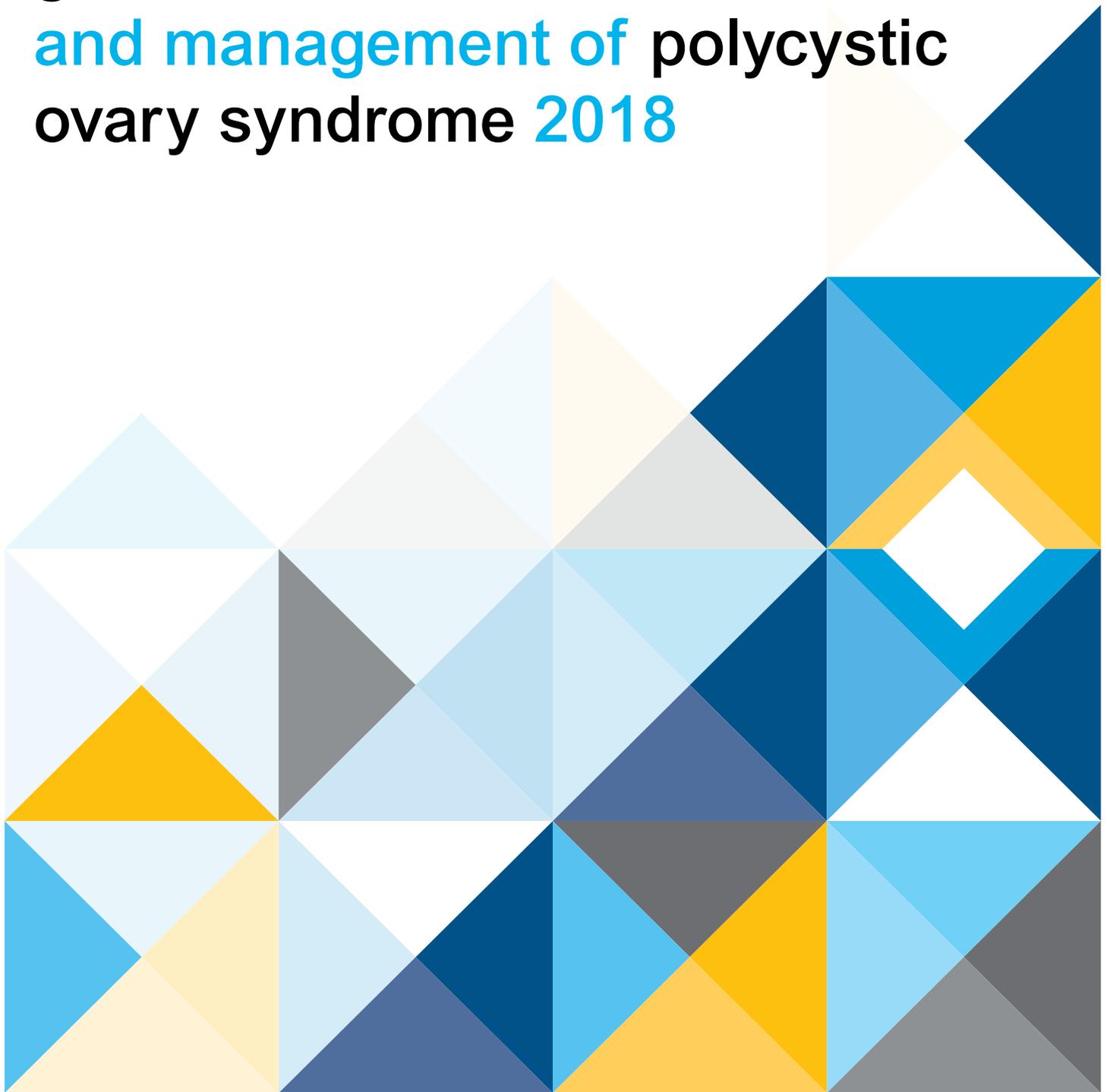# International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018

Publication approval

Australian Government

National Health and Medical Research Council

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 2 July 2018, under Section 14A of the National Health and Medical Research Council Act 1992. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of 5 years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Disclaimer

The Centre for Research Excellence in Polycystic Ovary Syndrome (CREPCOS) 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 evidence-based guideline to provide evidence-based recommendations to improve the quality of healthcare, health outcomes and quality of life of women with PCOS. The 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 guideline 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. All recommendations and practice points need to be considered in the context of regional regulations.

Adherence to the guideline 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.

The guideline partners make no warranty, express or implied, regarding the guideline and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The partners shall not be liable for direct, indirect, special, incidental, or consequential damages related to the use of the information contained herein. While the partners have made every effort to compile accurate current information, however we cannot guarantee the correctness, completeness, and accuracy of the guideline in every respect at all times. Guidelines do not necessarily represent the views of all clinicians that are members of the partner and collaborating societies. The information provided in this document does not constitute business, medical or other professional advice, and is subject to change.

