strength) or a combination, further subgrouped by exercise intensity into light, moderate, vigorous or high-intensity [342] (Table 5). Two small RCT’s are relevant in PCOS. Regular moderate intensity cycle exercise, had greater metabolic benefit over 24 compared to 12 weeks, without impact on reproductive biomarkers [19, 343, 344]. Whilst 20 weeks of aerobic compared to combined exercise, superimposed on a high protein diet, showed similarly improved PCOS features [19, 343, 345, 346]. Overall, in overweight women with PCOS, small RCT’s and high quality mechanistic studies (cohort and case control studies) show physical activity, including formal exercise (aerobic and muscle strengthening), improves body composition, metabolic, reproductive and psychological features [19, 343, 345-356], compared to minimum or no interventions. These benefits occur independent of significant weight loss [350] and can occur when exercise is used alone [293, 357].

The mechanistic impacts of exercise and physical activity on the cardiometabolic and reproductive features of PCOS are well described [343, 358-360]. While acknowledging the limitations in quality of evidence (sample size, study type, heterogeneity of interventions), improved glycaemic and reproductive outcomes, quality of life and functional capacities have been shown [19, 343, 345, 358-362]. Psychologically, limited community
based/epidemiological studies show positive associations between self-reported physical activity and mental health status [347, 348] and vigorous exercise and better health outcomes in women with PCOS [363]. Conversely, there is an increase in sedentary behaviour documented in PCOS [364]. Mechanistically, insulin resistance, underpinned by insulin signalling pathway defects, is involved in the aetiology [340, 341] and clinical features of PCOS [340, 341, 365-367]. Moderate aerobic exercise improves insulin sensitivity short-term in PCOS [368].

Insulin resistance is also ameliorated in high risk groups where exercise reduces DM2 risk [369, 370] and cardiovascular risk factors [371, 372]. Similarly, resistance or weight-bearing exercise either alone or in combination with aerobic exercise improves health outcomes in high risk groups [373-376]. In general populations, physical activity and structured exercise deliver metabolic, cardiovascular, and psychosocial benefits, whether alone or combined with diet changes [377-379]. Sedentary behaviours link to all-cause mortality and adverse health impacts [380, 381], whilst aerobic and resistance exercise reduce cardiometabolic risk factors [382]. Health impacts of exercise therapy may also reduce long-term healthcare costs [383]. Overall, current guidelines for the general population recommend 150 minutes of exercise per week with 90 minutes at moderate to high intensity [384-392] (Table 5).

### Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/ CR/ CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
</table>
| 3.4.1 | CR | Health professionals should encourage and advise the following for prevention of weight gain and maintenance of health:  
- in adults from 18-64 years, a minimum of 150 min/week of moderate intensity physical activity or 75 min/week of vigorous intensities or an equivalent combination of both including muscle strengthening activities on 2 non-consecutive days/week  
- in adolescents at least 60 minutes of moderate to vigorous intensity physical activity/day including those that strengthen muscle and bone, at least 3 times weekly  
- activity be performed in at least 10 minutes bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days | *** | _ |
| 3.4.2 | CR | Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits including:  
- a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity or an equivalent combination of both AND  
- muscle strengthening activities such as resistance or flexibility activities on 2 non-consecutive days/week  
- minimised sedentary or sitting time | *** | _ |
| 3.4.3 | CPP | Physical activity includes leisure time physical activity, transportation such as walking or cycling, occupational work, household chores, games, sports or planned exercise, in the context of daily, family and community activities with 10,000 steps per day being ideal, including activities of daily living plus 30 minutes of structured physical activity or around 3000 steps. Structuring of recommended activities around women’s and family preferences and cultural considerations is recommended | _ | _ |
| 3.4.4 | CPP | Realistic physical activity SMART goals could include progressively increasing physical activity 5% weekly up to and above recommendations | _ | _ |
| 3.4.5 | CPP | Self-monitoring including with fitness tracking devices and technologies could be used as an adjunct to support and promote active lifestyles and minimise sedentary behaviours | _ | _ |
Table 5: Physical activity intensity and examples.

<table>
<thead>
<tr>
<th>Intensity and measure</th>
<th>Description</th>
<th>Examples of activities and ADL’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIGHT</td>
<td>• Aerobic activity that does not cause noticeable changes in breathing rate</td>
<td>Casual walking, cycling &lt;8km/hr (5mph), stretching, light weight training, dancing slowly, leisurely sports (playing catch) golf (using cart), light yard/house work</td>
</tr>
<tr>
<td>1.6–3*METs 40–55%</td>
<td>• An intensity that can be sustained for at least 60 minutes</td>
<td></td>
</tr>
<tr>
<td>*HRmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MODERATE</td>
<td>• Aerobic activity that can be conducted whilst having an uninterrupted conversation</td>
<td>Brisk walking (5-7km/hr, 3-4.5mph), walking uphill, hiking, cycling (8-15km/hr, 5-9mph), low impact or aqua aerobics, yoga gymnastics, weight training, moderate dancing, aerobic machines (stair climber, elliptical, stationary bike) — most competitive tennis, volleyball, badminton, recreational swimming, golf—carrying clubs, intense house/yard work or occupations with extended standing or walking</td>
</tr>
<tr>
<td>3 – 6 *METs 55–70%</td>
<td>• An intensity that may last between 30 to 60 minutes</td>
<td></td>
</tr>
<tr>
<td>*HRmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIGOROUS</td>
<td>• Aerobic activity where an uninterrupted conversation generally can’t be maintained</td>
<td>Race walking, jogging/running, mountain climbing, cycling (&gt;16km/hr, 10 mph), high impact aerobics, karate or similar, circuit weight training, vigorous dancing and aerobic machines, competitive basketball, netball, soccer, football, rugby, hockey, swimming, water jogging, downhill or cross country skiing, non-motorized lawn mowing, occupations with heavy lifting or rapid movement</td>
</tr>
<tr>
<td>6 – 9 *METs 70–90%</td>
<td>• Intensity that may last up to 30 minutes</td>
<td></td>
</tr>
<tr>
<td>*HRmax</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Predicted maximal heart rate (HRmax) = 208 – (0.7 X AGE[years]); \* metabolic equivalent (MET) where 1 MET is the O₂/kg body weight/min required to sustain ones resting metabolic rate [3.5 mL/kg/min][342] and [393].

**Justification**

Exercise should be encouraged and advised in PCOS based on evidence in the general population and in PCOS. It was considered that exercise interventions and physical activity do not require clinical centres, expensive gyms and fitness centres. They can be delivered in community centres, sporting grounds/facilities, in groups and with minimal equipment. Low cost e-health (electronic health) and m-health (mobile health) options may also be utilised. As such, costs and resources need not be prohibitive. Where available and affordable, and where there is risk from injury, barriers to exercise or additional motivation required, due consideration should be given to involvement of exercise physiologists/specialists in structured exercise intervention, as captured in the 3.1 Lifestyle interventions.

**3.5 Obesity and weight assessment**

*Are women with PCOS at increased risk of obesity?*

*In women with PCOS, does obesity impact on prevalence and severity of hormonal and clinical features?*

**Clinical need for the questions**

Obesity affects the majority of women recruited from clinic populations and is common in community based studies. The complex pathophysiology and clinical heterogeneity of PCOS has contributed to the lack of a clear
understanding of interactions between PCOS, excess body weight and body fat distribution. Obesity, particularly central obesity, is well known to increase insulin resistance and hyperandrogenism, may increase PCOS prevalence and exacerbates the clinical features of PCOS. It is also of significant concern to women with PCOS and a key target for prevention and management in this condition. The degree of increased risk of excess weight and the impact on prevalence and severity of features of PCOS remain unclear.

Summary of narrative review evidence

A systematic review was not conducted to answer these questions, which were reviewed narratively based on clinical expertise. This review informs both the recommendations for assessment and screening in chapter 1 and the recommendations in chapter 3. In terms of prevalence of excess weight in PCOS, the great majority of women seeking treatment for PCOS are overweight or obese [394]. One in three overweight women are at risk of having PCOS. Rates of weight gain appear higher in PCOS, and one unit increase of BMI (kg/m²) increases the risk of diagnosis of PCOS by 9% [395]. The temporal trends of obesity prevalence in PCOS show an increase from 51% in the 90s to 74% in the following decades [396]. There is general recognition that women with PCOS who present for diagnosis and care may be more likely to have excess weight than those who do not, however longitudinal community based data supports higher weight gain and excess body weight. Long-term weight gain over 10 years among women with PCOS is significantly greater than in unaffected women in a longitudinal community based study (mean difference 2.6kg 95% CI 1.2-4.0) [397]. Weight gain escalates from adolescence and early vigilance and intervention is important. Central obesity increases over time with a progressive increase in waist hip ratio between 20-25 years and 40-45 years [114]. This is consistent with reports from a prospective birth cohort of increased weight gain in early adulthood in women with symptoms of or a diagnosis of PCOS compared with controls [398]. Overall rates of weight gain and excess weight are increased in PCOS.

Obesity influences the phenotypic expression of PCOS, with augmentation of metabolic, reproductive, and psychological features [399] (see chapter 2). Metabolic factors increase in PCOS with excess weight with Insulin resistance present in 75% of lean and 95% of overweight women with PCOS [400]. Lipid abnormalities are increased independently and are exacerbated by excess weight [396, 399, 401]. Central obesity is associated with more severe metabolic disturbance [399]. The prevalence of IGT and DM2 is further increased in women with PCOS with excess weight, especially in high risk ethnic groups [402]. Conversely, weight loss reduces abdominal fat and insulin resistance and improves clinical features of PCOS (see chapter 3) [403, 404].

Obesity exacerbates reproductive problems in PCOS including ovulatory dysfunction, irregular menstrual cycles, prolonged time to conception, infertility and poor-response to ovulation induction; increased risk of miscarriage, hyperglycaemia of pregnancy, pre-eclampsia, increased perinatal morbidity, fetal macrosomia and a greater potential for trans-generational transmission of obesity and metabolic problems [396, 401, 403, 405]. When combined with insulin resistance, type 2 diabetes and PCOS, the adverse outcomes can be more than additive [396, 401]. Expert opinion has therefore uniformly recommended that obese women with PCOS delay infertility therapy and pursue lifestyle modification [394, 397].

Psychological comorbidities of PCOS with overweight/obesity include anxiety, depression, low health related quality of life, sexual dissatisfaction, poor self-esteem and psychological distress [394, 401, 404]. Psychological health also requires consideration when assessing and managing excess weight, especially in PCOS. When assessing weight, related stigma, negative body image and/or low self-esteem should be considered and assessment should be respectful. Consistent with population recommendations, explanations on the purpose, how the information will be used and opportunity for questions and preferences should be provided and
permission sought. Implications of results should be explained and support provided as needed.

As outlined earlier in this chapter, lifestyle healthy lifestyle is recommended in all women with CPOS to maintain healthy weight and prevent excess weight gain and lifestyle intervention is recommended to induce weight loss in women with excess weight. Monitoring of weight is a component of behavioural interventions and self-management associated with better short and long term weight outcomes. General population guidelines recommend monitoring weight, BMI and where appropriate waist circumference. Whilst women with CPOS have increased central adiposity, the impact of measuring waist circumference in PCOS is not clear and it requires time and consistent methods.

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5.1</td>
<td>CR</td>
<td>Health professionals and women should be aware that women with PCOS have an increased risk of weight gain and obesity, presenting significant concerns for women, impacting on health and emotional wellbeing, with a clear need for prevention</td>
<td>***</td>
<td>_</td>
</tr>
<tr>
<td>3.5.2</td>
<td>CR</td>
<td>Assessment for excess weight and weight gain should be considered at every visit in women with PCOS, in consultation with and where acceptable to the individual woman</td>
<td>****</td>
<td>_</td>
</tr>
</tbody>
</table>
| 3.5.3 | CR         | Weight, height, BMI and where appropriate waist circumference should be assessed and the following considered:
• BMI categories and waist circumference should follow World Health Organisation guidelines
• Consideration should be given for Asian and high risk ethnicity and for adolescent specific ranges | ***   | _       |
| 3.5.4 | CPP        | When assessing weight, related stigma, negative body image and/or low self-esteem should be considered and assessment should be respectful and considerate. Beforehand, explanations on the purpose and how the information will be used and the opportunity for questions and preferences should be provided, permission sought and scales and tape measures adequate. Implications of results should be explained and where this impacts on emotional wellbeing, support provided | _     | _       |
| 3.5.5 | CPP        | Prevention of weight gain, monitoring of weight and encouraging evidence based and socio-culturally appropriate healthy lifestyle is important in PCOS, particularly from adolescence | _     | _       |

Justification

Rate of weight gain and excess weight/obesity is more prevalent in women with PCOS, compared to women without PCOS and cause considerable concern for affected women. Obesity exacerbates the clinical features of PCOS and given the significant burden, low adherence rates and challenges with weight loss and maintenance, prevention of weight gain through healthy lifestyle is vital including assessment and monitoring of weight, consistent with international public health recommendations. Awareness, respectful monitoring and early intervention are important considerations from adolescence.
CHAPTER FOUR
Pharmacological treatment for non-fertility indications

Medical therapies have a key role of the management of PCOS symptoms, with the need to consider risks and benefits and the individual characteristics and preferences of women with PCOS.

4.1 Pharmacological treatment principles in PCOS

In reviewing the literature on pharmacological treatments, general principles emerged that apply across all pharmacological therapies. These have been extracted into a set of clinical practice points to inform women and guide health professionals when considering or recommending pharmacological therapy in PCOS. These practice points apply to all pharmacological treatments prioritised and addressed in the guidelines.

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1.1</td>
<td>CPP</td>
<td>Consideration of the individual’s personal characteristics, preferences and values is important in recommending pharmacological treatment</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4.1.2</td>
<td>CPP</td>
<td>Combined oral contraceptive agents, metformin and other pharmacological treatments are generally off label in PCOS. However off label use is predominantly evidence-based and is allowed in many countries. Where is it allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4.1.3</td>
<td>CPP</td>
<td>Pharmacological therapy in PCOS should be considered in addition to lifestyle therapy</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

4.2 Combined Oral Contraceptive Pills (COCP)

Is the combined oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?

Clinical need for the question

Combined contraceptives, including oral contraceptive pills (OCPs) are commonly prescribed for adults and adolescents with PCOS to ameliorate the clinical symptoms and associated hormonal disturbances. The effects of combined oral contraceptive pills (COCPs) on menstrual cycle, hirsutism, weight loss, waist/hip ratio, testosterone concentrations, lipid profile and blood sugar levels are variably reported and depend on type of OCP used, duration of use, severity of presentation/ phenotype, adherence to the regimen, among other factors. Different combinations of COCPs are available with heterogeneous estrogen and progestin...
preparations with varying pharmacological and clinical properties. Thus, the efficacy and consequences of COCPs in PCOS may vary. Some preparations also comprise natural estrogen instead of synthetic ethinyl estradiol (EE) with benefits and contraindications considered similar.

**Summary of systematic review evidence – OCP alone**

**Research evidence - ADOLESCENTS**

**COCP versus placebo**

One randomised controlled trial (RCT) was identified to address this comparison in adolescents [406]. There was a statistically significant improvement with COCP (compared to placebo) for HDL in this very low quality study with low certainty. No statistically significant differences were found for outcomes: BMI (kg/m2); Waist (cm); Total testosterone (ng/dl); SHBG (nmol/liter); FAI; Hirsutism (FG score); Total cholesterol (mg/dl); LDL (mg/dl); Triglycerides (mg/dl); Fasting insulin (IU/ml); Fasting blood sugar (mg/dl); CRP (mg/l); PAI-1. Side effects were not reported.

**COCP versus lifestyle**

One RCT was identified to address this comparison in adolescents [406]. There was a statistically significant improvement with lifestyle (compared to COCP) for LDL in this very low quality study with very low certainty. No statistically significant differences were found for: BMI (kg/m2); Total testosterone (ng/dl); SHBG (nmol/liter); FAI; Hirsutism (FG score); Total cholesterol (mg/dl); HDL (mg/dl); Triglycerides (mg/dl); Fasting insulin (IU/ml); Fasting blood sugar (mg/dl); CRP (mg/l); PAI-1. Side effects were not reported.

**COCP versus metformin**

A systematic review including four RCTs that address this comparison in adolescents was identified [407]. The evidence team conducted additional analysis of outcomes not addressed in the systematic review. While a statistically significant improvement was found in BMI and LDL with use of metformin over COCP; and a statistically significant improvement was found in menstrual regulation with use of COCP over metformin, we remain cautious due to very low certainty in effect estimates and the quality of evidence. A statistically significant improvement in dysglycemia (OGTT) was found with the use of metformin over COCP, however it should be noted that there is low certainty in the effect estimates and the quality of evidence. No statistically significant differences were found for: Hirsutism; Total Testosterone (nmol/L); Triglyceride (mg/dL); Total Cholesterol (mg/dL); High-Density Lipoprotein (mg/dL); Weight (kg); Fasting insulin; SHBG; FAI; Fasting blood sugar (mg/dL); CRP (mg/L); PAI-1. Side effects included weight gain with COCP; and side effects were not specified with metformin.

**COCP versus metformin + anti-androgen**

One RCT was identified to address this comparison in adolescents [408]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m2); Hirsutism (FG score); Glucose/insulin ratio; SHBG (ug/dl); Testosterone (ng/dl); Triglycerides (mg/dl); HDL (mg/dl); LDL (mg/dl); Cycle regularity; Weight. Side effects were not reported.

**Research evidence - ADULTS**

**COCP versus metformin**
Nine RCTs were identified to address this comparison [409-417]. There were statistically significant improvements with metformin (compared with COCP) for fasting insulin, including for both BMI subgroups. Metformin improved HDL in the BMI>25 subgroup but not in the BMI<25 subgroup or when all participants were combined; and improved triglycerides when all participants were combined, in the BMI>25 subgroup and in the subgroup where BMI was not defined, but not in the BMI<25 subgroup. There were statistically significant improvements with COCP (compared with metformin) for SHBG, FAI, total testosterone and irregular cycles, including for all BMI subgroups. COCP improved LDL in the BMI>25 subgroup but not in the BMI<25 subgroup or when all participants were combined. No statistically significant differences were found for: Weight; Clamp (M value); HOMA (change from baseline); BMI (kg/m2); WHR; Hirsutism [FG score]; Fasting glucose [mmol/l], Total cholesterol [mmol/l]. Metformin use increased GI-related events, whereas the COCP group had none. While one of the included studies was of moderate quality and certainty, the majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

**COCP versus COCP + metformin**

Six RCTs were identified to address this comparison [415, 417-421]. There was a statistically significant improvement with COCP alone (compared with COCP plus metformin) for triglycerides. COCP alone improved SHBG in the BMI<25 subgroup but not in the BMI>25 subgroup or when all participants were combined. There were statistically significant improvements with COCP plus metformin (compared with COCP alone) for FAI. COCP plus metformin improved testosterone when all participants were combined but not in BMI subgroups; improved hirsutism and fasting glucose when all participants were combined and in the BMI>25 subgroup but not in the BMI<25 subgroup; improved SHBG and fasting insulin in the BMI<25 subgroup but not when all participants were combined or in the BMI>25 subgroup; and improved total cholesterol in the BMI>25 subgroup but not when all participants were combined or in the BMI<25 subgroup. No statistically significant differences were found for: HOMA; Weight (kg); BMI (kg/m2); WHR; HDL [mmol/l]; LDL [mmol/l]. The addition of metformin to COCP increased GI-related events, whereas the COCP alone group had none. While one of the included studies was of moderate quality and certainty, the majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

**COCP versus COCP + metformin + anti-androgen**

One RCT was identified to address this comparison in adults [408]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m2); Hirsutism (FG score); Glucose/insulin ratio; SHBG (ug/dl); Testosterone (ng/dl); Triglycerides (mg/dl); HDL (mg/dl); LDL (mg/dl); Cycle regularity; Weight. Side effects were not reported.

**COCP versus anti-androgen**

One RCT was identified to address this comparison is adults [422]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for the outcome hirsutism (FG score).

**Summary of systematic review evidence – combined OCP**

Research evidence - ADOLESCENTS
**COCP + metformin + lifestyle versus COCP + lifestyle + placebo**

One RCT was identified to address this comparison is adolescents [406]. There was a statistically significant improvement with the addition of metformin to COCP and lifestyle (compared to COCP and lifestyle plus placebo) for testosterone and HDL in this very low quality study with very low certainty. No statistically significant differences were found for: BMI (kg/m2); Waist (cm); SHBG (nmol/l); FAI; Hirsutism (FG score); Total cholesterol (mg/dl); LDL (mg/dl); Triglycerides (mg/dl); Fasting insulin (IU/ml); Fasting blood sugar (mg/dl); CRP (mg/liter). One in each group stopped metformin or placebo due to GI effects.