Publication history

Authorship

Copyright information

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1 The Australian National Health and Medical Research Council (NHMRC) through the funded Centre for Research Excellence in Polycystic Ovary Syndrome (CREPCOS) (APP1078444) and the members of this Centre who led and co-ordinated this international guideline effort

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 and engaged societies and consumer groups:
- Androgen Excess and Polycystic Ovary Syndrome Society (AEPCOS)
- American Paediatric Endocrine Society
- Asia Pacific Paediatric Endocrine Society (APPES)
- Asia Pacific Initiative on Reproduction (ASPIRE)
- Australasian Paediatric Endocrine Group (APEG)
- Australian Diabetes Society (ADS)
- British Fertility Society (BFS)
- Canadian Society of Endocrinology and Metabolism (CSEM)
- Dietitians Association Australia (DAA)
- Endocrine Society (US Endo)
- Endocrine Society Australia (ESA)
- European Society of Endocrinology (ESE)
- European Society for Paediatric Endocrinology (ESPE)
- Exercise and Sports Science Australia (ESSA)
- Federation of Obstetric and Gynaecological Societies of India (FOGSI)
- Fertility Society Australia (FSA)
- International Society of Endocrinology (ISE)
- International Federation of Fertility Societies (IFFS)
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- Polycystic Ovary Syndrome Association of Australia (POSAA)
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- Royal College of Obstetricians and Gynaecologists (RCOG)
- South African Society of Gynaecology and Obstetrics (SASOG)
- Verity UK
- Victorian Assisted Reproductive Technology Association (VARTA)

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

Contents

Preface

This International evidence-based guideline for the assessment and management of Polycystic Ovary Syndrome (PCOS), 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).

Acknowledgement goes to the tireless efforts, commitment, dedication and drive of the Project Manager, Ms Linda Downes, Evidence lead Dr Marie Misso, Translation lead Dr Rhonda Garad, Project Board Chair, Professor Robert Norman, and the guideline evidence team for their contribution. We acknowledge the enthusiasm and engagement of the health professionals and women affected by PCOS, our partners European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine and our collaborating and engaged professional societies and consumer advocacy and support organisations internationally. These stakeholders have guided scope, identification of gaps and needs, prioritisation of clinical questions and outcomes of importance, review of evidence, formulations of recommendations and the guideline, as well as development and implementation of the dissemination and translation program.

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Abstract

Objective: To develop and translate rigorous, comprehensive evidence-based diagnosis, assessment and treatment guidelines, to improve the lives of women with polycystic ovary syndrome (PCOS) worldwide.

Participants: Extensive health professional and patient engagement informed guideline priority areas. International Society-nominated panels included consumers, paediatrics, endocrinology, gynaecology, primary care, reproductive endocrinology, psychiatry, psychology, dietetics, exercise physiology, public health, project management, evidence synthesis and translation experts.

Evidence: Best practice evidence-based guideline development involved extensive evidence synthesis and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework covered evidence quality, feasibility, acceptability, cost, implementation and ultimately recommendation strength.

Process: Governance included an international advisory board from six continents, a project board, five guideline development groups with 63 members, consumer and translation committees. The Australian Centre for Research Excellence in PCOS, funded by the National Health and Medical Research Council (NHMRC), partnered with European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine. Thirty seven organisations across 71 countries collaborated with 23 face to face international meetings over 15 months. Sixty prioritised clinical questions involved 40 systematic and 20 narrative reviews, generating 166 recommendations and practice points. Convened Committees from partner and collaborating organisations provided peer review and the guideline was approved by the NHMRC.

Conclusions: We endorse the Rotterdam PCOS diagnostic criteria in adults (two of clinical or biochemical hyperandrogenism, ovulatory dysfunction, or polycystic ovaries on ultrasound) and where irregular menstrual cycles and hyperandrogenism are present, highlight that ultrasound is not necessary in diagnosis. Within eight years of menarche, both hyperandrogenism and ovulatory dysfunction are required, with ultrasound not recommended. Ultrasound criteria are tightened with advancing technology. Anti-Müllerian hormone levels are not yet adequate for diagnosis. Once diagnosed, assessment and management includes reproductive, metabolic and psychological features. Education, self-empowerment, multidisciplinary care and lifestyle intervention for prevention or management of excess weight are important. Depressive and anxiety symptoms should be screened, assessed and managed with the need for awareness of other impacts on emotional wellbeing. Combined oral contraceptive pills are first-line pharmacological management for menstrual irregularity and hyperandrogenism, with no specific recommended preparations and general preference for lower dose preparations. Metformin is recommended in addition or alone, primarily for metabolic features. Letrozole is first-line pharmacological infertility therapy; with clomiphene and metformin having a role alone and in combination. In women with PCOS and anovulatory infertility, gonadotrophins are second line. In the absence of an absolute indication for IVF, women with PCOS and anovulatory infertility, could be offered IVF third line where other ovulation induction therapies have failed. Overall evidence is low to moderate quality, requiring significant research expansion in this neglected, yet common condition. Guideline translation will be extensive including a multilingual patient mobile application and health professional training.