**COCP + anti-androgen versus COCP + anti-androgen + metformin**

One RCT was identified to address this comparison is adolescents [423]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m²); Fasting glucose/insulin ratio; SHBG (µg/dl); Testosterone (ng/dl); LDL (mg/dl); HDL (mg/dl); Triglycerides (mg/dl). Side effects were not reported.

**Research evidence - ADULTS**

**COCP versus COCP + metformin**

Six RCTs were identified to address this comparison [415, 417-421]. There was a statistically significant improvement with COCP alone (compared with COCP plus metformin) for triglycerides. COCP alone improved SHBG in the BMI<25 subgroup but not in the BMI>25 subgroup or when all participants were combined. There were statistically significant improvements with COCP plus metformin (compared with COCP alone) for FAI. COCP plus metformin improved testosterone when all participants were combined but not in BMI subgroups; improved hirsutism and fasting glucose when all participants were combined and in the BMI>25 subgroup but not in the BMI<25 subgroup; improved SHBG and fasting insulin in the BMI<25 subgroup but not when all participants were combined or in the BMI>25 subgroup; and improved total cholesterol in the BMI>25 subgroup but not when all participants were combined or in the BMI<25 subgroup. No statistically significant differences were found for: HOMA; Weight (kg); BMI (kg/m2); WHR; HDL [mmol/l]; LDL [mmol/l]. The addition of metformin to COCP increased GI-related events, whereas the COCP alone group had none. While one of the included studies was of moderate quality and certainty, the majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

**COCP versus COCP + metformin + anti-androgen**

One RCT was identified to address this comparison in adults [408]. Due to the lack of direct comparisons between groups (no p values reported for between groups) it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m2); Hirsutism (FG score); Glucose/insulin ratio; SHBG (ug/dl); Testosterone (ng/dl); Triglycerides (mg/dl); HDL (mg/dl); LDL (mg/dl); Cycle regularity; Weight. Side effects were not reported.

**COCP versus COCP + anti-androgen**

Four RCTs were identified to address this comparison in adults [424-427]. There was a statistically significant improvement with COCP alone (compared with COCP plus anti-androgen) for BMI and LDL. No statistically significant differences were found for: Weight (kg); WHR; Hirsutism (FG score); FAI (%); Testosterone (nmol/L); SHBG [nmol/l]; Fasting insulin (uIU/ml); Fasting glucose [mmol/l]; Total cholesterol [mmol/l]; HDL [mmol/l]; Triglycerides (mg/dL); HOMA; CRP (mg/l); Headache; Breast-related side effects; Vomit/Nausea;
Minor depressive state; Liver function. The majority of studies in these meta-analyses were of low to very low certainty in effect estimates and the quality of evidence and therefore all findings should be interpreted with caution.

**COCP + metformin + lifestyle versus COCP + metformin + lifestyle**

One study was identified to address this comparison in adults [428]. There were no statistically significant differences reported between the two interventions (differing by the combination in the COCP) in this very low quality study of very low certainty for outcomes: WHR; Fasting plasma glucose (mmol/L); HbA1c (%); Total cholesterol (mmol/L); LDL (mmol/L). Side effects were not reported.

**Summary of narrative review evidence**

Evidence on COCP use from the general population also informed recommendations by the guideline development group. Consideration of adverse effects is needed before prescribing COCPs. Absolute contraindications for COCP use according to WHO, include women with a history of migraine with aura, deep vein thrombosis (DVT)/pulmonary emboli (PE), known thrombogenic mutations, multiple risk factors for arterial cardiovascular disease, history of ischemic heart disease or stroke, complicated valvular heart disease, breast cancer, neuropathy, severe cirrhosis and malignant liver tumours [429]. Other risk factors for DVT need consideration including women up to 6 weeks postpartum immobility, transfusion at delivery, BMI > 30 kg/m2, postpartum haemorrhage, immediately post-caesarean delivery, preeclampsia or smoking. Current evidence suggests that COCPs containing levonorgestrel, norethisterone and norgestimate are associated with the lowest relative risk of DVT. Also, according to WHO recommendations COCPs with 35ug EE and cyproterone acetate (CPA) should only be used in adult and adolescent women when treating moderate or severe hirsutism or acne due to higher risk for DVT. Thus, for contraception and indications including irregular menstrual cycles and mild to moderate hirsutism, other preparations with lower risk profiles are recommended [430].

**Recommendations – OCP alone**

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/ CR/ CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2.1</td>
<td>EBR</td>
<td>The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and irregular menstrual cycles</td>
<td>****</td>
<td>⊕⊕⊕○</td>
</tr>
<tr>
<td>4.2.2</td>
<td>EBR</td>
<td>The COCP alone should be considered in adolescents with a clear diagnosis of PCOS for management of clinical hyperandrogenism and irregular menstrual cycles</td>
<td>***</td>
<td>⊕⊕⊕○</td>
</tr>
<tr>
<td>4.2.3</td>
<td>EBR</td>
<td>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</td>
<td>***</td>
<td>⊕⊕⊕○</td>
</tr>
<tr>
<td>4.2.4</td>
<td>EBR</td>
<td>Specific types or dose of progestins, estrogens or combinations of COCP cannot currently be recommended with inadequate evidence in adults and adolescents with PCOS and practice should be informed by general population guidelines</td>
<td>***</td>
<td>⊕⊕⊕○</td>
</tr>
<tr>
<td>4.2.5</td>
<td>CR</td>
<td>The 35ug ethinyl estradiol and cyproterone acetate preparations should not be considered first line in adults and adolescents with PCOS as per general population guidelines</td>
<td>*</td>
<td>—</td>
</tr>
<tr>
<td>4.2.6</td>
<td>CPP</td>
<td>When prescribing COCPs in adults and adolescents with PCOS: • various COCP preparations have similar efficacy in treating hirsutism • androgenic properties of progestins and venous thromboembolic risk should be considered</td>
<td>—</td>
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</tr>
</tbody>
</table>
lower dose estrogen preparations, and natural estrogen preparations (such as 20-30mcg of ethinyl estradiol or equivalent), should be considered balancing efficacy, metabolic risk profile and side effects

- the generally limited evidence on effects of COCP’s in PCOS should be appreciated with practice informed by general population guidelines

- side-effects of the COCP should be the subject of individualised discussion

- PCOS specific risk factors such as high BMI, hyperlipidemia and hypertension should be considered

### Recommendations – combined OCP

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/ CR/ CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
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<tr>
<td>4.3.1</td>
<td>EBR</td>
<td>In combination with the COCP, metformin should be considered in women with PCOS for management of metabolic features</td>
<td>****</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>4.3.2</td>
<td>EBR</td>
<td>In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI ≥25</td>
<td>****</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>4.3.3</td>
<td>CPP</td>
<td>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</td>
<td>_ _</td>
<td>_ _</td>
</tr>
<tr>
<td>4.3.4</td>
<td>EBR</td>
<td>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</td>
<td>**</td>
<td>⊕⊕⊕⊕</td>
</tr>
<tr>
<td>4.3.5</td>
<td>CR</td>
<td>In combination with the COCP, antiandrogens could be considered for the treatment of female pattern hair loss in PCOS</td>
<td>**</td>
<td>_ _</td>
</tr>
<tr>
<td>4.3.6</td>
<td>CPP</td>
<td>In PCOS, antiandrogens must be used with effective contraception, to avoid male foetal undervirilisation. Variable availability and regulatory status of these agents is notable and for some agents, potential liver toxicity requires caution</td>
<td>_ _</td>
<td>_ _</td>
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</tbody>
</table>

### Justification

Although relatively safe, COCPs have absolute and relative contraindications in the general population that apply here and women should be educated on risks and benefits of therapy. Although combination therapy of metformin and COCP was found to offer additional benefits, a combination regime can lead to increased mild gastrointestinal side effects, which can impact on adherence. Strategies to reduce side effects are available (see metformin recommendations below) With metformin therapy in addition to COCP, women with PCOS and obesity may yield the greatest benefit. The PCOS phenotype, BMI, ethnicity and the informed preference of the individual with PCOS need to be considered when recommending pharmacological agents for the treatment of PCOS.

COCPs, metformin and anti-androgens are not indicated for treatment of PCOS by regulatory bodies and use is off label. However, use is evidence based for the treatment of clinical features of PCOS and is generally not restricted for use in PCOS. Women should be informed of the benefits and risks.

The option of metformin in combination with the COCP is not routine practice and will require education and integration into algorithms. This is anticipated to significantly change practice.

Due to subgroup differences in recommendations, the personal characteristics of all women need to be considered.
4.4 Metformin

Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Clinical need for the question

Metformin is a low cost, readily available medication that has been extensively used as an insulin sensitiser for over seven decades in DM2 and for several decades in PCOS. However efficacy remains uncertain and clinical practice appears variable. Side effects cause some concern, and metformin use in PCOS is generally off label. Yet metformin is a low cost, readily available medication, and off label use in PCOS is allowed in many countries. Metformin works by decreasing gluconeogenesis, lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tis. It is known in other populations to prevent weight gain and appears to assist with weight loss, to prevent and manage DM2, gestational diabetes, and to reduce cardiovascular disease in DM2 [431]. Metformin is widely used by women with PCOS, yet there is variability in recommendations across health professional specialty, with endocrinologists familiar with metformin and more likely to prescribe this therapy. Lack of clarity around the role of metformin in PCOS remains.

Summary of systematic review evidence

Metformin versus placebo

Twenty RCTs that address outcomes for this comparison were identified [406, 432-450], of which 19 RCTs were in adults [432-450], and 1 was in adolescents [406].

Weight: When 5 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo [432, 439, 442, 448, 449]. When three of the studies in those with BMI>25kg/m2 were subgrouped [439, 442, 448], metformin was better than placebo.

BMI: When 15 RCTs were combined in meta-analysis [406, 432-435, 437, 439, 440, 443-447, 450, 451]; and when 11 of the RCTs in those with BMI>25kg/m2 was subgrouped [406, 433-435, 437, 439, 440, 444, 447, 450, 451]; metformin was better than placebo.

WHR: When 8 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo (p=0.06 in favour of metformin) [432, 433, 435, 439, 442, 444, 446, 449]. When 3 of the RCTs in those with BMI<25kg/m2 were subgrouped [432, 444, 446], metformin was better than placebo.

Hirsutism: When 6 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [406, 438, 440, 444-446].

SHBG: When 13 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [406, 432-435, 438-440, 443, 445, 446, 449, 451]. In one very small RCT (n=20), where BMI was not reported, there was a statistically significant difference in favour of metformin [438].

FAI: When 6 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [406, 438, 439, 445, 446, 451].
**Testosterone:** When 15 RCTs were combined in meta-analysis metformin was better than placebo, however there was no statistically significant difference for any of the BMI subgroups [406, 432-435, 438-440, 443, 445, 446, 448-451].

**Fasting insulin:** When 9 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo [433-435, 439, 440, 444, 448, 449, 451]. In one small RCT (n=60) of those with BMI <or>25kg/m², there was a statistically significant difference in favour of metformin [449].

**Fasting glucose:** When 13 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo [406, 432-435, 439, 440, 443, 444, 448-451]. In one small RCT (n=58) of those with BMI <or>25kg/m², there was a statistically significant difference in favour of metformin [449].

**Cholesterol:** When 10 RCTs were combined in meta-analysis [406, 433, 435, 437, 439, 440, 443, 444, 446, 449]; and when 6 of the RCTs in those with BMI>25kg/m² was subgrouped [406, 433, 435, 439, 440, 444]; metformin was better than placebo.

**HDL:** When 9 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [406, 433, 440, 444-446, 448, 449].

**LDL:** When 9 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo (p=0.07 in favour of metformin) [406, 433, 438-440, 444-446, 449]. When 6 of the RCTs in those with BMI>25kg/m² were subgrouped, metformin was better than placebo.

**Triglycerides:** When 13 RCTs were combined in meta-analysis metformin was better than placebo, however there was no statistically significant difference for any of the BMI subgroups [406, 433, 435, 438-440, 443, 444, 446, 449].

There were no statistically significant differences between metformin and placebo for HOMA, menstrual cycles, CRP or PAI-1.

It is important to remain cautious due to low to very low certainty in effect estimates and the quality of evidence across all outcomes.

Gastrointestinal side effects were more prevalent in the metformin groups, but only 5 out of 20 studies including in total 358 women and metformin doses of 1500 -1700mg/day reported on side effects without specific details. Ten to 62% of women taking metformin reported side effects. The majority of gastrointestinal side effects were mild to moderate and were self-limiting. The side effects reported included nausea, vomiting, diarrhoea, abdominal pain or non-specified gastrointestinal disturbance. Only one study reported higher drop out in the metformin treated due to unacceptable gastrointestinal side effects and suggested lower start metformin dose (500 mg/day),

There were no reports on Vitamin B12 levels.

**Metformin versus metformin + COCP**

Three RCTs that address this comparison in adults were identified [415, 417, 452]. While a statistically significant improvement was found in WHR and triglycerides with use of metformin over metformin plus COCP, regardless of BMI, we remain cautious due to very low certainty in effect estimates and the quality of evidence.

No statistically significant differences were found for: Weight, BMI, FAI, testosterone, Fasting glucose (mg/dl), Fasting insulin [mIU/ml], fasting glucose-insulin ratio, HOMA, OGTT, Total cholesterol [mg/dl], HDL [mg/dl] and LDL [mg/dl].

*Chapter 4: Pharmacological treatment for non-fertility indications* 82
Side effects were not reported.

**Metformin versus lifestyle**

Three RCTs that address this comparison in adolescents and adults were identified [406, 451, 453]. While a statistically significant improvement was found in testosterone with use of metformin over lifestyle; and in SHBG with the use of lifestyle over metformin, we remain cautious due to very low certainty in effect estimates and the quality of evidence. While not statistically significant, fasting glucose tended to favour metformin.

No statistically significant differences were found for: BMI, WHR, PAI 1, Hirsutism (FG score), Menstruation (cycle/mnth), FAI, Fasting glucose (mg/dl), Fasting insulin [mIU/ml], HOMA, Total cholesterol [mg/dl], HDL [mg/dl], LDL [mg/dl], Triglycerides [mg/dl], CRP [mg/dl].

Side effects were GI related with metformin and only reported in one study including adult women.

**Metformin + lifestyle versus lifestyle ± placebo**

A systematic review including seven relevant RCTs that address this comparison in adults and adolescents was identified [454]. The evidence team conducted additional analysis of outcomes not addressed in the systematic review. No statistically significant differences were found for any of the outcomes in this body of evidence of low to very low certainty and quality.

Side effects were not reported.

**Metformin versus metformin (dose)**

One study was identified to address this comparison [455]. Age was not reported. There was no difference in weight between the two interventions in this very low quality of very low certainty. Other relevant outcomes were mentioned in this study, however no useable data was reported.

The highest metformin dose used was 850 mg twice a day.

**Metformin versus anti-androgen + COCP**

One study was identified to address this comparison in adults [456]. 500g of metformin was better for fasting glucose; and 850g was better for CRP; however, there was no difference for BMI, HDL or triglycerides in this moderate quality study with low certainty.

**Metformin + lifestyle versus anti-androgen + lifestyle**

Four RCTs that address this comparison in adults was identified [457-460]. While a statistically significant improvement was found in cycles per year and HOMA-IR with use of metformin plus lifestyle over anti-androgen plus lifestyle; and a statistically significant improvement found in hirsutism, SHBG, fasting insulin and fasting glucose-insulin ration with use of anti-androgen plus lifestyle over metformin plus lifestyle, we remain cautious due to low to very low certainty in effect estimates and the quality of evidence.

No statistically significant differences were found for: Weight (kg); BMI; WHR; Testosterone (nmol/L); Fasting glucose (mg/dl); QUICKI [mg/dl]; FAI (pg/ml); OGTT (mg/dl) and HOMA-IR (mIU · mmol/L2).

Side effects were only reported in one study and included vomiting, nausea and diarrhea with metformin plus lifestyle; and abdominal pain, polyuria, menstrual irregularity and dryness of the mouth with anti-androgen plus lifestyle. Three subjects in the metformin group and four in the spironolactone group withdrew due to side effects.
Total cholesterol, HDL and LDL were reported in two studies however units were unclear and there was missing data. Of the data presented, there were no differences between interventions for these outcomes in one study and in the other, p values were not reported for direct comparisons.

Metformin + diet versus metformin + anti-androgen + diet

Four RCTs that address this comparison in adults was identified [457, 458, 460, 461]. While a statistically significant improvement was found in testosterone and fasting glucose with use of metformin plus anti-androgen plus lifestyle over metformin plus lifestyle, we remain cautious due to very low certainty in effect estimates and the quality of evidence.

No statistically significant differences were found for: Weight; BMI; WHR; cycles; hirsutism, SHBG, FAI, fasting insulin; OGTT (mg/dl) and HOMA-IR, total cholesterol, HDL, LDL and triglycerides.

Side effects were only reported in one study and included vomiting, nausea, diarrhoea symptoms with metformin plus lifestyle; and nausea, diarrhoea, abdominal pain and metrorrhagia with metformin plus anti-androgen plus lifestyle.

There was stronger evidence in higher BMI groups for metabolic outcomes; inadequate evidence to make a recommendation about the use of metformin for menstrual regulation. The maximum dose used in the included studies was 850bd and the optimum dose is not known.

Gastrointestinal side effects may be present and resolve within a short period of time. Side effects are usually mild, self-limiting and may be minimized with lower metformin starting dose. Extended release preparations and administration with food might also decrease gastrointestinal side effects.

Summary of narrative review evidence

Given the gaps in evidence in some areas in PCOS, the relevant literature on metformin in other populations was reviewed to inform recommendations. Metformin works by decreasing gluconeogenesis, lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue and ovaries [462]. It is known in other populations to prevent weight gain and appears to assist with weight loss, to prevent and manage DM2, gestational diabetes, and to reduce microvascular and cardiovascular disease in DM2 [431, 462]. Side effects have are not uncommon, yet these are primarily gastrointestinal, appear mild and self-limiting, with more severe side effects rare and primarily affecting those with other comorbidities [462]. Concerns on Vitamin B12 deficiency with longer term metformin use have also emerged [463], however more research is needed. Data from other populations suggests that side effects can be minimized with lower metformin starting dose, extended release preparations and/or administration with food [464].

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4.1</td>
<td>EBR</td>
<td>Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes</td>
<td>***</td>
<td>⊘⊕⊕</td>
</tr>
<tr>
<td>4.4.2</td>
<td>EBR</td>
<td>Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI≥25kg/m² for management of weight and metabolic outcomes</td>
<td>***</td>
<td>⊘⊕⊕</td>
</tr>
<tr>
<td>4.4.3</td>
<td>EBR</td>
<td>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</td>
<td>***</td>
<td>⊘⊕⊕</td>
</tr>
</tbody>
</table>
4.4.4 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

4.4.5 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

Justification
Study numbers were considerable, however the quality and certainty of the evidence was limited. Metformin has clear benefits in the other relevant populations including those with DM2. In PCOS, overall evidence indicated that metformin is effective in improving weight, BMI, WHR ratio, testosterone, SHBG and TG in women with PCOS including those defined by Rotterdam criteria. Evidence of metabolic benefits was generally stronger in women with increased BMI. There was inadequate evidence to make a recommendation about the use of metformin for irregular menstrual cycles and efficacy for infertility is addressed later in the guideline. Gastrointestinal side effects were noted, but appear to be mild, self-limiting and could be minimized with lower metformin starting dose, extended release preparations or administration with food. Overall, the beneficial effects in PCOS favoured the use of metformin, the undesirable effects were generally mild and self-limiting and on balance, evidence was felt to probably favour metformin use in PCOS. Whilst use is off label, it is also generally allowed. Cost was relatively low and availability generally widespread and implementation of recommendations were judged to be feasible.

4.5 Anti-obesity pharmacological agents

Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Clinical need for the question

As previously outlined, excess weight is a significant concern for adolescents and women with PCOS and is more prevalent than in women without PCOS. Whilst lifestyle intervention has a first line role in the prevention and management of excess weight in PCOS, the role of anti-obesity pharmacological agents in achieving and maintaining weight loss and in delivering potential health benefits is being increasingly recognised in general and other high risk populations. Challenges with adherence, efficacy and sustainability all appear to benefit from the addition of these agents to lifestyle interventions. Recent US Endocrine Society guidelines [465], systematic and Cochrane reviews [466] have focused on the role of these agents in general and high risk populations [465, 466] including in obese adolescents. A range of different agents are now approved as anti-obesity medications in adults, although approval status varies across countries, costs remain generally high and there are challenges in access and availability. Despite the challenges, these medications are increasingly being used in adults for assistance with weight loss and weight maintenance in
obesity management in other populations [465]. However, in PCOS and in reproductive-aged women generally, the role of anti-obesity pharmacological agents remains unclear.

Summary of systematic review evidence

We did not identify any evidence in adolescents with PCOS and below is a summary of the evidence identified in adults.

**Anti-obesity versus placebo**

One study was identified to address this comparison [467]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this low quality study with low certainty for outcomes: Weight loss (kg); WHR (cm); Menstrual periods (n/6 months); Triglycerides (mmol/L); Fasting glucose (mmol/L); Fasting insulin (mU/L); Fasting glucose/insulin ratio; HOMA-IR; Hs-CRP (mg/L); Testosterone (nmol/L); SHBG (nmol/L); FAI. Side effects were not reported.

**Anti-obesity versus anti-obesity**

One study was identified to address this comparison [468]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this low quality study with low certainty for outcomes: BMI (kg/m²); WHR (cm); Testosterone (ng/dl); Δ4-Androstenedione (ng/ml); DHEA-S (ng/ml); FAI; SHBG (nmol/l); Fasting glucose (mg/dl); Fasting insulin (μIU/ml); Fasting glucose/insulin; AUC OGTT; HOMA-IR; QUICKI; PAI-1 (ng/ml). Side effects were not reported.

Summary of narrative review evidence

Given the gaps in evidence in some areas in PCOS, the relevant literature on anti-obesity agents in other populations was reviewed to inform recommendations. Recent US Endocrine Society guidelines [465], systematic and Cochrane reviews [466] have focused on the role of these agents in general and high risk populations including in obese adolescents. A range of different agents are now approved as anti-obesity medications in adults, although approval status varies across countries, costs remain generally high and there are challenges in access, efficacy and availability. Despite the challenges, these medications are increasingly being used and recommended in adults for assistance with weight loss and weight maintenance in obesity management in other populations [465].

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>4.5.1</td>
<td>CR</td>
<td>Anti-obesity medications in addition to lifestyle, could be considered for the management of obesity in adults with PCOS after lifestyle intervention, as per general population recommendations</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>4.5.2</td>
<td>CPP</td>
<td>Anti-obesity medications are currently costly, contraindications and side effects need to be considered and availability and regulatory status is variable</td>
<td>_</td>
<td>_</td>
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</tbody>
</table>

Justification

Despite recommendations in the general population, in reproductive-aged women generally including those with PCOS, the role of anti-obesity pharmacological agents remains unclear. Given the absence of useful
evidence in PCOS, the guideline development group were unable to make any evidence-based recommendations in women with PCOS. However informed by evidence and guidelines on the use of anti-obesity pharmacological agents in the management of obesity in non-PCOS adults a consensus recommendation has been made. There are known contraindications and side effects of these medications that need to be considered and monitored. Concerns about cost effectiveness was also considered by the group, based on evidence in the general population [469].

4.6 Anti-androgen pharmacological agents

*Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?*

Clinical need for the question

The most common androgen-related features of PCOS are hirsutism, acne and female pattern hair loss (see Chapter 1: Screening, diagnostic assessment, risk assessment and life-stage). Given the adverse impact of clinical hyperandrogenism on emotional wellbeing in PCOS, the adverse impact of these features on quality of life (see Chapter 2: Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing), and the high priority given to clinical hyperandrogenism outcomes during guideline development, this clinical question was prioritised. Cosmetic and COCP therapy are first line treatments for hirsutism in women including in PCOS [470]. There are few studies of anti-androgen pharmacological agents in the treatment of PCOS and there are limited relevant studies on the use of anti-androgens in other populations that can guide practice in PCOS [470], with the majority of studies involving anti-androgen pharmacological agents combined with COCPs (see section 4.3 COCP in combination with other agents). Overall, the role of anti-androgens remains controversial and this question was prioritised.

Summary of systematic review evidence

*Anti-androgen versus placebo*

One study of adolescents was identified to address this comparison [471]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this very low quality study with very low certainty for outcomes: BMI (kg/m²); Modified Ferriman-Gallwey score; SHBG (µg/ml); Testosterone (ng/dL); DHEAS (µmol/L); Androstenedione (ng/ml); GI related adverse effects. Side effects were not reported.

*Anti-androgen + lifestyle versus placebo + lifestyle*

One study was identified to address this comparison in adults [458]. Due to the lack of direct comparisons between groups (no p values reported for between groups for end of treatment data), it is uncertain whether there were any differences in this moderate quality study with moderate certainty for outcomes: Weight (kg); BMI (kg/m²); Number of cycles in previous 6 months; Hirsutism (Ferriman-Gallwey score); SHBG (nmol/L); FAI (pg/ml); Testosterone (ng/ml); DHEAS (µg/ml); Androstenedione (ng/dl); Fasting insulin (µU/ml); Fasting glucose (mg/ml); Response of glucose to OGTT- glucose AUC (mg/ml⋅min); Response of insulin to OGTT- insulin AUC (µU/ml⋅min); QUICKI; ISI; HDL (mg/dL); LDL (mg/dl); Triglycerides (mg/dl). The only side effect reported in the anti-androgen group was a mild increment in transaminase levels.
**Anti-androgen (daily) versus anti-androgen (every 3 days)**

Two RCTs that address this comparison in adults were identified [472, 473]. While a statistically significant improvement was found in hirsutism FG score with use of the frequency of every 3 days over daily anti-androgens, we remain cautious due to very low certainty in effect estimates and the quality of evidence. No statistically significant differences were found for: BMI, testosterone, SHBG and fasting insulin.

GI related side effects were found in the group taking anti-androgen every 3 days (compared to those on daily treatment).

**Anti-androgen + diet versus metformin + anti-androgen + diet**

Three RCTs that address this comparison in adults were identified [457, 458, 460]. While a statistically significant improvement was found in fasting glucose and HOMA-IR with the addition of metformin to anti-androgen and lifestyle; and in triglycerides with anti-androgens and lifestyle (without metformin); we remain cautious due to low to very low certainty in effect estimates and the quality of evidence. No statistically significant differences were found for: Weight, WHR, BMI [kg/m2], Number of cycles/year, Number of cycles in previous 6 months, FAI [pg/ml], Hirsutism [FG score], SHBG [nmol/l], Testosterone [nmol/l], Fasting insulin [μU/mL], QUICKI, OGTT [mg/dl], Total cholesterol (mM/l), HDL (mmol/l), LDL (mmol/l).

As noted above, it is difficult to offer definitive evaluation of the use of anti-androgens because of the poor quality of evidence and lack of valid randomized controlled studies.

As the undesirable effect of antiandrogens is mostly related to mild hepatotoxicity, lifestyle does not seems to alleviate such a risk. Conversely, it seems that the addition of metformin does not increase either the risk of elevated liver indices or general side effects (same of, even increased, compliance with treatment in one study). The potential for teratogenicity for anti-androgens especially when used as a single agent in women at risk for conception limits the use of these medications. There is no evident dose-response relationship.

**Summary of narrative review evidence**

Other relevant evidence and guidelines not specific to the PCOS population, were considered to inform these recommendations, include those around side effects of anti-androgens. The guideline development group considered it is mandatory to use concomitant contraception with anti-androgens in order to avoid foetal male undervirilisation in the event of unplanned pregnancy [474]. Consistent with the Endocrine Society guidelines we recommend against antiandrogen monotherapy unless adequate contraception is used. Due to the growth cycle of hair, at least a 6–12 months course treatment is optimal to evaluate the effectiveness of the antiandrogen treatment in improving hirsutism and/or acne [474].

**Recommendations**

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<thead>
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<th>No.</th>
<th>EBR/CR/CPP</th>
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<tbody>
<tr>
<td>4.6.1</td>
<td>EBR</td>
<td>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 alopecia</td>
<td>***</td>
<td>☕️☕️☕️</td>
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</table>

**Justification**
There was insufficient evidence to make an evidence based recommendation. The group recognised plausible reasons for anticipating differences in the relative effectiveness of anti-androgens for different PCOS phenotypes, ages and anthropometric characteristics. There is no evidence on the direct and indirect costs of using anti-androgens, however the cost of available treatment is relatively high. Approval status and cost of these agents also varies across countries, with challenges in access and availability and contraception is considered mandatory in reproductive age women. For these reasons, most anti-androgen use in PCOS is in combination with COCPs (see section 4.3), however use could be considered with other forms of contraception.

4.7 Inositol

Is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Clinical need for the question

Women with PCOS are commonly treated with insulin sensitizing agents due to insulin resistance and hyperinsulinemia, common features of the syndrome both in obese and non-obese women. Mild gastrointestinal side effects related to metformin and more serious adverse effects related to glitazones other medical options are needed in treating insulin resistance in women with PCOS. Inositol (myo-inositol and di-chiro inositol) is a nutritional supplement that acts as a second messenger and has been shown to play a role in insulin signaling transduction [475]. Previous studies have suggested improvement of insulin resistance and hormonal profile in women with PCOS during inositol treatment [475, 476]. Furthermore, some data also suggests inositol may be effective in decreasing risk for gestational diabetes [477].

Summary of systematic review evidence

A Cochrane systematic review [478] was identified to address this question and compared inositol with placebo. No further, more current evidence was identified. Findings from meta-analysis demonstrated that whilst serum SHBG (nmol/L) favoured inositol, there were no statistically significant differences between inositol and placebo for BMI, waist-hip ratio, ovulation (no. that ovulated), serum testosterone (nmol/L), triglyceride (mmol/L), cholesterol (mmol/L), fasting glucose (mmol/L) or fasting insulin (uIU/L).

Summary of narrative review evidence

In a more recent systematic review published after the evidence synthesis for this guideline, yet completed before the guideline development group meeting, ovulation rate and menstrual cycles appear to improve with inositol in women with PCOS [475, 476]. Furthermore, some data also suggests inositol may be effective in decreasing risk for gestational diabetes [477]. The literature however is limited, many key questions remain [475] and research is prioritised.

Recommendations

<table>
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<th>No.</th>
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</table>

Chapter 4: Pharmacological treatment for non-fertility indications 89
Inositol (in any form) should currently be considered an experimental therapy in women with PCOS, with the evidence on efficacy too uncertain to advocate this therapy.

Women taking inositol and other alternative therapies are encouraged to advise their health professional.

| 4.7.1 | EBR | Inositol (in any form) should currently be considered an experimental therapy in women with PCOS, with the evidence on efficacy too uncertain to advocate this therapy | * | ☠️ठठठठ |
| 4.7.2 | CPP | Women taking inositol and other alternative therapies are encouraged to advise their health professional | - | - |

Justification

Whilst the evidence at the time of evidence synthesis to inform this guideline on the benefit of inositol (in all forms) was inadequate to make an evidence based recommendation for the use of inositol, there is some data suggesting metabolic, hormonal and ovulatory benefits. As this agent is freely available as a nutritional supplement, at low to moderate cost and appears to have a limited side effect profile, it may warrant consideration for use despite limited and low quality evidence. As with other supplements or complementary therapies, women taking this agent are encouraged to advise their health care team.
Assessment and treatment of infertility

The evidence synthesis team, guideline lead and guideline development group members were involved in the original Australian evidenced based guideline in PCOS and in the 2014 World Health Organisation (WHO) commissioned evidence synthesis update and development of guidelines for the management of anovulatory infertility in women with PCOS [479]. Here we expand the prioritised questions aligned with international consultation, extend the guideline development group, update and expand evidence synthesis and complete a full GRADE framework evaluation. The WHO guidance document is referenced below where relevant and a summary of subsequent and expanded evidence is provided.

5.1a Assessment of factors that may affect fertility, treatment response or pregnancy outcomes

Should women with PCOS undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may adversely affect fertility and response to infertility therapy?

Should women with PCOS and with or without infertility undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may lead to adverse (early or late) pregnancy outcomes?

Should women with PCOS undergo close (early or late) pregnancy monitoring for adverse pregnancy outcomes?

Clinical need for the questions

Ovulatory disturbance is a key diagnostic feature of PCOS, leading to infertility and women with PCOS also have adverse pregnancy outcomes. Modifiable lifestyle factors, especially excess weight, exacerbate infertility, response to infertility treatment and pregnancy health and prevention of weight gain and where needed lifestyle intervention for weight loss is recommended (Chapter 3). Whilst there is clear recognition of the need to optimise preconception and pregnancy health in the general population, there is currently no evidence based guideline in these areas in high risk women with PCOS.

Summary of narrative evidence

A systematic review was not conducted to answer this question which was reviewed narratively based on clinical expertise.

Modifiable risk factors known to impact fertility and response to Assisted Reproductive Technology (ART): BMI <18 or >25kg/m², waist to hip ratio (WHR – central adiposity), smoking status, alcohol consumption, prescribed and recreational drug use, exposure to endocrine disruptors, untreated sexually transmitted infections, nutritional status, supplementation with folate, vitamin D and dental health have all been identified as modifiable risk factors preconception (2, 3, 5, 13, 26). Anxiety, depression and psychological symptoms can impact relationship health, sexual intimacy and ART treatment adherence (19), whilst mental health care supports treatment adherence, relationship health and quality of life. These factors should be
optimised aligned with prior guidelines in PCOS including the WHO guidance, and priority areas and recommendations for the general population [480].

**Pregnancy and fertility complications:** Women with PCOS are at an increased risk of gestational diabetes, preterm birth, pre-eclampsia, miscarriage, still birth, longer time to conception and poor embryo development, reduced embryo implantation rates, ovarian hyper stimulation syndrome (OHSS) (1) and ectopic pregnancy (18), which are also exacerbated by obesity.

**Weight loss:** Lifestyle management is recommended for weight loss when the BMI is >25kg/m² (see chapter 3). A 2014 systematic review on weight loss prior to ART, noted improved natural conception, number of embryos for transfer, ART pregnancies, live birth rate, cancelled cycles, miscarriage rates and number of ART cycles required to achieve a pregnancy (20). A 2017 systematic review and meta-analysis, (14) found that lifestyle interventions benefited weight loss and natural pregnancy rate, with limited evidence for live birth rate or birth weight, yet natural birth rate did increase (16, 27). Lifestyle intervention also results in significant broader health benefits in pregnancy and beyond. Intensive weight loss is usually avoided just prior to conception as it is associated with adverse outcomes including cycle cancellation and decrease in fertilisation, implantation, ongoing pregnancy and live birth (17). Bariatric surgery should only be considered as a second-line therapy to improve fertility outcomes in PCOS women with anovulation and obesity (BMI ≥35 kg/m²) resistant to intensive lifestyle modification and/or pharmacotherapy (17).

Prospective randomized studies of preconception interventions that evaluate broad screening and lifestyle intervention are lacking in the general population and in PCOS [481], especially when considering pregnancy outcomes. However, aligned with lifestyle recommendations in PCOS outlined in chapter 3, healthy lifestyle and lifestyle intervention should be considered in all women with PCOS, especially preconception and those with infertility based on risk, potential benefit and unlikely risk of adverse effects, whilst highlighting the critical need for more research.

**Antenatal care:** Close monitoring of weight and screening for hyperglycaemia early in pregnancy are recommended, especially in high risk populations given the associated morbidity in pregnancy [482, 483]. In antenatal care, there was no evidence to guide screening for gestational diabetes or hypertension specifically in women with PCOS, although evidence shows an increased risk in PCOS and screening approaches in the general population involve identification of women at high risk.

### Recommendations

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<tbody>
<tr>
<td>5.1.1</td>
<td>CPP</td>
<td>Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health should be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with recommendations in the general population</td>
<td>_</td>
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</tr>
<tr>
<td>5.1.2</td>
<td>CPP</td>
<td>Monitoring during pregnancy is important in women with PCOS, given increased risk of adverse maternal and offspring outcomes</td>
<td>_</td>
<td>_</td>
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</tbody>
</table>

### Justification

General population recommendations highlight the vital role of healthy lifestyle, weight loss where women are overweight, smoking cessation, omitting alcohol, exercise and management of mental health issues to optimise reproductive outcomes, especially in high risk groups, which includes in PCOS. The recommendations here are expected to improve efficacy of treatment and potentially reduce ART costs.
Women with infertility and their health professionals are attuned to the need for healthy lifestyle and prevention strategies and are likely to accept these recommendations and consider them feasible. In antenatal care, recommendations for screening and monitoring in PCOS can only be informed by increased risks in pregnancy in PCOS with a lack of PCOS specific studies. Additional resources may be required in implementation.

5.1b) Tubal patency testing

*Should women with PCOS and infertility due to anovulation alone with normal semen analysis have tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment or delayed tubal patency testing?*

**Clinical need for the question**

One of the leading causes of female infertility is tubal pathology. It has been estimated that it affects around 30% of infertile women [484]. The diagnostic assessment of infertile women often includes tubal testing by hysterosalpingography or laparoscopy as outlined in the WHO guidance evidence report on infertility management in PCOS. PCOS is the most frequent cause of anovulation in infertile women and ovulation induction is the most common treatment, however there is little information about the prevalence of tubal pathology or for the need of intrauterine insemination with normal semen analysis in infertile women with PCOS.

**Summary of narrative evidence**

A systematic review was not conducted to answer this question and was reviewed narratively based on clinical expertise. There is no evidence to support that hydrosalpinges or other fallopian tube disorders are more frequent in PCOS women [485]. Yet the assessment of tubal patency is considered in the workup for infertility, as outlined in the evidence review to inform WHO guidance on infertility treatment in PCOS. Whilst adverse effects from this intervention are not common, false positives have been described and tubal patency testing may be more appropriate when targeted to those at increased risk of tubal infertility [486]. In this context consideration of risk factors for infertility associated with tubal pathology was considered clinically appropriate by the expert guideline development group where concomitant risk factors are present including:

1) Previous abdominal or pelvic sepsis
2) History of Sexual Transmitted Diseases or Pelvic Inflammatory Disease
3) Endometriosis

**Recommendations**

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<tr>
<th>No.</th>
<th>EBR/ CR/ CPP</th>
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<tbody>
<tr>
<td>5.1.3</td>
<td>CR</td>
<td>In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing of tubal patency testing should be discussed on an individual basis</td>
<td>***</td>
<td>-</td>
</tr>
<tr>
<td>5.1.4</td>
<td>CR</td>
<td>Tubal patency testing should be considered prior to ovulation induction in women with PCOS where there is suspected tubal infertility</td>
<td>***</td>
<td>-</td>
</tr>
</tbody>
</table>
Justification

If the patient has a clinical history of factors associated with tubal infertility it was deemed that hysterosalpingography could be considered, consistent with routine assessment of infertility. Hysterosalpingography requires dilation of the cervix that generally produces some discomfort, false positives are described and other related complications are uncommon. A lack of evidence to guide practice was noted in PCOS when considering these recommendations, however general population approaches were judged as applicable in this population.

5.2 Ovulation induction principles

In reviewing the literature on pharmacological treatment for ovulation induction, general principles emerged that apply across all recommendations. These have been extracted into a set of clinical practice points to inform women and guide health professionals when considering or recommending pharmacological therapy for ovulation induction in PCOS. These practice points apply to all pharmacological treatments prioritised and addressed in the guidelines.

<table>
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<th>No.</th>
<th>EBR/CR/CPP</th>
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<tbody>
<tr>
<td>5.2.1</td>
<td>CPP</td>
<td>The use of ovulation induction agents, including letrozole, metformin and clomid is still off label in many countries. Where off label use of ovulation induction agents is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2.2</td>
<td>CPP</td>
<td>Pregnancy should be excluded prior to ovulation induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2.3</td>
<td>CPP</td>
<td>Unsuccessful, prolonged (&gt;12 treatment cycles) use of ovulation induction agents should be avoided, due to poor success rates</td>
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</tr>
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5.3 Letrozole

**In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?**

Clinical need for the question

Aromatase inhibitors are effective as ovulation-inducing agents including letrozole and anastrozole, with letrozole being the most widely used [487, 488]. These agents catalyse the conversion of androgens to oestrogens, including in the ovary, yet mechanisms of ovulation induction are unknown, however they increase secretion of FSH stimulating ovarian follicle development and maturation [489]. The efficacy, adverse effects and overall role of letrozole in oral ovulation induction has remained controversial.

Summary of systematic review evidence

**Als versus placebo**

One small RCT [490] with a low risk of bias compared letrozole to placebo in women with clomiphene citrate resistant PCOS and found that letrozole was better than placebo for ovulation rate per patient (Letrozole: 6
patients/18 patients (33.33%), Placebo: 0 patients/18 patients (0%), p=0.006) but there was no difference between letrozole and placebo for pregnancy rate per patient or live birth rate per patient. It is important to note that the findings from this study are of low certainty due to serious risk of imprecision. This study was included in a meta-analysis by Franik 2014 [491] and Misso 2012 [492], however since there is only one study, the meta-analyses do not provide additional evidence.