Executive Summary

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

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 [1-4] with up to 70% of affected women remaining undiagnosed [3]. Presentation varies by ethnicity and in high-risk populations such as Indigenous women, prevalence and complications are higher [4, 5]. Women with PCOS present with diverse features including psychological (anxiety, depression, body image) [6-8], reproductive (irregular menstrual cycles, hirsutism, infertility and pregnancy complications) [9] and metabolic features (insulin resistance (IR), metabolic syndrome, prediabetes, type 2 diabetes (DM2) and cardiovascular risk factors) [10, 11].

Diagnosis and treatment of PCOS remain controversial with challenges defining individual components within the diagnostic criteria, significant clinical heterogeneity generating a range of phenotypes with or without obesity, 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 [12]. This culminates in delayed diagnosis, poor diagnosis experience and dissatisfaction with care reported by women internationally [13]. 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 [14]. 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 National Health and Medical Research Council (NHMRC) is the single approving body for the guideline.

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 (Figure 1, Figure 2 and Appendix I-III). Guideline development groups and special interest groups/experts were nominated by the partner and collaborator organisations. The Australian Centre for Research Excellence in PCOS (CREPCOS), funded by the National Health and Medical Research Council (NHMRC), led and primarily funded the guideline development. In this endeavour, we 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.

Guideline development engagement and processes were extensive and followed best practice. 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 166 recommendations and practice points.

International best practice comprehensive methods for evidence review and guideline development were applied, aligned with the NHMRC and ESHRE 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 Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [15] 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. Special interest groups of world experts and affected women were formulated to review and provide feedback on the guideline, with subsequent refinement and guideline development group approval. The guideline was then appraised independently by independent evidence synthesis experts and submitted to NHMRC for consideration of approval.

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.

The guideline aims 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 Appraisal of Guidelines for Research and Evaluation (AGREE) II-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; and
- delivering an international translation program with in-depth evaluation.

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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; and
- 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

The guideline is 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 (i.e. POSAA)
- General public
- Students

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

Governance

A formal international governance process was established as outlined in Figure 1.

Figure 1: Governance

Evidence-based guideline for assessment and management of PCOS update project governance

CRE in PCOS Steering Committee / Monash University (Chair Rob Norman)

Project Board

Project Owner and Project Director CRE Co-Director of CRE (Prof Helena Teede)

Senior User – PCOS consumer; GP; representation from clinical specialties and allied health, Chair – International Strategic Advisors Group

Senior Suppliers – GDG Chairs; Guideline Development Lead; representatives from international organisations contributing at least 10% project funding (ESHRE X 2 and ASRM X 1 included)

International Strategic Advisors Group

(Chair Prof Bart Fauser)

CRE Co-Director (Prof Rob Norman), CALD Advisor, international consumer representative(s), Evidence-based guidelines lead, international society representatives including ESHRE and ASRM and geographical representation

Project Director
Prof Helena Teede

Project Manager
Linda Downes

Evidence Synthesis, Guideline Development and Translation lead
(Marie Misso)

GDG Chair
Screening, diagnostic assessment, risk assessment, lifestage and adolescents

GDG Chair
Lifestyle management and models of care

GDG Chair
Screening, diagnostic assessment and management of emotional wellbeing

GDG Chair
Medical treatment (i.e. metformin/OCP etc for features of PCOS)

GDG Chair
Screening, diagnostic assessment and management of infertility

Translation Committee
International representation

GDG members
International representation

GDG members
International representation

GDG members
International representation

GDG members
International representation

GDG members
International representation

Consumer advisory panel and General practice advisory panel
International representation

Definitions:

- - - - - ▶ Decision making path ────▶ Advisory and feedback path

Project Owner:	Person ultimately accountable for the success of the project and owns the business case. Has the final say in decision making process.
Senior User:	Represents end users of the delivered service. Chairs Project User Group if there is one.
Senior Supplier:	Senior representative of project's suppliers. There may be more than one.
Project Director:	Project Owner's eyes and ears on the job. Undertakes day to day management and decisions on behalf of the Project Owner.
Strategic Advisors Group:	Represents key stakeholders with valid interest, but not sufficiently central to project success to warrant a seat on the Project Board. Concerns and issues in this group have a direct conduit to the Project Board.

CONTENTS

Guideline Development Groups

Guideline development groups (GDGs) were formed based on skills (clinical and academic interests), expertise, geographical spread **and were nominated by partner or collaborator organisations**. The GDGs encompassed the broad range of clinical expertise involved in the care of women with PCOS as well as 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. Representatives from all continents engaged in the process, however given primary funding was from the Australian Government, diverse Australian organisations engaged.

Prioritised clinical questions

Prioritisation of guideline clinical questions was informed by an International Delphi exercise and by the multidisciplinary GDGs, with final questions (detailed in the methods section) addressed across:

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

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 recommend that 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. All recommendations and practice points need to be considered in the context of regional regulations. This guideline does 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

Methods used to develop this guideline align with international best practice, and follow comprehensive evidence-based guideline development processes and criteria including the Appraisal of Guidelines for REsearch & Evaluation (AGREE II), the Australian National Health and Medical Research Council (NHMRC) and ESHRE criteria. The steps are summarised in Figure 2, with details found in Chapter 6: Guideline Development Methods.