**Als versus CC**

Thirteen RCTs compared letrozole with CC. Seven of these RCTs had a high risk of bias [493-499], two had a moderate risk of bias [500, 501] and four had a low risk of bias [502-505]. Upon meta-analysis, we found that letrozole was better than clomiphene citrate for ovulation rate per patient; pregnancy rate per patient; and live birth rate per patient. There was no difference between letrozole and clomiphene citrate for multiple pregnancy rate per patient; and miscarriage rate per patient. When subgroup analysis was conducted for studies that included women with PCOS who were therapy naive, there was no difference between the two interventions for any outcome though we note that for pregnancy rate per patient the OR 1.68 [95% CI 0.96, 2.94] had an I² of 0% and a p value of 0.07.

**AI versus CC + metformin**

One RCT with moderate risk of bias found that there is no statistical difference between letrozole and clomiphene citrate plus metformin for ovulation rate per cycle, pregnancy rate per cycle, miscarriage rate per pregnancy and multiple pregnancy rate per pregnancy in clomiphene citrate-resistant women with PCOS [506]. This study was included in a meta-analysis by Franik 2014 [491] and Misso 2012 [492], however since there is only one study, the meta-analysis does not provide additional evidence.

**AI versus laparoscopic ovarian surgery (LOS)**

Three RCTs with low risk of bias [507-509] compared letrozole to laparoscopic ovarian surgery and found that there was insufficient evidence of a difference between letrozole and laparoscopic ovarian surgery. One of the RCTs in 147 women with clomiphene citrate resistance found that letrozole was better than laparoscopic ovarian surgery for ovulation rate per cycle [507], however the evidence is of low certainty. The systematic review by Farquhar 2012 [510] combined these studies in meta-analysis for pregnancy rate per patient, multiple pregnancy rate per pregnancy and miscarriage rate per pregnancy and there was no statistical difference between the two interventions.

**Summary of narrative review evidence**

Aromatase inhibitors catalyse the conversion of androgens to oestrogens, including in the ovary and increase FSH secretion [489], stimulating ovarian follicle development and maturation. These agents were originally used to improve pregnancy rates and limit adverse effects [511, 512], especially with clomiphene resistance and failure [512-515]. Letrozole has side effects include gastrointestinal disturbances, hot flushes, headache and back pain [516, 517] and concerns have been raised on potential teratogenic effects [518] in an abstract, yet have not been confirmed in a peer-reviewed journal but have led to a series of warnings in various countries to avoid use as an infertility agent. Multiple subsequent case series [500, 519-522], multi-center RCTs [517, 523] and a recent systematic review and meta-analysis (yet to be published but authored and reviewed by guideline development group members), all failed to note an increased congenital anomaly rate with prevalence of anomalies with letrozole or clomiphene under 5% (the expected anomaly rate in this population is 5-8% [524]).

**Recommendations**
Chapter 5: Assessment and treatment of infertility

### 5.3.1 EBR

Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates.

**GRADE:****  
**Quality:**

### 5.3.2 CPP

Where letrozole is not available or use is not permitted, health professionals should use other ovulation induction agents.

### 5.3.3 CPP

Health professionals and women should be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate.

### Justification

Women with PCOS are significantly more likely both to ovulate and to have a live birth after use of letrozole compared to clomiphene, the previous first line agent. The likelihood of live birth is increased 40-60% with letrozole compared to clomiphene. Similarly the failure to ovulate (letrozole resistance) is lower with letrozole versus clomiphene. Multiple pregnancy rate appears lower than clomiphene. Hot flushes, generally the least desired side effect of any anti-oestrogen, is less common with letrozole than clomiphene, but still present. Fatigue and dizziness are more common. The balance of benefits in terms of improved live births with letrozole and less hot flushes currently outweighs the adverse effects of relatively increased fatigue and dizziness, multiple pregnancy, and unconfirmed concerns about higher congenital anomalies.

### 5.4 Clomiphene citrate and metformin

*In women with PCOS, is clomiphene citrate effective for improving fertility outcomes?*

*In women with PCOS, is metformin effective for improving fertility outcomes?*

*In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes?*

### Clinical need for the questions

Clomiphene citrate is a selective oestrogen receptor modulator with both oestrogenic and anti-oestrogenic properties [525]. It was first approved for use in women with anovulation in 1967 [526] and acts as an anti-oestrogen [527].

Clomiphene citrate resistance and failure is well documented [528] and a discrepancy is noted between good ovulation rates and lower pregnancy rates due to the anti-oestrogenic effects of clomiphene citrate on the endometrium and cervical mucus. Twin pregnancy and triplets with clomiphene citrate are 5–7% and 0.3%, respectively and OHSS is less than 1% [529]. The potential for borderline increased risk of ovarian tumours with 12 cycles or more has been noted [530].

Insulin resistance is common in PCOS [531, 532], driving ovarian androgen biosynthesis and increased bioavailability of free androgens (see chapter one). Excess local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation [533]. This led to insulin-sensitizing drugs use in ovulation induction. Metformin has been most widely studied in PCOS and has the most reassuring safety profile [534]. Efficacy has been controversial and therapeutic regimens are not well standardised in clinical practice, with variable doses in use [535].
Summary of systematic review evidence

**Metformin versus placebo**

One systematic review [536] with up to 14 studies; and one RCT [537] were identified to address this comparison. Metformin was better than placebo for live birth rate per participant, pregnancy rate per participant and ovulation rate per participant. Pregnancy rate and ovulation rate remained statistically significantly better than placebo when subgrouped by BMI (BMI<30kg/m^2 and BMI>30 or 32kg/m^2 subgroups); however live birth rate lost statistical significance when subgrouped by BMI. There was no statistically significant difference between metformin and placebo for miscarriage rate per pregnancy (including when subgrouped). Adverse events were statistically significantly lower with placebo than metformin (including when subgrouped). Multiple pregnancy and OHSS were not reported in the systematic review. It is important to note that the findings for live birth rate and miscarriage rate are of **low certainty** due to serious risk of bias and serious risk of imprecision in the body of evidence; and findings for pregnancy rate, ovulation rate and adverse events are of **moderate certainty** due to serious risk of bias. Risk of bias appraisals and GRADE assessments have been adopted from previous versions of this guideline [479].

In an RCT of 149 participants, with moderate certainty, there were no statistically significant differences between metformin and placebo for pregnancy rate per participant, multiple pregnancy rate per pregnancy or miscarriage rate per pregnancy. The majority of the trials stopped metformin at diagnosis of pregnancy or at week 12. Note: insufficient evidence of a differential effect of metformin on BMI.

**Clomiphene citrate v placebo**

One high quality systematic review with low risk of bias found that clomiphene citrate was better than placebo for pregnancy rate per participant and ovulation rate per participant, however the evidence was of **very low certainty** due to very serious risk of bias and imprecision.

**Metformin versus clomiphene citrate**

One systematic review [536] with up to 7 studies was identified to address this comparison. There were no statistically significant differences between metformin and clomiphene for live birth rate per pregnancy, multiple pregnancy per pregnancy, miscarriage rate per pregnancy, pregnancy rate or ovulation rate. When subgrouped by BMI, clomiphene citrate was better than metformin for live birth rate, pregnancy rate and ovulation rate in BMI>30kg/m^2; and metformin was better than clomiphene citrate for pregnancy rate in BMI<30kg/m^2. Adverse events and OHSS were not reported in the systematic review. It is important to note that the findings for live birth rate, multiple pregnancy rate and pregnancy rate are of **very low certainty** due to very serious risk of bias, serious risk of imprecision and for live birth rate, also serious risk of inconsistency; findings for miscarriage rate and ovulation rate are of **low certainty** due to serious risk of bias and serious risk of imprecision in the body of evidence.

**Metformin versus metformin + clomiphene citrate**

One high quality systematic review with low risk of bias evaluating two RCTs with a mean BMI ≥ 30 kg/m^2 [538] and two RCTs (one medium quality RCT with moderate risk of bias [539] and one low quality RCT with high risk of bias [540] were identified by the search. Metformin plus clomiphene citrate was better than metformin alone for ovulation rate, pregnancy rate and live birth rate. There was no statistically significant difference between metformin plus clomiphene citrate and metformin alone for miscarriage rate or adverse events.

**Clomiphene citrate versus metformin + clomiphene citrate**
One systematic review [536] with up to 21 studies; and one RCT [541] were identified to address this comparison. Metformin plus clomiphene citrate was statistically significantly better than clomiphene citrate alone for pregnancy rate per participant and ovulation rate per participant, including when subgrouped by BMI (BMI<30kg/m2 and BMI>30 subgroups). Adverse events were statistically significantly better with clomiphene citrate alone than with metformin plus clomiphene citrate. There was no statistically significant difference between metformin plus clomiphene citrate and clomiphene citrate alone for live birth rate per pregnancy, multiple pregnancy rate per pregnancy or miscarriage rate per pregnancy. OHSS was not reported in the systematic review. It is important to note that the findings for live birth rate, multiple pregnancy and miscarriage rate are of low certainty due to serious risk of bias and serious risk of imprecision in the body of evidence; and findings for pregnancy rate, ovulation rate and adverse events are of moderate certainty due to serious risk of bias. The additional RCT Maged 2015 [541] was insufficient evidence to supplement the findings of Morley 2017 [536].

**Clomiphene citrate versus aromatase inhibitors (letrozole)**

Thirteen RCTs (level II) compared letrozole with clomiphene citrate. Seven of these RCTs had a high risk of bias [493-499], two had a moderate risk of bias [500, 501] and four had a low risk of bias [502-505]. Upon meta-analysis, we found that letrozole was better than clomiphene citrate for ovulation rate per patient [493, 494, 496, 498, 500, 501, 504, 505]; pregnancy rate per patient [493-505]; and per cycle [496, 497, 505]; and live birth rate per patient [494, 500, 502, 504, 505]. There was no difference between letrozole and clomiphene citrate for ovulation rate per cycle [496, 497, 502, 503, 505]; multiple pregnancy rate per patient [493, 495, 496, 499, 500, 503-505]; and miscarriage rate per patient [494-496, 500-505]. When subgroup analysis was conducted for studies that included women with PCOS who were therapy naïve, there was no difference between the two interventions for any outcome though we note that for pregnancy rate per patient the OR 1.68 [95% CI 0.96, 2.94] had an I2 of 0% and a p value of 0.07.

**Clomiphene citrate versus gonadotrophin (FSH)**

Two RCTs were identified by the search to address this comparison. One RCT was low quality with high risk of bias [542] compared recombinant FSH with clomiphene citrate in women with PCOS who were therapy naïve and found that there was no difference between the two interventions for all fertility outcomes. The second was a multi-centre RCT with moderate risk of bias [543] comparing clomiphene citrate with low dose gonadotrophins, as the first line therapy for ovulation induction in anovulatory women with PCOS who were therapy naïve. They reported with per protocol analysis that the clinical pregnancy rate was significantly higher in the gonadotrophin treated group. Furthermore the chance of pregnancy was almost double in the first treatment cycle when compared to clomiphene citrate. Brown 2016 [544] meta-analysed these same two RCTs combining data for live birth rate and ongoing pregnancy rate and found that gonadotrophins were better than clomiphene citrate (OR 0.64 [ 0.41, 0.98 ] p=0.041, I2=0%). Meta-analysis of the two studies for clinical pregnancy rate found that clomiphene citrate was better than gonadotrophins (OR 0.61 [0.40, 0.93] p=0.021, I2=0%). It is important to be cautious of these results (using per protocol event rates), as the number of participants randomised has been used as the denominator when the denominator should have been the number of participants per protocol.

**Clomiphene citrate versus clomiphene citrate + gonadotrophin (FSH)**

Two RCTs were identified to address this comparison, however there was insufficient evidence to determine whether one intervention was better than the other [545, 546].

**Recommendations**
### Chapter 5: Assessment and treatment of infertility

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4.1</td>
<td>EBR</td>
<td>Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates</td>
<td>***</td>
<td>🟦🟢🟢</td>
</tr>
<tr>
<td>5.4.2</td>
<td>EBR</td>
<td>Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents</td>
<td>***</td>
<td>🟦🟢🟢</td>
</tr>
<tr>
<td>5.4.3</td>
<td>EBR</td>
<td>Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese (BMI ≥30 kg/m²) with anovulatory infertility and no other infertility factors</td>
<td>***</td>
<td>🟦🟢🟢</td>
</tr>
<tr>
<td>5.4.4</td>
<td>EBR</td>
<td>If metformin is being used for ovulation induction in women with PCOS who are obese (BMI ≥30 kg/m²) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates</td>
<td>***</td>
<td>🟦🟢🟢</td>
</tr>
<tr>
<td>5.4.5</td>
<td>EBR</td>
<td>Clomiphene citrate could be combined with metformin, rather than persisting with clomiphene citrate alone, in women with PCOS who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates</td>
<td>***</td>
<td>🟦🟢🟢</td>
</tr>
<tr>
<td>5.4.6</td>
<td>CPP</td>
<td>The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered</td>
<td>–</td>
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</tr>
</tbody>
</table>

**Justification**

Clomiphene citrate therapy requires specialist care. Costs to the patient of monitoring (tests and specialist visits) and accessibility to specialist care may present barriers, however increased costs will be offset by reduced multiple pregnancies. Metformin is low cost, accessible and can be used alone and/or in combination with clomiphene citrate, given efficacy on systematic review. This may result in a change in usual care as clinicians may now be more likely to prescribe metformin. Metformin may be associated with mild gastrointestinal related adverse events (see chapter 4). Whilst use is evidence-based, patient explanation and consent is appropriate as metformin therapy for infertility is off label.

### 5.5 Gonadotrophins

**In women with PCOS, are gonadotrophins effective for improving fertility outcomes?**

**Clinical need for the question**

Gonadotropin therapy is used clinically in anovulatory PCOS who have been treated with other first line ovulation induction agents if they have failed to ovulate or if responses reduce chances of conception (e.g., persistent hypersecretion of LH, or an anti-estrogenic endometrial effects. To prevent overstimulation and multiple pregnancy, the traditional standard step-up regimens [547] were replaced by either low-dose step-up regimens [548, 549] or step-down regimens [550] with gonadotropins used alone and different gonadotropin preparations appearing to work equally well [551]. It can be difficult to predict stimulation responses in PCOS and to achieve a single dominant follicle to reduce multiple pregnancy and OHSS and careful monitoring of follicular development by ultrasound is required with triggers only used with two or less follicles over 14mm. The efficacy, safety and role of gonadotrophins compared to other alternatives including single or combined oral ovulation induction agents or laproscopic surgery remains unclear.
Summary of systematic review evidence

Gonadotrophin (FSH) versus clomiphene citrate

Two RCTs were identified by the search to address this comparison. One RCT was low quality with high risk of bias [542] compared recombinant FSH with clomiphene citrate in women with PCOS who were therapy naïve and found that there was no difference between the two interventions for all fertility outcomes. The second was a multi-centre RCT with moderate risk of bias [543] comparing clomiphene citrate with low dose gonadotrophins, as the first line therapy for ovulation induction in anovulatory women with PCOS who were therapy naïve. They reported with per protocol analysis that the clinical pregnancy rate was significantly higher in the gonadotrophin treated group. Furthermore the chance of pregnancy was almost double in the first treatment cycle when compared to clomiphene citrate. Brown [544] meta-analysed these same two RCTs combining data for live birth rate and ongoing pregnancy rate and found that gonadotrophins were better than clomiphene citrate (OR 0.64 [0.41, 0.98] p=0.041, I²=0%). Meta-analysis of the two studies for clinical pregnancy rate found that clomiphene citrate was better than gonadotrophins (OR 0.61 [0.40, 0.93] p=0.021, I²=0%). It is important to be cautious of these results (using per protocol event rates), as the number of participants randomised has been used as the denominator when the denominator should have been the number of participants per protocol.

Gonadotrophins versus clomiphene citrate + metformin

Two RCTs compared FSH with clomiphene citrate plus metformin [552, 553]. The RCTs found that FSH was better than clomiphene citrate plus metformin for ovulation rate per participant and pregnancy rate per participant. There was no statistical difference between the two interventions for live birth rate per participant, multiple pregnancy rate per pregnancy, OHSS, miscarriage rate per pregnancy or GI side effects or adverse events. A systematic review by Abu Hashim [554] conducted meta-analysis including studies that do not meet our PICO, however some sensitivity analysis was conducted with the two RCTs listed below. A sensitivity analysis for ovulation rate in 263 patients demonstrated that gonadotrophins are better for ovulation rate (OR 0.13; 95% CI 0.07–0.25; p < 0.00001, I² = 7%); but there was no statistically significant difference between the two interventions for multiple pregnancy rate (n = 263, OR 0.33; 95% CI 0.06–1.68; p = 0.18, heterogeneity not reported).

Gonadotrophins versus gonadotrophins + metformin

One RCT with moderate risk of bias found that FSH plus metformin was better than FSH alone for live birth rate per participant, ovulation rate per participant and pregnancy rate per participant [553]. There was no statistical difference between the two interventions for multiple pregnancy rate per pregnancy, miscarriage rate per pregnancy or adverse events.

Gonadotrophins versus laparoscopic ovarian surgery (LOS)

One high quality systematic review of RCTs (level I) with low risk of bias compared laparoscopic ovarian surgery to gonadotrophins and found that there was no difference between the interventions for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy, but laparoscopic ovarian surgery was better than gonadotrophins for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] I² = 0%, 4 studies, 303 participants) [510].

Gonadotrophins versus gonadotrophins + clomiphene citrate

One RCT [555] with moderate risk of bias found that FSH plus clomiphene citrate was better than FSH alone for ovulation rate per woman randomized and per protocol, total FSH dose used per woman randomized and per protocol, and duration of stimulation per woman randomized and per protocol. There was no statistical
difference between the two interventions for pregnancy rate and live birth rate per woman randomized and per protocol.

**Recommendations**

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5.1</td>
<td>EBR</td>
<td>Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors</td>
<td>***</td>
<td>⊕⊕</td>
</tr>
<tr>
<td>5.5.2</td>
<td>EBR</td>
<td>Gonadotrophins could be considered as first line treatment, in the presence of ultrasound monitoring, following counselling on cost and potential risk of multiple pregnancy, in women with PCOS with anovulatory infertility and no other infertility factors</td>
<td>***</td>
<td>⊕⊕</td>
</tr>
<tr>
<td>5.5.3</td>
<td>EBR</td>
<td>Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate combined with metformin therapy for ovulation induction, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates</td>
<td>*****</td>
<td>⊕⊕⊕</td>
</tr>
<tr>
<td>5.5.4</td>
<td>EBR</td>
<td>Gonadotrophins with the addition of metformin, could be used rather than gonadotrophin alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates</td>
<td>***</td>
<td>⊕⊕⊕</td>
</tr>
<tr>
<td>5.5.5</td>
<td>EBR</td>
<td>Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, following counselling on benefits and risks of each therapy</td>
<td>****</td>
<td>⊕⊕⊕</td>
</tr>
<tr>
<td>5.5.6</td>
<td>CPP</td>
<td>Where gonadotrophins are prescribed, the following should be considered: • cost and availability • expertise required for use in ovulation induction • degree of intensive ultrasound monitoring required • lack of difference in clinical efficacy of available gonadotrophin preparations • low dose gonadotrophin protocols optimize monofollicular development • risk and implications of potential multiple pregnancy</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5.5.7</td>
<td>CPP</td>
<td>Gonadotrophin induced ovulation should only be triggered when there is two or less follicles in total of over 14mm in diameter and should be cancelled if there are more than two follicles of this size, with the patient advised to avoid unprotected intercourse</td>
<td>-</td>
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</tbody>
</table>

**Justification**

Gonadotrophin therapy is suitable for improving infertility in women with PCOS in specialist care, with close monitoring. Gonadotropin therapy provides better per cycle and cumulative pregnancy and live birth rates compared with the use of oral anti-oestrogens and or no therapy in anovulatory women with PCOS; and there is no evidence of teratogenicity. It is important to note that gonadotrophin therapy requires daily injections and the need for intensive monitoring with ultrasound; with a risk of multiple pregnancy and increased cost of medication compared with oral agents.

**5.6 Anti-obesity agents**

**In women with PCOS, are anti-obesity pharmacological agents effective for improving fertility outcomes?**
Clinical need for the question

A 2017 systematic review and meta-analysis [556], found that lifestyle interventions benefited weight loss and natural pregnancy rate, with limited evidence for live birth rate or birth weight, yet natural birth rate did increase [297, 304]. Hence, the impact of non-pharmacological lifestyle interventions on live birth rates remains controversial. Engagement and adherence in lifestyle interventions are challenging. There is a need to assess other weight loss methods, such those pharmacological agents commenced preconception period with some evidence they can induce weight loss and improve fertility outcomes in PCOS.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative evidence

A randomised trial (that did not meet the inclusion criteria for this systematic review due to a change in interventions and combination of treatments) evaluated pre-conception treatment in women with PCOS with a) lifestyle weight loss intervention incorporating caloric restriction, increased physical activity and pharmacological agent (initially sibutramine, and then orlistat), b) oral contraceptive pill c) combined lifestyle and contraceptive pill on fertility outcomes [557]. The trial randomised 149 women, and was prematurely stopped due to supposed futility with a low likelihood of showing a clinically meaningful difference. Given the small sample size, particularly for a three-arm trial, no meaningful robust conclusions can be inferred. Furthermore, all three are interventional arms, and there is no control group. Within the lifestyle arm, including anti-obesity agents, there was a significant reduction in weight from baseline (-6.2Kg, 95% CI -07.1 to -5.3), and compared to the women on OCP pre-conception, those on lifestyle with anti-obesity agents showed no differences in pregnancy outcomes. Evidence for these agents in other relevant population groups is also lacking.