Figure 2: Guideline development process

(adapted from Misso and Teede, Knowledge Transfer: Practice, Types and Challenges 2012, Nova Publishers)

22 Revise and update
21 Evaluate
20 Implement
19 Disseminate[*]
18 Obtain endorsements
17 Public consultation
16 Finalise guideline content

1 Create multidisciplinary guideline development group including consumers
2 Scope & define topics[*]
3 Identify & prioritise clinical questions[*]
4 Define PICO[*]
5 **Identify existing guidelines to adapt**

Disseminate, implement, update
Steps 16 to 18
up to 6 months

Establish GDG and scope
Up to 6 months

If < 5yrs and high quality, skip to step 13 to adapt for local use

If > 5yrs and high quality, update

Formulate guidance
3 months

Systematic review of evidence
6 months to 1 year

15 Write narrative clinical context[*]
14 Reach consensus among GDG[*]
13 Grade recommendation(s)[*]
12 Draft recommendations[*]
11 Synthesise evidence

6 Systematically search for evidence
7 Identify & select evidence[*]
8 Appraise methodological quality of included studies
9 Extract data
10 Synthesise data

[*] Time points and tasks where prioritisation of engagement from GDG is required.

Community and consumer engagement

Extensive engagement and formative research on unmet needs of women with PCOS was a key driver for this work. Far-reaching engagement included focus groups and then surveys of over 1500 women with PCOS. We adopted the International Association for Public Participation (IPA), Public Participation Spectrum framework, in which consumer's capacity to participate was built and enhanced throughout the process. Consumers were engaged in all phases as active contributors within a distributed decision making environment, ensuring that the lived experiences of women with PCOS were prioritised. Consumer representatives were informed about the process of participation and at GDG meetings were present to embed consumer perspectives within the GRADE decision-making process. Consumers were empowered to ensure that all decisions optimised participation in care. Consumer organisations proactively participated in feedback and public consultation processes and have co-designed and will continue to guide and influence the implementation, translation and dissemination program.

CONTENTS

Funding

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 GDGs. ESHRE and ASRM formed special interest groups to provide feedback on the guideline during public consultation and all feedback was reviewed by the project board and GDGs, blinded by the organisation providing the feedback. All members of committees and GDGs publicly disclosed all relevant interests and these were reviewed at each meeting and considered when making recommendations.

Guideline translation

A comprehensive, international translation program will disseminate, translate and amplify the impact of the international evidence-based guideline on the assessment and management of PCOS (see Dissemination and implementation).

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; and
- 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 37 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.

Context statement on diagnosis: Prelude to the guideline

In the international evidence-based guideline for the assessment, diagnosis and management of PCOS, we endorse the Rotterdam diagnostic criteria in adults and recommend tighter criteria requiring both hyperandrogenism and irregular cycles, with ultrasound not indicated in adolescents, due to overlap with normal reproductive physiology. Exclusion of thyroid disease (thyroid stimulating hormone), hyperprolactinemia (prolactin), and non-classic congenital adrenal hyperplasia (17-hydroxy progesterone) is recommended with further evaluation recommended in those with amenorrhea and more severe clinical features including consideration of hypogonadotropic hypogonadism, Cushing's disease, or androgen producing tumours.

We acknowledge the challenges in defining specific diagnostic features, including around menarche and menopause, where diagnostic features naturally evolve.

The guideline aims to facilitate timely and appropriate diagnosis for women with PCOS, whilst avoiding over diagnosis, especially in adolescents. Specific recommendations of relevance here include:

- ultrasound is now not recommended in diagnosis in those within 8 years of menarche;
- young women "at risk" can be identified, where diagnosis is unclear, with follow-up reassessment
- diagnostic features are refined to limit overlap with those without PCOS to improve diagnostic accuracy

Resource use in diagnosis will also be reduced with a stronger focus on clinical features in diagnosis, more limited indications for ultrasound and simpler tests for biochemical hyperandrogenism.

We endorse the recommendation of the National Institutes of Health (NIH) evidence-based methodology workshop of PCOS 2012 that specific phenotypes should be reported explicitly in all research [16]. The natural history and clinical implications of the phenotypes remain unclear at this stage:

- Androgen excess + ovulatory dysfunction + polycystic ovarian morphology (Phenotype A)
- Androgen excess + ovulatory dysfunction (Phenotype B)
- Androgen excess + polycystic ovarian morphology (Phenotype C)
- Ovulatory dysfunction + polycystic ovarian morphology (Phenotype D)

We recognise that PCOS is an insulin resistant and metabolic disorder; tests for insulin resistance, however, lack accuracy and should not be incorporated into the diagnostic criteria for PCOS at this time.

We recognise PCOS has psychological features and poorer quality of life and whilst assessment is vital, these are not currently included in PCOS diagnostic criteria.

The value and optimal timing of assessment and diagnosis of PCOS should be discussed with the individual patient, taking into account psychosocial and cultural factors and patient preferences. Education is vitally important to women at the time of diagnosis, including reassurance about the potential for prevention of complications and about good general reproductive potential and family size, acknowledging some medical assistance may be required. As a general guiding principal, in partnering with women with PCOS in their diagnosis and care, self-empowerment is a priority and personal characteristics, preferences, culture and values should be considered when undertaking assessment, providing information or recommending intervention or treatments.

Interpreting the recommendations

Detailed methods for stakeholder engagement and guideline development can be found in Chapter six: Guideline development methods. In developing and interpreting the guideline, evidence has been evaluated alongside multidisciplinary health professional expertise and consumer perspectives throughout all stages from conceptualisation, prioritisation, development, review and translation. Variability in resources, health systems and access to health professionals, investigations and therapies were considered across international settings and consistent with best practice, adaptation may be required in translation. The process for adaptation is available at website link to be inserted here.

To assist in interpreting guideline recommendations, these are presented by **category, terms used, GRADE and quality of evidence. The category of the recommendations** includes evidence-based or consensus recommendations and have accompanying relevant clinical practice points as described in table 1. 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 also considered and if appropriate and there was consensus, the GDG made clinical consensus recommendations. Clinical practice points highlighted important clinical and implementation issues arising from GDG consideration of evidence-based or clinical consensus recommendations and from peer review.

Table 1: Categories of the PCOS guideline recommendations

EBR	Evidence based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CCR	Clinical Consensus Recommendations: In the absence of evidence, a clinical consensus recommendation has been made by the guideline development group.
CPP	Clinical Practice Points: Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations.

The recommendation terms include "should", "could" and "should not". These terms are informed by the nature of the recommendation (evidence or consensus), the GRADE framework and evidence quality and are independent descriptors reflecting the judgement of multidisciplinary GDG including consumers. They refer to overall interpretation and practical application of the recommendation, balancing benefits and harms. "Should" is used where benefits of the recommendation exceed harms, and where the recommendation can be trusted to guide practice. "Could" is used where either the quality of evidence was limited or the available studies demonstrate little clear advantage of one approach over another, or the balance of benefits to harm was unclear. "Should not" is used where there is either a lack of appropriate evidence, or the harms may outweigh the benefits.

The GRADE of the recommendation is determined by the GDG from structured consideration of the GRADE framework [15] including desirable effects, undesirable effects, balance of effects, resource requirements and cost effectiveness, equity, acceptability and 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.

Quality of the evidence is categorised (see table 2) according to:

- 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: key statistical data;
- and classification of the importance of the 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 [15] and was largely determined by the expert evidence synthesis team.

Table 2: Quality (certainty) of evidence categories (adapted from GRADE [15]):

High	⊕⊕⊕⊕	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	⊕⊕⊕◯	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	⊕⊕◯◯	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very Low	⊕◯◯◯	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE note that quality of evidence is a continuum; any discrete categorisation involves a degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations [15].

The recommendations summary table below applies the **category, descriptive terms, GRADE of the recommendations and the quality of the evidence**. Within the body of the guideline, we outline the clinical need for the question, the clinical question, the evidence summary, the recommendation and practice points and a summary of the justification developed by the GDG and modified by extensive international peer review. The comprehensive evidence reviews, profiles and GRADE frameworks supporting each recommendation, can be found in the supplementary Technical report.

Recommendations Summary

Table notes:

The recommendation number reflects the corresponding evidence section.

Clinical consensus recommendations (CCR) and clinical practice points (CCP) do not have a 'GRADE' rating.

NO.	CATE- GORY	RECOMMENDATION	QUALITY## AND GRADE
1		Screening, diagnostic assessment, risk assessment and life-stage	
1.1		Irregular cycles and ovulatory dysfunction	
1.1.1	CCR	Irregular menstrual cycles are defined as: • normal in the first year post menarche as part of the pubertal transition • > 1 to < 3 years post menarche: < 21 or > 45 days • > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year • > 1 year post menarche > 90 days for any one cycle • Primary amenorrhea by age 15 or > 3 years post thelarche (breast development) When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.	❖❖❖❖
1.1.2	CCR	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.	❖❖❖❖
1.1.3	CPP	For adolescents who have features of PCOS but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence.	
1.1.4	CPP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	
1.2		Biochemical hyperandrogenism	
1.2.1	EBR	Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.	❖❖❖❖ ⊕⊕○○
1.2.2	EBR	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.	❖❖❖ ⊕⊕○○

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
1.2.3	EBR	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.	❖❖❖ ⊕⊕○○
1.2.4	CCR	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.	❖❖❖❖
1.2.5	CPP	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.	
1.2.6	CPP	Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal is recommended for three months or longer before measurement, and contraception management with a non-hormonal alternative is needed during this time.	
1.2.7	CPP	Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent.	
1.2.8	CPP	Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values are ideally based on levels from a well phenotyped healthy control population or by cluster analysis of a large general population considering age and pubertal specific stages.	
1.2.9	CPP	Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to 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	CCR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, alopecia and hirsutism and, in adolescents, severe acne and hirsutism	❖❖❖❖
1.3.2	CCR	Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. Reported unwanted excess hair growth and/or alopecia should be considered important, regardless of apparent clinical severity.	❖❖❖❖
1.3.3	CCR	Standardised visual scales are preferred when assessing hirsutism, such as the modified Ferriman Gallwey score (mFG) with a level ≥ 4 - 6 indicating hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment. (See recommendations on ethnic variation)	❖❖❖❖
1.3.4	CCR	The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.	❖❖❖❖