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
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<tbody>
<tr>
<td>5.6.1</td>
<td>CR</td>
<td>Pharmacological anti-obesity agents should be considered an experimental therapy in women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy</td>
<td>*</td>
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</tbody>
</table>

Justification

With inadequate evidence in both PCOS and in fertility settings in other populations, the risk/benefit ratio is too uncertain at the moment to advocate this as a fertility treatment and it was deemed that it should remain an experimental treatment for this indication.

5.7 Laparoscopic ovarian surgery

In women with PCOS, is ovarian surgery effective for improving fertility outcomes?
Clinical need for the question

Historically, early observations that women with PCOS resumed regular ovulation following ovarian biopsies, resulted in development of surgical wedge resection via laparotomy [558]. Observational data looked promising, but surgery was surpassed by ovulation induction agents, until the availability of less invasive laparoscopic surgery [559] with potential for less adhesions and lower cost. Minor variations are reported (electrocautery, laser vaporization, multiple ovarian biopsies and others), all seemingly with effects on the endocrine profile. OHSS and multiple pregnancy risks are lower than with other options, but other risks potentially are higher, and it is now important to clarify the role of laparoscopic ovarian surgery, particularly in comparison to other treatments, in infertile women with PCOS.

Summary of systematic review evidence

Laparoscopic ovarian surgery versus metformin

Two medium quality RCTs (level II) (published across three papers) with a moderate risk of bias compared laparoscopic ovarian surgery to metformin and found that there was insufficient evidence to make a recommendation about laparoscopic ovarian surgery compared to metformin for live birth rate per patient, ovulation rate per cycle, pregnancy rate per cycle, pregnancy rate per patient, multiple pregnancies, miscarriage rate per pregnancy, adverse effects and QoL [560-562] largely because the evidence was conflicting. One RCT reported that laparoscopic ovarian surgery was better than metformin for ovulation (OR 2.05; [1.4–2.9] p=0.001) and pregnancy rate (per cycle: OR 2.19 [1.03–4.63] p=0.03; per patient: OR 2.47 [1.05–5.81] p=0.03) [560] and the other study reported that metformin was better than laparoscopic ovarian surgery for live birth rate (metformin: 82.1%, LOS: 64.5%, p<0.05), pregnancy rate per cycle (metformin: 18.6%, LOS: 13.4%, p<0.05), and miscarriage rate (metformin: 15.4%, LOS:29.0%, p<0.05) [561, 562]. Both medium quality single centre studies had a small sample size and moderate risk of bias and therefore need to be interpreted with caution.

Laparoscopic ovarian surgery versus CC

Two high quality RCTs (level II) with a low risk of bias compared laparoscopic ovarian surgery to clomiphene citrate [563, 564] and found that there was no difference between laparoscopic ovarian surgery and clomiphene citrate for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy [563, 564]. There was insufficient evidence to support or refute the use of laparoscopic ovarian surgery over clomiphene citrate for multiple pregnancies [563, 564].

Laparoscopic ovarian surgery versus CC + metformin

Three low to moderate quality RCTs with low to moderate risk of bias compared laparoscopic ovarian surgery to clomiphene citrate plus metformin (all three studies reported in Farquhar 2012 systematic review [510]). Meta-analyses found that clomiphene citrate plus metformin (CC+M) was better than laparoscopic ovarian surgery for live birth rate, but there was no difference for pregnancy rate per patient, multiple pregnancy rate, or miscarriage rate per pregnancy [510]. There was insufficient evidence to support or refute the use of laparoscopic ovarian surgery over clomiphene citrate plus metformin for ovulation rate per patient, and OHSS [510].

Laparoscopic ovarian surgery versus aromatase inhibitors

Three RCTs with low risk of bias [507-509] compared letrozole to laparoscopic ovarian surgery and found that there was insufficient evidence of a difference between letrozole and laparoscopic ovarian surgery. One of the RCTs in 147 women with clomiphene citrate resistance found that letrozole was better than
laparoscopic ovarian surgery for ovulation rate per cycle [507], however the evidence is of low certainty. The systematic review by Farquhar 2012 [510] combined these studies in meta-analysis for pregnancy rate per patient, multiple pregnancy rate per pregnancy and miscarriage rate per pregnancy and there was no statistical difference between the two interventions.

Laparoscopic ovarian surgery versus aromatase inhibitors + metformin

One low quality RCT with moderate risk of bias compared laparoscopic ovarian surgery with letrozole plus metformin and found that there was insufficient evidence of a difference between the two interventions for ovulation, pregnancy and miscarriage rate per pregnancy [565].

Laparoscopic ovarian surgery versus gonadotrophins

One high quality systematic review of RCTs (level I) with low risk of bias compared laparoscopic ovarian surgery to gonadotrophins and found that there was no difference between the interventions for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy, but laparoscopic ovarian surgery was better than gonadotrophins for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] I² = 0%, 4 studies, 303 participants) [510].

Summary of narrative review evidence

Observational data was sourced to evaluate long term impacts. A 15-25 year follow-up of nearly 150 women after ovarian wedge resection shows that regular menstrual patterns lasting up to 25 years after surgery were restored in 88% of patients with a cumulative pregnancy/live birth rate of 78% [566]. This was considered along with the RCT data as long term follow-up is important in this context.

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/ CR/ CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>5.7.1</td>
<td>EBR</td>
<td>Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors</td>
<td>***</td>
<td>⊕⊕○○</td>
</tr>
<tr>
<td>5.7.2</td>
<td>CR</td>
<td>Laparoscopic ovarian surgery could potentially be first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors</td>
<td>***</td>
<td>–</td>
</tr>
<tr>
<td>5.7.3</td>
<td>CPP</td>
<td>Risks should be explained to all women with PCOS considering laparoscopic ovarian surgery</td>
<td>–</td>
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</tbody>
</table>
| 5.7.4 | CPP | Where laparoscopic ovarian surgery is to be recommended, the following should be considered:  
• comparative cost  
• expertise required for use in ovulation induction  
• intra-operative and post-operative risks are higher in women who are overweight and obese  
• there may be a small associated risk of lower ovarian reserve or loss of ovarian function  
• periadnexal adhesion formation may be an associated risk | – | – |

Justification

Laparoscopic ovarian surgery is a single intervention that can lead to a singleton birth in women with PCOS. There is no convincing evidence of inferiority over other common ovulation induction agents, there is no need for monitoring (because of mono-ovulation) and only a background risk of multiple pregnancy.
However, it is important to note that laparoscopic ovarian surgery is an invasive surgical intervention; there is a small risk of reduced ovarian reserve or loss of ovarian function; and adhesion formation should be considered. Issues covered in the clinical practice points should be carefully considered.

5.8 Bariatric surgery

*In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility and adverse outcomes?*

**Clinical need for the question**

Obesity is increasing in prevalence throughout the world, as is morbid obesity (BMI≥ 40 kg/m2) [567]. Women with PCOS appear to have higher rates of weight gain and of obesity. Obesity adversely affects female fertility and weight loss improves outcomes as previously outlined. In severe obesity, lifestyle interventions have limited efficacy. Substantial efficacy of bariatric surgery on weight loss has been demonstrated in women who are severely obese. Potential benefits also need to be balanced with the delay in infertility treatment and pregnancy for surgery and stabilisation of weight, the risks of bariatric surgery and the potential risks of pregnancy after bariatric surgery. Controversy persists around efficacy for fertility and pregnancy outcomes, optimal timing, adverse effects and comparative efficacy with other treatments as well as on adverse effects on subsequent pregnancies.

**Summary of systematic review evidence**

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

**Summary of narrative review evidence**

UK clinical guidelines for obesity management in the general population [568] recommend considering bariatric surgery with a BMI ≥35kg/m² with one or more severe complications, expected to improve with weight loss and failure of structured lifestyle intervention [568]. Obesity surgery can be considered after non-surgical treatment has failed with a BMI ≥40kg/m² and obesity surgery can be first line treatment with a BMI ≥50kg/m² [569]. Other guidelines, recommend lower barriers to surgery [570]. For type of surgery, Vertical Sleeve Gastrectomy (VSG) has overtaken the Roux-en-Y Gastric Bypass (RYGB) and gastric band surgery as the most commonly performed bariatric surgery with lower operative morbidity [571]. Adjustable gastric banding, once the choice for women planning pregnancy is now less common given complications and overall lower long term weight loss [571].

High quality RCTs of bariatric surgery versus medical management in DM2 show persistent benefits and superiority of weight loss and bariatric surgery in curing or ameliorating diabetes [572, 573]. Yet these studies are absent in PCOS for fertility and pregnancy outcomes, with current PCOS studies poorly designed [574], and with failure to report key perinatal outcomes to inform risk to benefit ratio. In PCOS, the balance between delaying infertility treatment and pregnancy whilst undertaking bariatric surgery and attaining stable post-operative weight, is also unclear [575], as is the optimal type of bariatric surgery.

Bariatric surgery can cause malabsorption and psychological issues including disordered eating [576] and may adversely on maternal and neonatal health. Adequate intake and absorption of iron, folate, iodine and
other nutrients are of concern. While supplement use is widely recommended following bariatric surgery and for pregnant women, there are reports of poor compliance [577] and challenges tolerating fortified foods such as bread. National registries (surgery, pregnancy, infants) have been linked and show that obese women who undergo bariatric surgery and conceive compared to similarly obese controls had more small for gestational age babies, shorter gestations, and a trend towards increased neonatal mortality [578], with similar findings in retrospective studies [579]. Benefits have included less GDM and large for gestational age babies after bariatric surgery.

Recommendations

<table>
<thead>
<tr>
<th>No.</th>
<th>EBR/CR/CPP</th>
<th>Recommendation</th>
<th>GRADE</th>
<th>Quality</th>
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<tbody>
<tr>
<td>5.8.1</td>
<td>CR</td>
<td>Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy</td>
<td>*</td>
<td>–</td>
</tr>
<tr>
<td>5.8.2</td>
<td>CPP</td>
<td>If bariatric surgery is to be prescribed, the following should be considered: • comparative cost • the need for a structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health to continue post-operatively • perinatal risks such as small for gestational age, premature delivery, possibly increased infant mortality • potential benefits such as reduced incidence of large for gestational age fetus and gestational diabetes • recommendations for pregnancy avoidance during periods of rapid weight loss and for at least 12 months after bariatric surgery with appropriate contraception If pregnancy occurs, the following should be considered: • awareness and preventative management of pre-and post-operative nutritional deficiencies is important, ideally in a specialist interdisciplinary care setting • monitoring of fetal growth during pregnancy</td>
<td>–</td>
<td>–</td>
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</table>

Justification

Bariatric surgery improves weight loss and can improve comorbidities associated with PCOS. However, evidence in relation to fertility and pregnancy outcomes is limited with some concerns about potential perinatal adverse effects of bariatric surgery. Overall, the indications, role, comparative effectiveness with other fertility therapies, ideal timing, optimal type of surgery, adverse effects and risk to benefit ratio in PCOS are still to be resolved. Given the concerns about the potential perinatal adverse effects of bariatric surgery and the remaining controversies, no recommendation can be made at this time about the use of bariatric surgery to improve fertility in women with PCOS.

5.9a In-vitro fertilisation (IVF)

In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?

Clinical need for the question
Ovulation induction therapies are first and second line infertility therapy in women with PCOS, anovulation and no other fertility factors. Yet resistance to and failure of ovulation induction therapies and inability to overcome other concomitant causes of infertility means that Assisted Reproductive Technology (ART) therapies including IVF and intracytoplasmic sperm injection (ICSI) used in male factor infertility, have a role in PCOS. IVF has risks and limitations, yet also offers the opportunity for pregnancy and live birth outcomes. Challenges exist across the diversity of protocols available for IVF and concerns in PCOS including OHSS, high oestradiol levels, accelerated endometrial maturation and optimally the use of “freeze all” interventions. The clinical practice questions here including indications, timing and comparative efficacy with other treatments, as RCTs in this area are very limited in women with anovulatory PCOS.

**Summary of systematic review evidence**

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

**Summary of narrative review evidence**

There are no RCTs identified by the guideline development team, comparing stimulated IVF ± ICSI therapy with ovulation induction in women diagnosed with PCOS. The role of IVF in PCOS was explored by the WHO guidance group and the review and recommendations were considered here by the guideline development group, in making their recommendations [479]. IVF factors that influenced considerations here include access, cost and risks. The patient and societal benefits of ovulation induction compared with IVF treatments in anovulatory PCOS women require RCTs and systematic analysis. Outcomes as time to conception, cost of therapy, quality of life, risk of OHSS, multiple pregnancy, miscarriage and livebirth rates should be investigated.

**Recommendations**

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<th>No.</th>
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<tbody>
<tr>
<td>5.9.1</td>
<td>CR</td>
<td>In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory infertility could be offered IVF if first or second line ovulation induction therapies have failed</td>
<td>***</td>
<td>–</td>
</tr>
<tr>
<td>5.9.2</td>
<td>CPP</td>
<td>In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used multiple pregnancies can be minimised.</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5.9.3</td>
<td>CPP</td>
<td>Women with PCOS undergoing IVF ± ICSI therapy should be counselled prior to starting treatment including on: • availability, cost and convenience • increased risk of ovarian hyperstimulation syndrome • options to reduce the ovarian hyperstimulation</td>
<td>–</td>
<td>–</td>
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</table>

**Justification**

The guideline development group deemed IVF should be considered after failed ovulation induction treatment with high pregnancy rates per cycle, especially in younger women. Given the high cost of IVF that are prohibitive for many patients and the risks, it should be considered third line medical therapy. It was noted that conception and delivery may outcomes are highly valued by health professionals and women with PCOS and even when cost and risks are increased, many may elect to undertake IVF. Health Professionals must weigh benefits and risk when advising PCOS patients to enable an informed decision.
5.9b GnRH protocol

In women with PCOS undergoing IVF/ICSI treatment, is the GnRH antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?

Clinical need for the question

Women with PCOS are particularly vulnerable to OHSS with IVF ± ICSI treatment, prompting caution and leading to exploration of different protocols including with GnRH and other options including in-vitro maturation (see below) [580]. One of the proposed methods to reduce the risk of OHSS is to use a GnRH antagonist (as opposed to an agonist) (Mancini et al, 2011, Al-Inany et al, 2007, Lin et al 2014, ASRM 2016). There is acknowledged complexity in interpreting outcomes from IVF treatments in PCOS, with variable protocols and endpoint reporting, requiring close evaluation of the literature. One of the proposed methods to reduce the risk of OHSS is to use a GnRH antagonist (as opposed to an agonist) to suppress pituitary LH secretion.

Summary of systematic review evidence

In the eight included studies of low [581-583], moderate [584-587], and high risk of bias [588] comparing an antagonist protocol with a long agonist protocol, there were statistically significant differences in the amount of gonadotropin required (5 studies in favour of the antagonist protocol) [581-583, 586, 588], in the duration of gonadotropin use (6 studies in favour of the antagonist protocol) [582-586, 588], in OHSS rates (2 studies in favour of the antagonist protocol) [583, 585]. No statistically significant differences were found between groups for clinical pregnancy rates, miscarriage rates, number of oocytes collected, cancellation rates, and multiple pregnancy rates.

Recommendations

<table>
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<tr>
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<tr>
<td>5.9.6</td>
<td>EBR</td>
<td>A gonadotrophin releasing hormone antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle, over a gonadotrophin releasing hormone agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose and incidence of ovarian hyperstimulation syndrome (OHSS)</td>
<td>***</td>
<td>⊘⊕⊕</td>
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<tr>
<td>5.9.7</td>
<td>CPP</td>
<td>Human chorionic gonadotrophins should be used at the lowest doses to trigger final oocyte maturation in women with PCOS undergoing an IVF ± ICSI cycle to reduce the incidence of OHSS</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5.9.8</td>
<td>CPP</td>
<td>Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5.9.9</td>
<td>CPP</td>
<td>In IVF ± ICSI cycles using the gonadotrophin releasing hormone antagonist protocol in women with PCOS, consideration should be given to an elective freeze of all embryos</td>
<td>–</td>
<td>–</td>
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</table>

Justification

The duration of stimulation with a GnRH antagonist approach is around a day shorter than the standard ‘long-down regulation’ approach with a GnRH agonist. The rate of OHSS appears less with a GnRH
antagonist approach in comparison to the standard ‘long-down regulation’ approach with a GnRH agonist. The effect size is difficult to quantify, as all most of these studies used a high dose human chorionic gonadotrophin (hCG) trigger in both arms, whereas this may not reflect clinical practice. There does not appear to be an increase in undesirable side-effects with an antagonist down-regulation approach. The choice to trigger final oocyte maturation with GnRH antagonist instead of hCG is important to prevent OHSS.

5.9c Trigger type

**In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?**

Clinical need for the question

One of the prominent causes of ovarian hyperstimulation syndrome (OHSS) is the occurrence in women with PCOS undergoing ovarian hyperstimulation for IVF particularly where hCG is used to trigger ovulation. Early in 1990 an alternative to exogenous hCG triggering emerged with GnRH-agonist use, providing an additional ovulatory option for IVF. A single bolus of GnRH-agonist administration during late follicular development in women with PCOS treated with gonadotropins, results in a surge of endogenous FSH and LH for final oocyte maturation and fertilisation. OHSS appears reduced yet lower pregnancy rates with GnRH-agonist triggers are observed and may vary when transferring fresh versus frozen thawed embryos in cycles from the same cohort, suggesting that the pregnancy rate is dependent of endometrial quality. An alternative option therefore in women with PCOS at high risk of OHSS, is to freeze oocytes or embryos after GnRH agonist triggering and transfer the embryos in subsequent cycles. The choice to trigger final oocyte maturation with GnRH-agonist, instead of hCG, and to transfer frozen embryos requires clarification.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

This question was addressed in a Cochrane review in 2014 (Youssef 2014). In 17 RCTs (n = 1847), in fresh autologous cycles, GnRH-agonists were associated with a lower live birth rate than HCG (OR 0.47, 95% CI 0.31 to 0.70; five RCTs, 532 women, I^2 = 56%, moderate-quality evidence), yet there was also a lower incidence of mild, moderate or severe OHSS than with HCG (OR 0.15, 95% CI 0.05 to 0.47; eight RCTs, 989 women, I^2 = 42%, moderate-quality evidence). In fresh autologous cycles, GnRH-agonists were associated with a lower ongoing pregnancy rate than HCG (OR 0.70, 95% CI 0.54 to 0.91; 11 studies, 1198 women, I^2 = 59%, low-quality evidence) and a higher early miscarriage rate (OR 1.74, 95% CI 1.10 to 2.75; 11 RCTs, 1198 women, I^2 = 1%, moderate-quality evidence). However, the effect was dependent on the type of luteal phase support provided. Multiple pregnancy rates were similar. The authors concluded that final oocyte maturation triggering with GnRH-agonist instead of hCG in fresh autologous GnRH-antagonist IVF ± ICSI cycles prevents OHSS to the detriment of the live birth rate. In donor-recipient cycles, use of GnRH agonists instead of hCG resulted in a lower incidence of OHSS, with no evidence of a difference in live birth rate. GnRH agonist as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers, where donate oocytes are used or in women who wish to freeze their eggs for later use.
Recommendations

See recommendations in 5.9b GnRH protocol.

Justification

The choice to trigger final oocyte maturation with GnRH-agonist instead of hCG is important in prevention of OHSS as hCG alone induces oocyte maturation but is associated with OHSS. GnRH- agonist triggers are associated with lower pregnancy rates, primarily in fresh embryo transfers, which can be overcome in frozen cycles.

5.9d Choice of FSH

In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?

Clinical need for the question

FSH can be purified from human urine (uFSH) or synthesised from recombinant DNA techniques (rFSH). Urinary preparations have impurities with LH activity known to stimulate androgen production in theca cells and completing maturation of follicles. However, it is known that less than 1% of follicular LH receptors needs to be occupied in order to elicit maximal steroidogenesis and it is therefore possible that enough endogenous LH is present during controlled ovarian stimulation to promote androgen synthesis and oocyte maturation without the need for extra LH activity in FSH preparations. The perceived clinical benefits of rFSH versus uFSH are the subject of ongoing debate and both types of preparations remain commonly used.