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
1.3.5	CPP	There are no universally accepted visual assessments for evaluating acne.	
1.3.6	CPP	The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism and the severity of hirsutism varies by ethnicity.	
1.3.7	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 need to be considered in pathological hirsutism, with terminal hairs clinically growing > 5mm in length if untreated, varying in shape and texture and generally being pigmented.	
1.4		Ultrasound and polycystic ovarian morphology (PCOM)	
1.4.1	CCR	Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage.	❖❖❖❖
1.4.2	CCR	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	CCR	The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.	❖❖❖❖
1.4.4	CCR	Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be on either ovary, a follicle number per ovary of > 20 and/or an ovarian volume ≥ 10ml, ensuring no corpora lutea, cysts or dominant follicles are present.	❖❖❖
1.4.5	CPP	If using older technology, the threshold for PCOM could be an ovarian volume ≥ 10ml on either ovary.	
1.4.6	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.	
1.4.7	CPP	In transabdominal ultrasound reporting is best focused on ovarian volume with a threshold of ≥ 10ml, given the difficulty of reliably assessing follicle number with this approach.	
1.4.8	CPP	Clear protocols are recommended for reporting follicle number per ovary and ovarian volume on ultrasound. Recommended minimum reporting standards include: • last menstrual period • transducer bandwidth frequency • approach/route assessed • total follicle number per ovary measuring 2-9mm • three dimensions and volume of each ovary • reporting of endometrial thickness and appearance is preferred – 3-layer endometrial assessment may be useful to screen for endometrial pathology • other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles ≥ equal 10mm	
1.4.9	CPP	There is a need for training in careful and meticulous follicle counting per ovary, to improve reporting.	

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
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	There is emerging evidence that 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 assays will be more accurate in the detection of PCOM.	
1.6		Ethnic variation	
1.6.1	CCR	Health professionals should consider ethnic variation in the presentation and manifestations of PCOS, including: • a relatively mild phenotype in Caucasians • higher body mass index (BMI) in Caucasian women, especially in North America and Australia • more severe hirsutism in Middle Eastern, Hispanic and Mediterranean women • increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians • lower BMI and milder hirsutism in East Asians • higher BMI and metabolic features in Africans	❖❖❖❖
1.7		Menopause life stage	
1.7.1	CCR	Postmenopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism.	❖❖❖
1.7.2	CCR	A diagnosis of PCOS postmenopause could be considered if there is a past diagnosis of PCOS, 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, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.	
1.8		Cardiovascular disease risk (CVD)	
1.8.1	CCR	All those with PCOS should be offered regular monitoring for weight changes and excess weight, in consultation with and where acceptable to the individual woman. Monitoring could be at each visit or at a minimum 6-12 monthly, with frequency planned and agreed between the health professional and the individual (see 3.5).	❖❖❖❖
1.8.2	CCR	Weight, height and ideally waist circumference should be measured and BMI calculated with the following considered: • BMI categories and waist circumference should follow World Health Organisation guidelines, also noting ethnic and adolescent ranges. • Consideration should be given for Asian and high-risk ethnic groups including recommended monitoring of waist circumference.	❖❖❖❖
1.8.3	CCR	All women with PCOS should be assessed for cardiovascular risk factors and global CVD risk	❖❖❖❖

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
1.8.4	CCR	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	CCR	Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (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	CCR	All women with PCOS should have blood pressure measured annually, or more frequently based on global CVD risk.	❖❖❖❖
1.8.7	CPP	Health professionals need to be aware that CVD risk in women with PCOS remains unclear pending high quality studies, however prevalence of CVD risk factors is increased, warranting consideration of screening.	
1.8.8	CPP	Consideration needs to be given to the significant differences in CVD risk across ethnicities (see 1.6.1) when determining frequency of risk assessment.	
1.9		Gestational diabetes, impaired glucose tolerance and type 2 diabetes	
1.9.1	CCR	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	❖❖❖❖
1.9.2	CCR	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	❖❖❖❖
1.9.3	CCR	An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c should be performed to assess glycaemic status. In high-risk women with PCOS (including a BMI > 25kg/m^2 or in Asians > 23kg/m^2, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of diabetes mellitus type 2, hypertension or high-risk ethnicity), an OGTT is recommended.	❖❖❖❖
1.9.4	CCR	A 75-g OGTT should be offered in all women with PCOS preconception when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation.	❖❖❖❖
1.10		Obstructive sleep apnea (OSA)	
1.10.1	CCR	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.	❖❖❖❖

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
1.10.2	CCR	A simple screening questionnaire, preferably the Berlin tool, could be applied and if positive, referral to a specialist considered.	❖❖❖
1.10.3	CPP	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, consideration can be given to be referral to a specialist centre for further evaluation.	

1.11 Endometrial cancer

NO.	CATE-GORY	RECOMMENDATION	QUALITY AND GRADE
1.11.1	CCR	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.	❖❖❖
1.11.2	CPP	Health professionals require 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 risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. However, routine ultrasound screening of endometrial thickness in PCOS is not recommended.	
1.11.3	CPP	Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.	

2 Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

2.1 Quality of life

NO.	CATE-GORY	RECOMMENDATION	QUALITY AND GRADE
2.1.1	CCR	Health professionals and women should be aware of the adverse impact of PCOS on quality of life.	❖❖❖❖
2.1.2	CCR	Health professionals should capture and consider perceptions of symptoms, impact on quality of life and personal priorities for care to improve patient outcomes.	❖❖❖❖
2.1.3	CPP	The PCOS quality of life tool (PCOSQ), or the modified PCOSQ, may be useful clinically to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns.	

2.2 Depressive and anxiety symptoms, screening and treatment

NO.	CATE-GORY	RECOMMENDATION	QUALITY AND GRADE
2.2.1	CCR	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.	❖❖❖❖
2.2.2	CCR	Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.	❖❖❖❖

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
2.2.3	CCR	If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered in PCOS, informed by regional clinical practice guidelines.	❖❖❖❖
2.2.4	CPP	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.	
2.2.5	CPP	Assessment of anxiety and or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened according to regional guidelines, or by 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 for anxiety and depression is offered in PCOS, the following need consideration: - 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 need to be informed by clinical regional practice guidelines. - Use of agents that exacerbate PCOS symptoms, including weight gain, need careful consideration.	
2.2.7	CPP	Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, as they may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	
2.3		Psychosexual function	
2.3.1	CCR	All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider exploring how features of PCOS, including hirsutism and body image, impact on sex life and relationships in PCOS.	❖❖❖❖
2.3.2	CCR	If psychosexual dysfunction is suspected, tools such as the Female Sexual Function Index can be considered.	❖❖❖❖

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
2.4		Body image	
2.4.1	CCR	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 according to regional guidelines or by 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

NO.	CATE-GORY	RECOMMENDATION	QUALITY AND GRADE
2.5		Eating disorders and disordered eating	
2.5.1	CCR	All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS.	❖❖
2.5.2	CCR	If eating disorders and disordered eating are suspected, further assessment, referral and treatment, including psychological therapy, could be offered by appropriately trained health professionals, informed by regional clinical practice guidelines.	❖❖
2.5.3	CPP	Eating disorders and disordered eating can be screened using the following stepped approach.	

Step 1: The SCOFF (Sick, Control, One stone, Fat, Food) 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.

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
2.6		Information resources, models of care, cultural and linguistic considerations	
2.6.1	CCR	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.	❖❖❖❖
2.6.2	CCR	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	CCR	PCOS information should be comprehensive, evidence-based and inclusive of the biopsychosocial dimensions of PCOS across the life-span.	❖❖❖❖
2.6.4	CCR	Women's needs, communication preferences, beliefs and culture should be considered and addressed through provision of culturally and linguistically appropriate co-designed resources and care.	❖❖❖❖
2.6.5	CCR	Interdisciplinary care needs to be considered for those with PCOS where appropriate and available. Primary care is generally well placed to diagnose, screen and coordinate interdisciplinary care.	❖❖❖❖
2.6.6	CCR	Care needs to be person centred, address women's priorities and be provided in partnership with those with PCOS and where appropriate, their families.	❖❖❖❖
2.6.7	CPP	Guideline dissemination and translation including multimodal education tools and resources is important, with consultation and engagement with stakeholders internationally.	
3		Lifestyle	
3.1		Effectiveness of lifestyle interventions	
3.1.1	CCR	Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to achieve and/or maintain healthy weight and to optimise hormonal outcomes, general health, and quality of life across the life course.	❖❖❖❖
3.1.2	EBR	Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural strategies) should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity and insulin resistance.	❖❖❖ ⊕⊕○○
3.1.3	CPP	Achievable goals such as 5% to 10% weight loss in those with excess weight 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.	
3.1.4	CPP	SMART (Specific Measurable, Achievable, Realistic and Timely), goal setting and self-monitoring can enable achievement of realistic lifestyle goals.	
3.1.5	CPP	Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, need consideration and management to optimise engagement and adherence to lifestyle interventions.	

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
3.1.6	CPP	Health professional interactions around healthy lifestyle, including diet and exercise, need to be respectful, patient-centred and to value women's individualised healthy lifestyle preferences and cultural, socioeconomic and ethnic differences. Health professionals need to also consider personal sensitivities, marginalisation and potential weight-related stigma.	
3.1.7	CPP	Adolescent and ethnic-specific BMI and waist circumference categories need to be considered when optimising lifestyle and weight.	
3.1.8	CPP	Healthy lifestyle may contribute to health and quality of life benefits in the absence of weight loss.	
3.1.9	CPP	Healthy lifestyle and optimal weight management appears equally effective in PCOS as in the general population and is the joint responsibility of all health professionals, partnering with women with PCOS. Where complex issues arise, referral to suitably trained allied health professionals needs to be considered.	
3.1.10	CPP	Ethnic groups with PCOS who are at high cardiometabolic risk as per 1.6.1 require greater consideration in terms of healthy lifestyle and lifestyle intervention.	
3.2		Behavioural strategies	
3.2.1	CCR	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.	❖❖❖❖
3.2.2	CPP	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.	
3.3		Dietary intervention	
3.3.1	CCR	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.	❖❖❖❖
3.3.2	CCR	General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations.	❖❖❖❖
3.3.3	CPP	To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels.	
3.3.4	CPP	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.	
3.3.5	CPP	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.	