Summary of systematic review evidence

One small study (80 participants) of moderate risk of bias compared rFSH with hMG and found that rFSH was better for the duration of ovarian stimulation required and the number of oocytes retrieved; whereas hMG was better for the maximum serum estradiol level [589]. No statistically significant differences were found between groups for the total dose of gonadotropin used, OHSS rate, clinical pregnancy rate per cycle and take home baby rate per cycle.

Summary of narrative review evidence

Given the limited evidence in PCOS, additional information was sought from rFSH and uFSH use in the general population. In a Cochrane systematic review and meta-analysis, 42 trials with a total of 9606 couples compared rFSH against three different uFSH preparations. rFSH irrespective of the down-regulation protocol, did not result in a statistically significant different live birth rate or OHSS rate, concluding that clinical choice of gonadotrophin should depend on availability, convenience and costs and that further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.

Recommendations

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Chapter 5: Assessment and treatment of infertility 110
5.9.4 CPP
Urinary or recombinant follicle stimulation hormone can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI, with insufficient evidence to recommend specific FSH preparations

### Justification

Only one small study in PCOS has been identified investigating uFSH versus rFSH in PCOS during ovarian stimulation for IVF/ICSI [589]. This study shows similar results to a systematic review and meta-analysis in the general IVF population, where extensive research has concluded no significant difference in birth rate or OHSS was detected and no further research in the general population was recommended. Hence clinical choice of gonadotrophin should depend on availability, convenience and costs.

5.9e Exogenous LH

**In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF±ICSI effective for improving fertility outcome?**

### Clinical need for the question

Given increase OHSS risk in IVF/ICSI in PCOS, options have been explored to reduce this risk. The chronic low dose step-up protocol with exogenous FSH in securing single (fewer) dominant follicle selection is an alternative method to avoid multi-follicular development. During late follicular development, LH is essential to achieve adequate ovarian steroidogenesis and develop the subsequent capacity of the follicle to ovulate and luteinize. Increased LH secretion or elevated LH/FSH ratio in PCOS may influence fertility, with inhibition of oocyte maturation, deleterious effects on granulosa cell steroidogenesis and endometrial receptivity and with potential increased early pregnancy loss [590-592]. The lack of clarity around the role of exogenous LH in the setting of IVF/ICSI prompted this clinical question.

### Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

### Summary of narrative review evidence

Obesity adversely impacts on ovulation and on responses to ovulation induction in PCOS [593]. In PCOS, granulosa cells respond to LH at a relatively earlier follicular stage and are significantly more responsive than for ovulatory women with PCOS or women without PCOS [591]. Granulosa cell differentiation may be prematurely advanced. Controlled ovarian stimulation for multiple follicular development in ART can be performed in a variety of ways to increase efficacy and reduce risks. Systematic reviews and meta-analysis have demonstrated that there is no significant difference between different ovarian stimulation protocols (hMG, purified FSH, recombinant FSH) regarding the fertility outcomes. Therefore, clinical gonadotropin choice depends on availability, convenience, and cost. In standard IVF/ICSI protocols, the types of controlled ovarian stimulation (FSH alone or addition of LH as a supplement) have little impact on the fertility outcomes [594, 595]. Endogenous LH levels may fall too low in older women (> 35) during ovarian stimulation, especially with GnRH-antagonist use and LH supplementation has been proposed. However, a multicentre RCT of exogenous LH during the follicular phase showed no fertility benefits outcomes in women over 35.
No current study investigates efficacy of exogenous LH supplement for fertility outcomes in PCOS during IVF/ICSI. Careful monitoring of follicular development during ovarian stimulation is critical.

**Recommendations**

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<tr>
<td>5.9.5</td>
<td>CPP</td>
<td>Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI</td>
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</table>

**Justification**

There is no anticipated effect or benefit to add exogenous LH supplement in women with PCOS undergoing ovarian stimulation for IVF±ICSI. There is insufficient evidence to determine the benefits of using or not using exogenous LH.

**5.9f Adjunct metformin**

*In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF±ICSI, is adjunct metformin effective for improving fertility outcomes?*

**Clinical need for the question**

IVF±ICSI treatment in women with PCOS is usually recommended either as a third-line treatment (after failed ovulation induction) or in those with other infertility factors such as tubal damage, severe endometriosis or male factors [597]. IVF±ICSI treatment in PCOS poses challenges, including OHSS [598]. Metformin has been studied to restore ovulation and enhance pregnancy rates in PCOS [599], through a range of mechanisms [537, 600, 601]. These mechanisms provide a physiological rationale for management of insulin resistance in IVF in PCOS. It has also been suggested that metformin may reduce serum estradiol levels during ovarian stimulation and it has also been hypothesized that metformin may reduce the production of vascular endothelial growth factor, both of which are important factors involved in the pathophysiology of OHSS [602]. Therefore, it was deemed important to explore the effectiveness and safety of metformin as a co-treatment in achieving pregnancy or live birth and reducing OHSS in IVF in PCOS.

**Summary of systematic review evidence**

Six RCTs of low [600, 603, 604], moderate [537], and high risk of bias [605, 606] found that IVF with adjuvant metformin was better for OHSS, clinical pregnancy rate, cancellation rate and live birth rate. No statistically significant differences were found between groups for the amount of gonadotropins used, the duration of ovarian stimulation, miscarriage rates, number of oocytes collected, and multiple pregnancy rates.

**Summary of narrative review evidence**

A Cochrane review [607] was identified by the search, however it included studies that did not meet the selection criteria for this question. The guideline development group considered the meta-analyses in the Cochrane review as clinically relevant and noted that there was no evidence of a difference with adjunct metformin for live birth rate, miscarriage rate, number of oocytes collected, days of ovarian stimulation or...
cycle cancellation rate; and clinical pregnancy rate was increased with adjuvant metformin whilst ovarian hyperstimulation syndrome (OHSS) reduced. Mild generally self-limiting side-effects were noted with adjunct metformin, as outlined in chapter 4.

**Recommendations**

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<tr>
<td>5.9.10</td>
<td>EBR</td>
<td>Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing a IVF ± ICSI therapy with a gonadotrophin releasing hormone agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS</td>
<td>***</td>
<td>⊕⊕⊕○○</td>
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<tr>
<td>5.9.11</td>
<td>CPP</td>
<td>In a gonadotrophin releasing hormone agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF ± ICSI treatment, the following could be considered: • metformin commencement at the start of gonadotrophin releasing hormone agonist treatment • metformin use at a dose of between 1000mg to 2550mg daily • metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated) • metformin side-effects (link to above metformin section)</td>
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</tr>
<tr>
<td>5.9.12</td>
<td>CPP</td>
<td>In IVF ± ICSI cycles, women with PCOS could be counselled on potential benefits of adjunct metformin in a gonadotrophin releasing hormone antagonist protocol to reduce ovarian hyperstimulation syndrome (link to metformin therapy considerations)</td>
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**Justification**

Women and health professionals would generally value an increased clinical pregnancy rate (with no evidence of a difference in miscarriage rate) and reduced OHSS (with its associated morbidity and rarely mortality). Gastrointestinal side effects were recognised, but noted as mild and self-limiting and may be minimised with lower metformin starting dose and extended release preparations. Metformin was noted to be low cost and readily available, and while off label, use was generally allowed, with explanation required for use.

**5.9g In-vitro maturation (IVM)**

**In women with PCOS, is in-vitro maturation (IVM) effective for improving fertility outcomes?**

**Clinical need for the question**

Where IVF is indicated in PCOS, OHSS risks are increased with gonadotrophin stimulation. In-vitro maturation (IVM) of oocytes limits or omits ovarian stimulation prior to oocyte retrieval, with maturation of oocytes post retrieval, avoiding OHSS risk [580]. The definition of an IVM cycle requires clarification [608], as cycles employing an hCG trigger injection are generally associated with asynchronous oocyte maturation rates, poor embryo implantation rates and lower pregnancy rates [609, 610]. There are no RCTs of IVM versus ICSI or ovulation induction in PCOS, however observational studies suggest that offspring from IVM
are not adversely affected. Given that IVM is used in practice and has theoretical benefits, this questions was prioritised.

Summary of systematic review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively.

Summary of narrative review evidence

With an absence of relevant RCTs [611], retrospective studies suggest IVM is similarly successful for livebirth with frozen embryos generated with IVM as embryo transfers generated by standard IVF treatment [580]. However pregnancy rates are reduced and miscarriage rates are higher if a fresh embryo transfer is performed with IVM [580]. Embryo development appears slower with a greater degree of embryo arrest in IVM [612].

Recommendations

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<tr>
<td>5.9.13</td>
<td>CR</td>
<td>In units with sufficient expertise, IVM could be offered to achieve pregnancy and livebirth rates approaching those of standard IVF ± ICSI treatment without the risk of OHSS for women with PCOS, where an embryo is generated, then vitrified and thawed and transferred in a subsequent cycle</td>
<td>**</td>
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| 5.9.14 | CPP | The term in vitro maturation (IVM) treatment cycle should be applied to “the maturation in vitro of immature cumulus oocyte complexes collected from antral follicles” (encompassing both stimulated and unstimulated cycles, but without the use of a human gonadotrophin trigger). | - | - |

Justification

The guideline development group deemed that key elements to consider with IVM included; a clear definition of the term IVM, use in clinical units with sufficient expertise and advantages of reduced risk of OHSS. The group considered the lack of evidence as important. It was considered that IVM could be offered to achieve pregnancy and livebirth rates that may approach those of standard IVF ± ICSI treatment, where frozen embryos are used. Given the lack of evidence the group voted for a conditional consensus recommendation that neither favoured this option or other options (IVF), with strong research recommendations.
CHAPTER SIX

Guideline development methods

This guideline was developed as outlined in NHMRC standards and procedures for externally developed guidelines [613] and according to the GRADE approach [16]. These methods were aligned with ESHRE approaches to guideline development.

The work builds on the original Australian guideline in PCOS [19], the update in 2014 as well as the WHO guideline in infertility management [479].

Here, the International Evidence–based Guideline for the Assessment and Management of PCOS is part of an international initiative to engage women affected by PCOS and their health professionals to improve health outcomes. Extensive international health professional and consumer engagement informed the gaps, needs, priorities and core clinical outcomes for the guideline. Over 40 organisations were engaged with formal partnerships with ESHRE and ASRM. Guideline development groups included members nominated by the engaged international societies. International Society-nominated panel members including women with PCOS, paediatricians, endocrinologists, gynaecologists, primary care physicians, reproductive endocrinologists, psychiatrists, psychologists, dermatologists, dieticians, exercise physiology, public health experts, researchers, other co-opted experts as required. They were supported by a project management, and evidence synthesis and translation team to develop the guideline. Here we provide a comprehensive review of the evidence and formulate recommendations using the GRADE Framework.

Governance

Governance included an international advisory board from six continents, a project board, five guideline development groups, advisors and a translation committee. The Australian Centre for Research Excellence in PCOS and the NHMRC partnered with the ESHRE and ASRM to fund and deliver the guideline. Four advisory, five project board and 15 guideline development group face to face meetings occurred across Europe, USA and Australia over 15 months, and enabled guideline training, development and informed translation. Sixty prioritised clinical questions were addressed with evidence synthesis involving 40 systematic and 20 narrative reviews, generating 170 recommendations and practice points. Feedback from over 40 convened special interest groups of experts and consumers from collaborating professional societies and consumer groups internationally as well as public consultation will inform the final guideline.

Multidisciplinary international guideline development groups

Guideline development groups were convened to address each of the five key clinical areas. Expertise was sought through PCOS networks to ensure multidisciplinary participation within each guideline development group. Each guideline development group comprised a chair, professional group members with specific expertise in PCOS and the clinical area of interest (i.e. psychologists/ psychiatrist in the emotional wellbeing guideline development group), a consumer representative, evidence officers and representative to consider cultural aspects. See Appendix III.

Consumer participation

In the development of this guideline, we have sought not only to inform or consult with women affected by PCOS, but to partner with and empower these women who are the ultimate beneficiaries of this work. We have engaged with international consumer bodies in PCOS and infertility to this end. This included Polycystic...
Ovary Syndrome Association Australia (POSAA) (Australia), Verity (United Kingdom), PCOS Challenge (United States), RESOLVE (United States), and Victorian Assisted Reproductive Treatment Authority (Australia) engaged throughout the guideline process.

A international survey was completed by 1800 women and focus groups were held with women with PCOS to inform gaps in care, guideline priority questions, prioritised outcomes for each intervention and to inform guideline translation, education and support needs and preferred methods of delivery.

Consumer representatives participated in the development of the Centre for Research Excellence Funding submission, in the Guideline Project Board, International Consumer Advisory Group and in the guideline development groups. Consumers have been involved in every stage, including development of the guideline scope, public consultation on the scope and developing and refining the clinical questions and recommendations as part of the guideline development groups. Consumer representatives will also be extensively engaged and are partnering in the translation activities of the guidelines.

Indigenous representation and CALD

Ethnicity and culture was considered when making all recommendations. Indigenous representation was present on the PCOS Australian Alliance Strategic Advisory Group (a member of the Australian Indigenous Doctors Association) and the guideline development groups comprised clinicians with experience working with CALD and Indigenous communities. The translation of the guideline allows for adaptions on cultural and ethnicity grounds.

Conflict of interest and confidentiality

Conflict of interest has been proactively managed throughout the guideline development process as outlined in NHMRC standards and procedures for externally developed guidelines [613]. All members of the guideline development groups have provided signed declarations of interest and a confidentiality agreement. Additionally, declarations of interest were a standing agenda item at each monthly meeting and guideline development group members were requested to detail areas for potential conflict. The process for managing conflict of interest and confidentiality and recorded declarations can be provided on request (linda.downes@monash.edu).

Training of guideline development groups in evidence review and guideline development methods

All guideline development group members attended a workshop, where the methods of reviewing evidence and guideline development were described in detail. The purpose of this workshop was to familiarise the chairs and guideline development groups members with:

- the process of guideline development overall
- the process of identifying, appraising and synthesising evidence in a format to facilitate the formulation of evidence-based recommendations
- grading the strength of evidence and its suitability to support evidence-based recommendations
- when to facilitate discussion and clinical judgement to formulate clinical consensus recommendations in the absence of evidence.

Clinical question development and prioritisation
An International survey and Delphi exercise was conducted to develop and prioritise (existing and newly developed) clinical questions to be addressed. A further prioritisation exercise was conducted within the topic specific guideline development groups and consumer advisory groups to rank the importance of clinical questions to guide the evidence team and to reach consensus on which clinical questions were to be addressed by a systematic review or by narrative review.

Systematic reviews were performed for highly prioritised questions and for those areas of greatest controversy.

Narrative evidence reviews were completed for lower prioritised questions; or where recent or concurrent systematic reviews were being completed by GDG members that could be captured on narrative review; or where questions were less well suited to a PICO systematic review format.

Forty questions were addressed by guideline systematic reviews, many others by systematic reviews captured in the narrative reviews by and some by narrative reviews of isolated PCOS studies supported by systematic reviews/guidelines in the general population.

The clinical questions addressed by each guideline development group are as follows:

**Guideline development group 1 – Screening, diagnostic assessment, risk assessment and life-stage**

- At what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction related to PCOS?
- In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (biochemical)?
- In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism (clinical)?
- What is the most effective ultrasound criteria to diagnose PCOS?
- Is AMH effective for diagnosis of PCOS?
- Is AMH effective to diagnosis of PCOM?
- What is the post-menopausal phenotype of PCOS?
- Are women with PCOS at increased risk for cardiovascular disease (CVD)?
- In women with PCOS, what is the most effective tool/method to assess risk of cardiovascular disease (CVD)?
- Are women with PCOS at increased risk for impaired glucose tolerance, gestational diabetes and type 2 diabetes mellitus?
- In women with PCOS, what is the most effective tool/method to assess risk of type 2 diabetes mellitus?
- Are women with PCOS at increased risk for sleep apnea?
- What is the method/tool most effective to screen for sleep apnea in PCOS?
- What is the risk of PCOS in relatives of women with PCOS and should they be screened?
- What is the disease risk in relatives of PCOS (CVD, T2DM)?

**Guideline development group 2 - Prevalence, screening, diagnostic assessment and management of emotional wellbeing**
• In women with PCOS: 1) What is the prevalence and severity of reduced QoL? And 2) Should QoL be assessed as part of standard care?

• In women with PCOS, what is the most effective tool/method to screen for symptoms of depression and anxiety?

• In women with PCOS, what is the most effective tool/method to assess quality of life?

• Is psychological therapy effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?

• Is acupuncture effective for management and support of depression and/or anxiety, disordered eating, body image distress, self-esteem, feminine identity or psychosexual dysfunction in women with PCOS?

• Are anti-depressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?

• What is the effectiveness of different models of care compared to usual care?

• In women with PCOS, what is the most effective tool/method to screen body image distress?

• In women with PCOS, what is the most effective tool/method to screen disordered eating?

• In women with PCOS, what is the most effective tool/method to screen psychosexual dysfunction?

Guideline development group 3 – Lifestyle management and models of care

• In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

• In women with PCOS, are diet interventions (compared to different diets) effective for improving anthropometric, metabolic, fertility, and emotional wellbeing outcomes?

• In women with PCOS, are exercise interventions (compared to different exercises) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

• In women with PCOS, are behavioural interventions (compared to different types of behavioural interventions) effective for improving anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

• Are women with PCOS at increased risk of obesity?

• In women with PCOS, does obesity impact on prevalence and severity of hormonal and clinical features?

Guideline development group 4 – Medical treatment

• Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?

• Is metformin alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

• Are anti-obesity pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
• Are anti-androgen pharmacological agents alone or in combination, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
• Is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

Guideline development group 5 – Screening, diagnostic assessment and management of infertility

• Should women with PCOS and infertility undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may adversely affect fertility and response to infertility therapy?
• Should women with PCOS undergo pre-conception (pre-pregnancy) evaluation (assessment) for (and where possible correction of) risk factors that may lead to adverse (early or late) pregnancy outcomes?
• Should women with PCOS undergo close (early or late) pregnancy monitoring for adverse pregnancy outcomes?
• Should women with PCOS and infertility due to anovulation alone with normal semen analysis have tubal patency testing prior to starting ovulation induction with timed intercourse or IUI treatment or delayed tubal patency testing?
• In women with PCOS, is clomiphene citrate effective for improving fertility outcomes?
• In women with PCOS, is metformin effective for improving fertility outcomes?
• In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes?
• In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?
• In women with PCOS, are gonadotrophins effective for improving fertility outcomes?
• In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?
• In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous LH treatment during IVF/ICSI effective for improving fertility outcomes?
• In women with PCOS, is stimulated IVF/ICSI effective for improving fertility outcomes?
• In women with PCOS undergoing IVF/ICSI treatment, is the GnRH antagonist protocol or GnRH agonist long protocol the most effective for improving fertility outcomes?
• In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is adjuvant metformin effective for improving fertility outcomes?
• In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?
• In women with PCOS, is In Vitro Maturation (IVM) effective for improving fertility outcomes?
• In women with PCOS, are anti-obesity pharmacological agents effective for improving fertility outcomes?

• In women with PCOS, is ovarian surgery effective for improving fertility outcomes?
• In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility and adverse outcomes?
Outcome prioritisation using the GRADE method

Outcomes were prioritised by ranking their importance by health professionals and consumers to focus attention on the most relevant outcomes, help to resolve or clarify disagreements and assist with grading the evidence. The importance of outcomes may vary across cultures and from different perspectives e.g. patients, public, health professionals or policy-makers. Table 6 outlines the considerations when deciding importance of outcomes [16]. Guideline development group members, including consumers also participated in this exercise.

Table 6: Steps for considering the relative importance of outcomes

<table>
<thead>
<tr>
<th>What</th>
<th>Why</th>
<th>How</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment and prioritisation of outcomes as critical, important but not critical, or low importance.</td>
<td>To focus attention on those outcomes that are considered most important when conducting evidence review and to resolve or clarify disagreements.</td>
<td>Scoping the relevant literature.</td>
<td>These judgments are ideally informed by a systematic review of the literature focusing on what the target population considers as critical or important outcomes for decision making.</td>
</tr>
<tr>
<td>Requires judgement of the balance between the desirable and undesirable health outcomes of an intervention.</td>
<td>To support making a recommendation and to determine the strength of the recommendation.</td>
<td>By asking GDG members, including consumers to prioritise outcomes in light of the considerations for ‘what’ and ‘why’.</td>
<td>Prior knowledge of the research evidence through systematic reviews; and information about values, preferences or utilities has been explored in the original guideline, that was systematic in nature, will inform this process.</td>
</tr>
</tbody>
</table>

To facilitate ranking of outcomes according to their importance the following scale was be used [16].

| rating scale: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |

Chapter 6: Guideline development methods  120
Outcomes considered critical (rated 7-9) most greatly influenced a recommendation and the overall quality of evidence supporting the recommendation and the strength of the recommendation.

**Adaptation of existing evidence based guidelines**

Given the time and resource-intensive nature of guideline development, existing high quality evidence-based guidelines that address the clinical questions and PICO of interest should be sought for adaptation before starting a new one. Apart from the original Australian guideline, to date no international PCOS guideline covering all health aspects related to the syndrome is available. The evidence-based sections of the WHO guideline, supported by this evidence synthesis team is aligned with the scope here, yet is now out of date. The NICE guideline is limited in scope and is not available electronically outside the UK. It too is adapted from the 2011 Australian guideline. Professional society positions statements or clinical practice guidelines are more limited in scope, do not follow AGREEII process, involve more limited expertise and geographical representation and are often conflicting in recommendations. Here we have updated and expanded the scope and evidence contained in the 2011 Australian guideline and, where appropriate methods have been applied, integrated the WHO guideline.

**Evidence reviews to answer the clinical questions**

Evidence reviews were conducted for each clinical question and from the evidence reviews the guideline development groups were able to develop guideline recommendations. The evidence reviews for each question can be found in the supporting document titled Technical report.

The links between the body of evidence, the clinical need for the question and the clinical impact of the resulting recommendation(s), including potential changes in usual care and the way care is organised, acceptability, feasibility and resource implications are clearly explained in the accompanying GRADE evidence to decision framework supporting the recommendation.

**Selection criteria**

The PICO (Population, Intervention, Comparison, Outcome) framework was used by the guideline development groups to explore the components of each clinical question and finalise the selection criteria for each question. These components were used to include and exclude studies in the evidence review. Details of the selection criteria for each question can be found in the supporting document titled Technical report.
The highest form of evidence, the most current (within 5 years), comprehensive (with the most outcomes relevant to PICO) and high quality systematic review that meets our benchmark criteria (see table 7) and meets the selection criteria, was used to inform a recommendation. Additional systematic reviews that met benchmark and selection criteria were used if it reported additional outcomes relevant to the PICO, that were not addressed in the first, most comprehensive systematic review. Additional RCT(s) that met the selection criteria and were not included in the systematic reviews were also be used. Where a systematic review met the benchmark criteria but did not meet the selection criteria, or synthesised studies that did not meet out selection criteria the risk of bias appraisals from that systematic review were adopted.

Table 7. Benchmark criteria for a systematic review to be included:

1) Must have completed a search in at least Medline and another relevant database;
2) Must have listed key search terms;
3) Must have listed selection criteria;
4) Must have used an appropriate framework to assess risk of bias/quality appraisal;
5) Where the evidence is sought for an intervention question and a systematic review has included non-RCTs, the analysis must be subgrouped by RCTs to be eligible for inclusion.

Systematic search for evidence

A broad-ranging systematic search for terms related to PCOS was developed by the evidence team. This PCOS search string was then combined with specific searches tailored for each clinical question according to the PICO developed by the guideline development group. The search terms used to identify studies addressing the population of interest (i.e., women with PCOS) were only limited to PCOS terms. Therefore studies addressing women with PCOS in all cultural, geographical and socioeconomic backgrounds and settings would be identified by the search. The search strategy was limited to English language articles and limits on year of publication are specified in the PICO for each clinical question according to whether an update search was conducted or in cases where interventions were only available from a particular point in time.

The following electronic databases were employed to identify relevant literature:

- CINAHL
- The Cochrane Library
- Cochrane Database of Systematic Reviews (Cochrane Reviews)
- Database of Abstracts of Reviews of Effects (Other Reviews)
- Cochrane Central Register of Controlled Trials (Clinical Trials)
- Cochrane Database of Methodology Reviews (Methods Reviews)
- The Cochrane Methodology Register (Methods Studies)
- Health Technology Assessment Database (Technology Assessments)
- NHS Economic Evaluation Database (Economic Evaluations)
We also searched the bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analysis for identification of additional studies. Details of the search strategies and search results for each evidence review can be found in the supporting document titled Technical report.

Inclusion of studies

To determine the literature to be assessed further, a reviewer scanned the titles, abstract sections and keywords of every record retrieved by the search strategy. Full articles were retrieved for further assessment if the information given suggested that the study met the selection criteria. Studies were selected by one reviewer in consultation with colleagues, using the PICO selection criteria established a priori. Where there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification.

Appraisal of the methodological quality/risk of bias of the evidence

Methodological quality of the included studies was assessed using criteria developed a priori according to study design (ie. quality appraisal criteria used for an RCT is different to that used for a cohort study) [614]. Individual quality items were investigated using a descriptive component approach. Any disagreement or uncertainty was resolved by discussion among the guideline development team to reach a consensus. Using this approach, each study was allocated a risk of bias rating (see Table 8). Quality appraisal tables for each evidence review can be found in the supporting document titled Technical report.

Table 8. Risk of bias ratings [614]

<table>
<thead>
<tr>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>All of the criteria have been fulfilled or where criteria have not been fulfilled it is very unlikely the conclusions of the study would be affected.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.</td>
</tr>
<tr>
<td>High</td>
<td>Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.</td>
</tr>
<tr>
<td>Insufficient information</td>
<td>Not enough information provided on methodological quality to be able to determine risk of bias.</td>
</tr>
</tbody>
</table>

Data extraction

Data, according to the selection criteria, were extracted from included studies using a specially developed data extraction form [614]. Information was collected on general details (title, authors, reference/source, country, year of publication, setting), participants (age, sex, inclusion/exclusion criteria, withdrawals/losses
to follow-up, subgroups), results (point estimates and measures of variability, frequency counts for dichotomous variables, number of participants, intention-to-treat analysis) and validity results. Data extraction tables for each evidence review can be found in the supporting document titled Technical report.

Data synthesis

In order to make a summary statement about the effect of the intervention and thus inform evidence-based recommendations, data were presented qualitatively by presenting the findings narratively in tables or discussion text; or quantitatively, using statistical methods such as meta-analyses. A meta-analysis is a statistical technique for combining (pooling) the results of a number of studies, that report data for the same outcome for the same intervention, to produce a summary statistic to represent the effect of one intervention compared to another. When high quality trials are used, a meta-analysis summary statistic can be more powerful than an individual study to confirm or refute effectiveness of an intervention and thus to inform an evidence-based recommendation. Data were summarised statistically using meta-analyses if data were available, sufficiently homogenous, and of sufficient quality. Clinical homogeneity was be satisfied when participants, interventions, outcome measures and timing of outcome measurement were considered to be similar. The Review Manager 5.3 software was used for meta-analyses. Where appropriate, subgroup analysis was conducted according to factors that may cause variations in outcomes; are likely to be a confounder; or may change the way the treatment works e.g. age, subtype of treatment, duration of intervention. These can be found in the supporting document titled Technical report.

Quality (certainty) of the body of evidence using GRADE evidence profiles

A GRADE evidence profile was prepared for each comparison within each clinical question addressed by a systematic review. For each prioritised outcome, a certainty rating was documented with consideration of the following:

- 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. The definitions of these factors are described below;
- overall quality of evidence rating using the judgments made above (see ratings in table 9);
- key statistical data;
- classification of the importance of the outcome.

The certainty of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation [16].

Although the quality of evidence represents a continuum, the GRADE approach results in an assessment of the quality of a body of evidence in one of four grades (adapted from GRADE [16]).

Table 9. Quality of evidence
High

⊕⊕⊕⊕ We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate

⊕⊕⊕ We are moderately confident 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

⊕⊕ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very Low

⊕ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

GRADE note that the quality of evidence is a continuum; any discrete categorisation involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations [16].

Evidence profiles can be found in the Technical report.

**Formulation of recommendations using the GRADE evidence to decision framework**

The Evidence to Decision (iEtD) framework was used to document the judgments and decisions using the GRADE method for development of evidence-based recommendations. The framework prompts transparent documentation and discussion of decisions through assessment of the evidence, clinical expertise and patient preference for factors including: desirable and undesirable effects of the intervention; certainty of the evidence; values associated with the recommended intervention; balance of effects; resource requirements; cost-effectiveness; equity; acceptability; feasibility; subgroup considerations; implementation considerations; monitoring and evaluation; and research priorities.

Using the framework, each of the evidence-based and consensus recommendations are given an overall grading of conditional or strong [16]. Clinical practice points have also been included, where important issues (such as safety, side effects or risks) arose from discussion of evidence-based or clinical consensus recommendations.

<table>
<thead>
<tr>
<th>EBR</th>
<th>Evidence sufficient to inform an evidence-based recommendation (EBR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR</td>
<td>In the absence of adequate evidence in PCOS, a clinical consensus recommendation (CCR) was made</td>
</tr>
<tr>
<td>CPP</td>
<td>Evidence not sought. A clinical practice point (CPP) was made where important issues arose from discussion of evidence-based or clinical consensus recommendations</td>
</tr>
</tbody>
</table>
The strength of the recommendations can be identified throughout the guideline by the following (adapted from ESHRE manual for guideline development [615] and the GRADE approach [16]):

<table>
<thead>
<tr>
<th>Target group</th>
<th>Strong recommendations *</th>
<th>Conditional (weak) recommendations for the option (test or treatment)</th>
<th>Conditional (weak) recommendation for either the option or the comparison</th>
<th>Research only recommendations</th>
<th>Clinical practice points (CPP)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumers</td>
<td>Most people in your situation would want the recommended course of action and only a small proportion would not</td>
<td>The majority of people in your situation would want the recommended course of action, but some would not.</td>
<td>There is considerable lack of clarity over whether the majority of people in your situation would want the recommended course of action or not</td>
<td>The test or intervention should only be considered by patients and clinicians within the setting of a research trial for which appropriate approvals and safety precautions have been established</td>
<td>Clinicians, patients and policy makers are informed on the clinical implications relevant to implementation of recommendation</td>
</tr>
<tr>
<td>Health Professionals</td>
<td>Most patients should receive the recommended course of action.</td>
<td>Recognise that different choices will be appropriate for different patients and that greater effort is needed with individuals to arrive at management decisions consistent with values and preferences. Decision aids and shared decision making are important here.</td>
<td>Policy making needs to consider perspectives and involvement of diverse stakeholders</td>
<td>Policy decisions remain unclear</td>
<td>Policy makers need to be aware of the need for evidence gaps and health professional and consumer prioritised research gaps</td>
</tr>
<tr>
<td>Policy makers</td>
<td>The recommendation can be adopted as policy in most situations</td>
<td>Policy making needs to consider perspectives and involvement of diverse stakeholders</td>
<td>Policy decisions remain unclear</td>
<td>Policy makers need to be aware of the need for evidence gaps and health professional and consumer prioritised research gaps</td>
<td>Policy makers need to be aware of the need for evidence gaps and health professional and consumer prioritised research gaps</td>
</tr>
</tbody>
</table>
* Strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the often-compelling unique features of individual patients and clinical circumstances.

** A clinical practice point (CPP) is developed by the GDG to support recommendations. Advice can be provided to enhance shared decision making, and on factors to be considered in implementing a specific test or intervention.

The words “should”, “could” and “should not” do not directly reflect the strength (strong or conditional) allocated to a recommendation and are independent descriptors intended to reflect the judgment of the multidisciplinary guideline development group on the practical application of the recommendation, balancing benefits and harms. Where the word “should” is used in the recommendations, the guideline development group judged that the benefits of the recommendation (whether evidence-based or clinical consensus) clearly exceed the harms, and that the recommendation can be trusted to guide practice. Where the word “could” is used, either the quality of evidence was underpowered, or the available studies demonstrated little clear advantage of one approach over another, or the balance of benefits to harm was unclear. Where the words “should not” are used, there is either a lack of appropriate evidence, or the harms outweigh the benefits.

Evidence to decision frameworks can be found in the supplementary document titled Technical report.

Each recommendation is supported by a discussion (in the chapters of this document) about the clinical need for the question, the body of evidence identified to answer the question and a clinical justification for the recommendation(s).

The guideline development groups acknowledge that lack of evidence is not evidence of lack of effect and have attempted to reflect this in the strength of the grading given to recommendations on interventions that are not supported by evidence. In addition, some interventions were not supported by evidence in the recommendations due to lack of evidence of effect. The guideline development groups acknowledge that this refers to lack of evidence of effect over placebo; that is, patients may receive some beneficial outcomes from the intervention but these do not exceed the beneficial effects that can be expected from a placebo therapy [616].

**Public consultation**

Public and targeted consultation will be conducted for a period of 30 days commencing 10th February 2018 to 12th March in accordance with the legislative requirements set out in section 14A of the National Health and Medical Research Council Act 1992 as outlined in the NHMRC standards and procedures for externally developed guidelines (2007) [613]. The public consultation strategy is available upon request, email linda.downes@monash.edu.

**External review**

This guideline will be reviewed by the International Advisory Group, and independently by relevant professional colleges and societies and through public consultation.
Scheduled review and update of the guideline

The guideline development groups will be re-convened to review relevant sections of this guideline if any of the following occur within five years:

- a change in the indications registered by the Therapeutic Goods Administration for any drug included in this guideline; or
- publication of any new major randomised controlled trials or systematic reviews that potentially have a bearing on the safety of the recommendations in this guideline.
Translation and implementation

A comprehensive, international translation and dissemination program will be undertaken to amplify the impact of the PCOS guideline (insert correct name). The three guiding principles underpinning the translation and dissemination program are:

1. All components of the translation program are informed by the needs and preferences of PCOS consumers;
2. All translation materials are co-created with, and attuned to, the needs of end-users; and,
3. Dissemination strategies are multi-faceted, multi-modal and refined to the communications channels of end-users.

The aims of the 18 month, international translation program are to:

- Build the capability of health professionals to deliver high-quality, evidence-based assessment and management of PCOS;
- Augment the health literacy of PCOS health consumers, leading to improved health outcomes;
- Promote a best-practice PCOS model of care;
- Orientate international health policy towards an evidence-based, best practice approach.

Significant outcomes of the translation and dissemination plan include a consistent and improved standard of care and greater consumer empowerment by enhancing both consumer engagement and the capacity of health professionals to deliver high quality, evidence-based care.

Central to the success of translation and dissemination program is the active engagement of 44 international collaborating partners who represent the leading, invested health organisations such as European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). Health experts from these organisations will leverage their extensive influence within the health sector to promote the uptake of PCOS guideline recommendations. In addition, a further essential component is the engagement of leading consumer groups such as; the Polycystic Ovary Association of Australia (POSAA), Verity in the United Kingdom, PCOS Challenge: The National Polycystic Ovary Syndrome Association in the United States and organisations with strong links to health consumers such as Jean Hailes for Women’s Health and the Victorian Assisted Reproductive Treatment Authority (VARTA). Finally, the translation and dissemination plan is supported by a comprehensive evaluation framework, measuring international impacts and outcomes.
### Consumers

<table>
<thead>
<tr>
<th>Translation strategy</th>
<th>Deliverable/s</th>
<th>Collaborator/s</th>
<th>Dissemination</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim: Increase the health literacy of women and girls affected by PCOS through the co-creation of a consumer focused, accessible PCOS education and health information platform.</td>
<td>PCOS APP (AskPCOS)</td>
<td>-Monash University</td>
<td>-Apple itunes</td>
<td>-A low cost, internationally accessible PCOS APP</td>
</tr>
<tr>
<td>Co-create an internationally accessible, interactive, low cost mobile application providing high quality, evidence-based, PCOS information tailored to the needs of the individual user.</td>
<td>-PCOS-CRE</td>
<td>-Social media channels (Dedicated facebook page, twitter)</td>
<td>-Self-diagnosis function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-MHCRI</td>
<td>-Range of conventional media</td>
<td>-Chatbot interactive functionality tailoring information provision to individual consumer needs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-PCOS consumers</td>
<td></td>
<td>-Referral information to appropriate health professionals</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Peer support access</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Access to secondary data to inform PCOS research</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-A cache of google analytics to enhance the PCOS APP</td>
<td></td>
</tr>
</tbody>
</table>
Provision of translated, e-health, evidence-informed PCOS information, informed by consumer needs and preferences.

- Jean Hailes for Women’s Health
- Victorian Assisted Reproductive Treatment Authority (VARTA)
- Women’s Health Victoria
- Polycystic Ovary Syndrome Association of Australia (POSSA)

Co-develop and deliver a PCOS Lifestyle Education Program for women with PCOS

- Monash Health
- Victorian Government

Co-develop and deliver an accessible, interactive, no cost, internationally available online PCOS course for consumers.

- Monash University
- PCOS-CRE
- MHCRI

Co-develop a PCOS Model of Care underpinned by a sustainable, psychosocial multidisciplinary approach and incorporating a

- Monash Health
- Victorian Government

Accessible, translated PCOS e-health information informed by the highest quality evidence and consumer needs and preferences.
A comprehensive PCOS translation platform.

To provide a range of translated, accessible PCOS written materials that are tailored to the needs of consumers.

A range of PCOS written materials: fact sheets, booklets for different consumer groups, language translated health materials.

- Jean Hailes for Women’s Health
- Victorian Assisted Reproductive Treatment Authority (VARTA)
- Women’s Health Victoria
- Polycystic Ovary Syndrome Association of Australia (POSSA)
- CaLD and Aboriginal and Torres Strait Islander organisations

Health professionals

<table>
<thead>
<tr>
<th>Translation strategy</th>
<th>Deliverable/s</th>
<th>Collaborator/s</th>
<th>Dissemination</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim: Increase the uptake of PCOS evidence-based practice among health professionals internationally.</td>
<td>Implement an extensive publication plan targeting international journals, discipline specific publications and in the general medical media domain.</td>
<td>16 publications published in high impact journals and discipline specific publications</td>
<td>Experts from the 44 international collaborating organisations of the PCOS guideline</td>
<td>16 publications published in high impact international journals and discipline specific publications</td>
</tr>
</tbody>
</table>
To deliver a co-ordinated, international expert speaker program at international conferences, annual meetings and invited speak events in the US, Aust, Africa, India and Europe, covering of the topics of; fertility, reproduction, chronic disease prevention and lifestyle.

Up to 35 workshops, symposiums, key note speaker and panel speaker events delivered internationally

Experts from the 44 international collaborating organisations of the PCOS guideline

Multiple conferences, annual meeting and events across US, Aust, Africa, India and Europe

35 workshops, symposiums, key note speaker and panel speaker events delivered internationally

Develop a range of PCOS educational resources with high utility with health professionals.

Webinars

Face-to-face events

Flexible learning opportunities

PCOS accredited CPD for-fee online course

-Jean Hailes for Women’s Health

-RACGP

-Peak bodies

-Monash University

-PCOS-CRE

-MHCRI

Peak body learning portals

Jean Hailes for Women’s Health CPD program

-Monash University

-Futurelearn FOOC (For-fee online course)

A range of PCOS educational resources with high utility with health professionals

To co-develop and deliver an accessible, interactive, for-fee, accredited, internationally available online PCOS course for health professionals.

-Accessible, accredited, online, interactive, for-fee, internationally available PCOS course for health professionals
<table>
<thead>
<tr>
<th>Government</th>
<th>PCOS health policy is based on the highest quality evidence and consumer needs and preferences</th>
<th>International and national Governments, health organisations.</th>
<th>Health professional experts</th>
<th>Multi-faceted dissemination strategy</th>
<th>PCOS health policy based on the highest quality evidence and informed by health professional expertise and consumer needs and preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>To influence international/national health policy leveraging high level health professional expertise and informed by the highest quality evidence and consumer needs and preferences.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
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References 161


## Appendix I: Project board

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Discipline</th>
<th>Organisational affiliation/ Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair</td>
<td>Professor Helena Teede</td>
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<td>Evidence synthesis and guidelines advisor</td>
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## Appendix II: International Advisory Panel

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Appendix III: Guideline development groups

Terms of reference for each committee can be provided upon request (linda.downes@monash.edu).

GDG1: Topic area - Screening, diagnostic assessment, risk assessment and life-stage

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## GDG2: Topic area - Prevalence, screening, diagnostic assessment and management of emotional wellbeing

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### Appendix III: Membership Guideline Development Groups

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### Appendix III: Membership Guideline Development Groups

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**GDG5: Topic area - Screening, diagnostic assessment and management of infertility**

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<tr>
<td>Member</td>
<td>Professor</td>
<td>Raymond Rodgers</td>
<td>Reproductive Endocrinologist</td>
<td>The Robinson Research Institute at the University of Adelaide</td>
<td>Australia</td>
</tr>
<tr>
<td>Member</td>
<td>Professor</td>
<td>Luk Rombauts</td>
<td>Obstetrician-Gynaecologist; Infertility Specialist</td>
<td>Monash Health</td>
<td>Australia</td>
</tr>
<tr>
<td>Member</td>
<td>Professor</td>
<td>Shakila Thangaratinam</td>
<td>Obstetrician-Gynaecologist; Clinical Academic</td>
<td>Queen Mary University of London</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member</td>
<td>Professor</td>
<td>Eszter Vanky</td>
<td>Obstetrician-Gynaecologist</td>
<td>Dept. of Clinical and Molecular Medicine,</td>
<td>Norway</td>
</tr>
</tbody>
</table>
Guideline development technical team members

- Professor Helena Teede, Project Director – Monash Centre for Health Research and Implementation
- Doctor Marie Misso, Evidence Synthesis Lead and Guidelines Advisor, Monash Centre for Health Research and Implementation
- Ms Linda Downes, Project Manager – Monash Centre for Health Research and Implementation
- Doctor Rhonda Garad, Senior Project Officer, Knowledge Translation in Polycystic Ovary Syndrome, Monash Centre for Health Research and Implementation
- Miss Eliza Tassone, Evidence Synthesis Officer, Monash Centre for Health Research and Implementation
- Mr Estifanos Baye, Evidence Synthesis Officer, Monash Centre for Health Research and Implementation
- Ms Ching Shan Wan, Evidence Synthesis Officer, Monash Centre for Health Research and Implementation
Appendix IV:

**Berlin Questionnaire**

*SLEEP EVALUATION IN PRIMARY CARE*

1. Complete the following:
   - Height ________ Age ________
   - Weight ________ Male/female ________

2. Do you snore?
   - [ ] Yes
   - [ ] No
   - [ ] Don’t know

   *If you snore:*
   3. Your snoring is?
      - [ ] Slightly louder than breathing
      - [ ] As loud as talking
      - [ ] Louder than talking
      - [ ] Very loud. Can be heard in adjacent rooms.

4. How often do you snore?
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

5. Has your snoring ever bothered other people?
   - [ ] Yes
   - [ ] No

6. Has anyone noticed that you quit breathing during your sleep?
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

7. How often do you feel tired or fatigued after your sleep?
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

8. During your waketime, do you feel tired, fatigued, or not up to par?
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

9. Have you ever nodded off or fallen asleep while driving a vehicle?
   - [ ] Yes
   - [ ] No

   *If yes, how often does it occur?*
   - [ ] Nearly every day
   - [ ] 3-4 times a week
   - [ ] 1-2 times a week
   - [ ] 1-2 times a month
   - [ ] Never or nearly never

10. Do you have high blood pressure?
    - [ ] Yes
    - [ ] No
    - [ ] Don’t know

    **BMI =**

**Scoring questions:** Any answer within box outline is a positive response.

**Scoring categories:**
- Category 1 is positive with 2 or more positive responses to questions 2-6
- Category 2 is positive with 2 or more positive responses to questions 7-9
- Category 3 is positive with 1 positive response and/or a BMI >30

**Final result:** 2 or more positive categories indicates a high likelihood of sleep disordered breathing.
### Appendix V: Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>Area under the receiver operating characteristic curve (analysis)</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CCR</td>
<td>Clomiphene citrate resistant</td>
</tr>
<tr>
<td>Dietitian</td>
<td>Accredited Practising Dietitian</td>
</tr>
<tr>
<td>DM2</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>FBG</td>
<td>Fasting blood glucose</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>GAD</td>
<td>Generalised Anxiety disorder scale</td>
</tr>
<tr>
<td>GDM</td>
<td>Gestational Diabetes</td>
</tr>
<tr>
<td>GnRH</td>
<td>Gonadotrophin releasing hormone</td>
</tr>
<tr>
<td>hCG</td>
<td>Human Chorionic Gonadotrophin</td>
</tr>
<tr>
<td>ICSI</td>
<td>Intracytoplasmic sperm injection</td>
</tr>
<tr>
<td>IGT</td>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Homeostasis model of assessment-insulin resistance</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>IVM</td>
<td>In vitro maturation</td>
</tr>
<tr>
<td>IVF</td>
<td>In vitro fertilisation</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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</tr>
<tr>
<td>LH</td>
<td>Luteinising hormone</td>
</tr>
<tr>
<td>MPCOSQ</td>
<td>Modified PCOS quality of life questionnaire</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>Non-CCR</td>
<td>Non-clomiphene citrate resistant</td>
</tr>
<tr>
<td>COCP</td>
<td>Combined oral contraceptive pill</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
<td>OHSS</td>
<td>Ovarian hyperstimulation syndrome</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>PCOM</td>
<td>Polycystic ovary morphology</td>
</tr>
<tr>
<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>PCOSQ</td>
<td>PCOS quality of life questionnaire</td>
</tr>
<tr>
<td>PHQ</td>
<td>Patient Health questionnaire</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCO</td>
<td>Polycystic ovary</td>
</tr>
<tr>
<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>PICO</td>
<td>Participants/Population, Intervention/Exposure, Comparison/Control, Outcome</td>
</tr>
<tr>
<td>POSAA</td>
<td>Polycystic Ovary Syndrome Association Australia</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SHBG</td>
<td>Sex hormone-binding globulin</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration (Australian Government)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>-------------</td>
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</tr>
<tr>
<td>P-value</td>
<td>Measure of statistical precision</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effect</td>
<td>An adverse event for which the causal relation between the drug/intervention and the event is at least a reasonable possibility.</td>
</tr>
<tr>
<td>Aerobic exercise/activity</td>
<td>Any physical activity that produces energy by combining oxygen with blood glucose or body fat.</td>
</tr>
<tr>
<td>AGREE II</td>
<td>An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (<a href="http://www.agreetrust.org">http://www.agreetrust.org</a>). The AGREE II instrument developed by the collaboration is designed to assess the quality of clinical guidelines.</td>
</tr>
<tr>
<td>Algorithm</td>
<td>A flow chart of the clinical decision pathway described in the guideline, where recommendations are presented in boxes, linked with arrows.</td>
</tr>
<tr>
<td>Anovulation</td>
<td>A condition in which the ovary does not produce and release an egg each menstrual cycle.</td>
</tr>
<tr>
<td>Anxiety</td>
<td>When fears or thoughts that are chronic (constant) and distressing interfere with daily living.</td>
</tr>
<tr>
<td>Area under the receiver operating characteristic curve (AUC)</td>
<td>In this guideline, it is used as a method of analysis that measures the ability and reliability of a risk assessment method or diagnostic test to correctly identify the optimal balance between false-positive and false-negative tests.</td>
</tr>
<tr>
<td>Assess</td>
<td>In this guideline, assess refers to the process of identifying the severity of the condition.</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Blood pressure is the pressure of the blood in the arteries as it is pumped around the body by the heart.</td>
</tr>
<tr>
<td>Body image</td>
<td>The way a person may feel, think and view their body including their appearance.</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>A calculated number used to discriminate between lean, overweight, obesity and morbid obesity, calculated from an individual’s height (kg) and weight (m).</td>
</tr>
<tr>
<td>Glossary Term</td>
<td>Definition</td>
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<tr>
<td>---------------</td>
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</tr>
<tr>
<td>BMI</td>
<td>( \text{BMI} = \frac{\text{weight}}{\text{height}^2} )</td>
</tr>
<tr>
<td>Cardiometabolic</td>
<td>Metabolic factors that increase the risk of cardiovascular disease.</td>
</tr>
<tr>
<td>Cardiovascular disease (CVD)</td>
<td>A condition that affects either the heart or major blood vessels (arteries) supplying the heart, brain and other parts of the body.</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>The potential benefit from application of the recommendations in the guideline on the treatment or treatment outcomes of the target population.</td>
</tr>
<tr>
<td>Clinical question (guideline development)</td>
<td>One of a set of questions about an intervention or process that define the content of the evidence reviews and subsequent recommendations in the guideline.</td>
</tr>
<tr>
<td>Clomiphene citrate resistant (CCR)</td>
<td>When the patient is unable to ovulate with clomiphene citrate treatment.</td>
</tr>
<tr>
<td>Clomiphene citrate failure</td>
<td>When the patient is able to ovulate with clomiphene citrate treatment but does not conceive.</td>
</tr>
<tr>
<td>Clomiphene citrate sensitive</td>
<td>When the patient is able to ovulate and conceive with clomiphene citrate treatment.</td>
</tr>
<tr>
<td>Cochrane review</td>
<td>Cochrane Reviews are systematic summaries of evidence of the effects of healthcare interventions. The specific methods used in a Review are described in the text of the review. Cochrane Reviews are prepared using Review Manager (RevMan) software provided by the Collaboration, and adhere to a structured format that is described in the Cochrane Handbook for Systematic Reviews of Interventions.</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>The presence of one or more diseases or conditions other than those of primary interest. In a study looking at treatment for one disease or condition, some of the individuals may have other diseases or conditions that could affect their outcomes. (A co-morbidity may be a confounder.)</td>
</tr>
<tr>
<td>Compliance</td>
<td>The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as ‘adherence’ or ‘concordance’.</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>A range of values for an unknown population parameter with a stated ‘confidence’ (conventionally 95%) that it contains the true value. The interval is calculated from sample data, and generally straddles the sample estimate. The ‘confidence’ value means that if the method used to calculate the interval is repeated many times, then that proportion of intervals will actually contain the true value.</td>
</tr>
<tr>
<td>Glossary Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
<td>Congenital adrenal hyperplasia is a condition where the enzyme needed by the adrenal gland to make the hormones cortisol and aldosterone is lacking and thus the body produces more androgen and causes male characteristics to appear early or inappropriately.</td>
</tr>
<tr>
<td>Consensus methods</td>
<td>Techniques that aim to reach an agreement on a particular issue. Formal consensus methods include Delphi and nominal group techniques, and consensus development conferences. In the development of clinical guidelines, consensus methods may be used where there is a lack of strong research evidence on a particular topic. Expert consensus methods will aim to reach agreement between experts in a particular field.</td>
</tr>
<tr>
<td>Contraindication</td>
<td>A condition or factor that serves as a reason to withhold a certain medical treatment.</td>
</tr>
<tr>
<td>Depression</td>
<td>Depression is more than low mood and sadness at a loss and is a serious medical illness. It is the result of chemical imbalances in the brain. The sufferer feels extremely sad, dejected and unmotivated.</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td>The accuracy of a test to diagnose a condition which can be expressed through sensitivity and specificity, positive and negative predictive values, or positive and negative diagnostic likelihood ratios.</td>
</tr>
<tr>
<td>Disordered eating</td>
<td>Eating and weight related symptoms commonly associated with an eating disorder including behavioural (e.g. bingeing, restriction), cognitive (e.g. dietary restraint, negative body image) and emotional (e.g. Emotional eating) factors.</td>
</tr>
<tr>
<td>Dosage</td>
<td>The prescribed amount of a drug to be taken, including the size and timing of the doses.</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>Eating disorders include anorexia, bulimia nervosa and other binge eating disorders.</td>
</tr>
<tr>
<td>Effect (as in effect measure,</td>
<td>The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.</td>
</tr>
<tr>
<td>treatment effect, estimate of</td>
<td></td>
</tr>
<tr>
<td>effect, effect size)</td>
<td></td>
</tr>
<tr>
<td>Evidence statement table</td>
<td>A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.</td>
</tr>
<tr>
<td>Exclusion criteria (for a</td>
<td>Explicit criteria used to decide which studies should be excluded from consideration as potential sources of evidence.</td>
</tr>
<tr>
<td>systematic evidence review)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity</td>
<td>Describes the variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of</td>
</tr>
</tbody>
</table>
studies, or the variation in internal validity of those studies. It can be used specifically, as statistical heterogeneity, to describe the degree of variation in the effect estimates from a set of studies. Also used to indicate the presence of variability among studies beyond the amount expected due solely to the play of chance.

The term is used in meta-analyses and systematic reviews when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal profile</td>
<td>Cyclical levels of hormones.</td>
</tr>
<tr>
<td>Hyperandrogenism</td>
<td>Clinical hyperandrogenism is characterised by hirsutism, acne and male pattern alopecia. Biochemical hyperandrogenism is characterised by excessive production and/or secretion of androgens.</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>When fasting morning blood glucose levels are higher than normal but not high enough to diagnose diabetes.</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>When glucose levels are above normal during or after an oral glucose tolerance test but are not high enough to diagnose diabetes.</td>
</tr>
<tr>
<td>Incidence</td>
<td>The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.</td>
</tr>
<tr>
<td>Inclusion criteria (for a systematic evidence review)</td>
<td>Explicit criteria used to decide which studies should be considered as potential sources of evidence.</td>
</tr>
<tr>
<td>Infertility (women)</td>
<td>Infertility problems in women include failure to ovulate, blockages in the fallopian tubes, and disorders of the uterus, such as fibroids or endometriosis.</td>
</tr>
<tr>
<td>Interdisciplinary care</td>
<td>An interdisciplinary care model is the collaboration between a woman with PCOS and a care team who have shared goals for her total wellbeing.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Any action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.</td>
</tr>
<tr>
<td>Insulin resistance (IR)</td>
<td>A rise in glucose occurs because the body can’t make enough insulin or the insulin produced is not working properly.</td>
</tr>
<tr>
<td>Glossary Term</td>
<td>Definition</td>
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</tr>
<tr>
<td>Irregular cycles/oligomenorrhea</td>
<td>When the duration of menstrual cycles is &gt;35 or &lt;21 days.</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>A medical procedure used to examine the interior of the abdominal or pelvic cavities to diagnose or treat (or both) a number of different diseases and conditions, including female infertility.</td>
</tr>
<tr>
<td>Lean</td>
<td>BMI ≤ 25kg/m²</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>A group of blood tests that are often ordered together to determine risk of cardiovascular disease, including total cholesterol, HDL-C, LDL-C and triglycerides.</td>
</tr>
<tr>
<td>Menarche</td>
<td>The onset of the first period of the menstrual cycle, which occurs on average between the ages of 11 and 14 years.</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result. The aim is to derive more precise and clear information from a large data pool. It is generally more reliably likely to confirm or refute a hypothesis than the individual trials.</td>
</tr>
<tr>
<td>Morbidly obese</td>
<td>BMI ≥ 35kg/m²</td>
</tr>
<tr>
<td>Non-clomiphene citrate resistant (Non-CCR)</td>
<td>Those who are either clomiphene citrate sensitive or who have unknown clomiphene citrate sensitivity.</td>
</tr>
<tr>
<td>Obese</td>
<td>BMI ≥ 30-35kg/m²</td>
</tr>
<tr>
<td>Odds ratio (OR)</td>
<td>The ratio of the odds of an event in one group to the odds of an event in another group. In studies of treatment effect, the odds in the treatment group are usually divided by the odds in the control group. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.</td>
</tr>
<tr>
<td>Oligo-anovulation</td>
<td>Clinically, irregular cycles lasting &lt;21 or more than 35 days or less than 8 periods per year. Endocrinologically, the absence of raised serum progesterone greater than 20nmol/l 7 days prior to a period.</td>
</tr>
<tr>
<td>Oligomenorrhea/irregular cycles</td>
<td>When the duration of menstrual cycles is &gt;35 or &lt;21 days.</td>
</tr>
<tr>
<td>Oral glucose tolerance test (OGTT)</td>
<td>A test to diagnose diabetes where a high-glucose drink is given and blood samples are checked at regular intervals for two hours.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition/description</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome (OHSS)</td>
<td>A condition where too many follicles develop (following ovulation induction) which can result in marked abdominal swelling, nausea, vomiting and diarrhoea, lower abdominal pain and shortness of breath.</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI $\geq 25.1$-30kg/m$^2$</td>
</tr>
<tr>
<td>Ovulation</td>
<td>Ovulation is the release of an egg from one of the ovaries.</td>
</tr>
<tr>
<td>Ovulation induction</td>
<td>Ovulation induction is the use of medication to stimulate the ovary to increase egg production.</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>Characterised by clusters of blister-like cysts on the ovary.</td>
</tr>
<tr>
<td>Polycystic ovary syndrome (PCOS)</td>
<td>PCOS is a chronic metabolic and hormonal condition, which can impact on physical health and emotional wellbeing.</td>
</tr>
<tr>
<td>Placebo</td>
<td>An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug. Placebos are used in clinical trials to blind people to their treatment allocation. Placebos should be indistinguishable from the active intervention to ensure adequate blinding.</td>
</tr>
<tr>
<td>Post-operative</td>
<td>The period after a patient leaves the operating theatre, following surgery.</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>Where blood glucose levels are higher than normal, but not high enough to be classified as diabetes. Pre-diabetes includes impaired fasting glucose and impaired glucose tolerance.</td>
</tr>
<tr>
<td>Pre-operative</td>
<td>The period before surgery commences.</td>
</tr>
<tr>
<td>Psychosexual dysfunction</td>
<td>Sexual problems or difficulties that have a psychological origin based in cognitions and/or emotions such as depression, low self-esteem and negative body image.</td>
</tr>
<tr>
<td>P value</td>
<td>Measure of statistical precision. The probability that an observed difference could have occurred by chance, assuming that there is in fact no underlying difference between the means of the observations. If the probability is less than 1 in 20, the P value is less than 0.05; a result with a P value of less than 0.05 is conventionally considered to be ‘statistically significant’.</td>
</tr>
<tr>
<td>Randomisation</td>
<td>Allocation of participants in a research study to two or more alternative groups using a chance procedure, such as computer-generated random numbers. This approach is used in an attempt to ensure there is an even distribution of participants with different characteristics between groups and thus reduce sources of bias.</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<tr>
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</tr>
<tr>
<td>Randomised controlled trial (RCT)</td>
<td>A comparative study in which participants are randomly allocated to two or more alternative groups and followed up to examine differences in outcomes between the groups.</td>
</tr>
<tr>
<td>Resource implication</td>
<td>The likely impact of the recommendation in terms of cost, workforce or other health system resources.</td>
</tr>
<tr>
<td>Risk of bias</td>
<td>Also called methodological quality, it is the degree to which the results of a study are likely to approximate the ‘truth’ for the participants recruited in a study (that is, are the results free of bias?). It refers to the integrity of the design and specifically the extent to which the design and conduct of a study are likely to have prevented bias. More rigorously designed (better quality, low risk of bias) trials are more likely to yield results that are closer to the truth.</td>
</tr>
<tr>
<td>Relative risk (RR)</td>
<td>The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A relative risk (also called risk ratio) of one indicates no difference between comparison groups. For undesirable outcomes, a relative risk that is less than one indicates that the intervention was effective in reducing the risk of that outcome.</td>
</tr>
<tr>
<td>Screen</td>
<td>In this guideline, screen refers to the process of identifying whether the condition exists and is the first step in offering appropriate management.</td>
</tr>
<tr>
<td>Selection criteria</td>
<td>Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.</td>
</tr>
<tr>
<td>Stakeholder</td>
<td>Those with an interest in the topic. Stakeholders include healthcare professionals, patient/consumer and carer groups, manufacturers and sponsors.</td>
</tr>
<tr>
<td>Statistical power</td>
<td>The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.</td>
</tr>
<tr>
<td>Systematic review</td>
<td>A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.</td>
</tr>
<tr>
<td>Therapy naive</td>
<td>A patient who has not been administered prior treatment for the condition.</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (DM2)</td>
<td>When the pancreas makes some insulin but it is not produced in the amount your body needs and it does not work effectively. Type 2 diabetes results from a combination of genetic and environmental factors and risk is greatly increased when associated with lifestyle factors such as high blood pressure, overweight or obesity, insufficient physical activity, poor diet and the classic ‘apple shape’ body where extra weight is carried around the waist.</td>
</tr>
</tbody>
</table>
Appendix VII: Evidence-based guideline development pathway

Diagram 1: Key steps in seeking NHMRC approval of externally developed guidelines

Origin of request:
- Minister
- Council
- Government
- Professional and consumer organisations

CEO responds to originator with reasons for decision and alternative suggestions

Submit a formal request to the CEO of the NHMRC seeking advice or assistance in guideline development

Considered by NHMRC (using assessment criteria)

Is NHMRC involvement appropriate?

Yes

Advice referred to CEO for consideration

CEO gives ‘in-principle’ approval

CEO declines approval

Which type of advice is most appropriate?

Information paper or other product

Guidelines

Process depends on type of product

Guidelines developed according to NHMRC requirements and standards

With support from a GAR consultant

Final draft subject to independent review and resubmitted as necessary

Guidelines referred to Council for advice to the CEO. Council makes a recommendation to the CEO.

CEO agrees to approve guidelines

CEO declines to approve guidelines

Dissemination and implementation

NHMRC standards and procedures for externally developed guidelines

*Updated September 2007*
Diagram 2: Flow chart of the NHMRC’s development process for evidence based guidelines

NHMRC standards and procedures for externally developed guidelines
Updated September 2007