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
3.4		Exercise intervention	
3.4.1	CCR	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-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.	❖❖❖
3.4.2	CCR	Health professionals should encourage and advise the following for modest weight-loss, prevention of weight-regain and greater health benefits: • 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 involving major muscle groups on 2 non-consecutive days/ week • minimised sedentary, screen 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. Daily, 10000 steps is ideal, including activities of daily living and 30 minutes of structured physical activity or around 3000 steps. Structuring of recommended activities need to consider women's and family routines as well as cultural preferences.	
3.4.4	CPP	Realistic physical activity SMART (Specific, Measureable, Achievable, Relevant, Time limited) goals could include 10 minute bouts, progressively increasing physical activity 5% weekly, up to and above recommendations.	
3.4.5	CPP	Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be used as an adjunct to support and promote active lifestyles and minimise sedentary behaviours.	
3.5		Obesity and weight assessment	
3.5.1	CCR	Health professionals and women should be aware that women with PCOS have a higher prevalence of weight gain and obesity, presenting significant concerns for women, impacting on health and emotional wellbeing, with a clear need for prevention.	❖❖❖
3.5.2	CCR	All those with PCOS should be offered regular monitoring for weight changes and excess weight as per 1.8.1 and 1.8.2.	❖❖❖❖

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
3.5.3	CPP	When assessing weight, related stigma, negative body image and/or low self-esteem need to be considered and assessment needs to be respectful and considerate. Beforehand, explanations on the purpose and how the information will be used and the opportunity for questions and preferences need to be provided, permission sought and scales and tape measures adequate. Implications of results need to be explained and where this impacts on emotional wellbeing, support provided.	
3.5.4	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	When prescribing pharmacological therapy in PCOS, benefits, adverse effects and contraindications in PCOS and general populations need to be considered and discussed before commencement.	
4.1.3	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 need to inform women and discuss the evidence, possible concerns and side effects of treatment.	
4.1.4	CPP	Holistic approaches are required and pharmacological therapy in PCOS needs to be considered alongside education, lifestyle and other options including cosmetic therapy and counselling.	
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/or 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/or 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 in adults and adolescents with PCOS and practice should be informed by general population guidelines.	❖❖❖ ⊕⊕◯◯

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
4.2.5	CCR	The 35 microgram ethinyloestradiol plus cyproterone acetate preparations should not be considered first line in PCOS as per general population guidelines, due to adverse effects including venous thromboembolic risks.	❖
4.2.6	CPP	When prescribing COCPs in adults and adolescents with PCOS: • various COCP preparations have similar efficacy in treating hirsutism • the lowest effective estrogen doses (such as 20-30 micrograms of ethinyloestradiol or equivalent), and natural estrogen preparations need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability • the generally limited evidence on effects of COCPs in PCOS needs to be appreciated with practice informed by general population guidelines (WHO Guidelines) • the relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualised discussion • PCOS specific risk factors such as high BMI, hyperlipidemia and hypertension need to 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 where COCP and lifestyle changes do not achieve desired goals.	❖❖❖❖ ⊕⊕○○
4.3.2	EBR	In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI ≥ 25kg/m2 where COCP and lifestyle changes do not achieve desired goals.	❖❖❖❖ ⊕⊕○○
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 considered in PCOS to treat hirsutism, after six months or more of COCP and cosmetic therapy have failed to adequately improve symptoms.	❖❖ ⊕⊕○○
4.3.5	CCR	In combination with the COCP, antiandrogens could be considered for the treatment of androgen-related alopecia 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.	❖❖❖ ⊕⊕○○
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.	❖❖❖ ⊕⊕○○

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
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.	❖❖❖ ⊕⊕○○
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 (see 1.6.1).	
4.4.5	CPP	Where metformin is prescribed the following need to be considered: ● adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting, need to be the subject of individualised discussion ● starting at a low dose, with 500mg increments 1-2 weekly and extended release preparations may minimise side effects ● metformin use appears safe long-term, based on use in other populations, however ongoing requirement needs to be considered and use may be associated with low vitamin B12 levels ● use is generally off label and health professionals need to inform women and discuss the evidence, possible concerns and side effects.	
4.5		Anti-obesity pharmacological agents	
4.5.1	CCR	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	For anti-obesity medications, cost, contraindications, side effects, variable availability and regulatory status need to be considered and pregnancy needs to be avoided whilst taking these medications.	
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 androgen-related alopecia.	❖❖❖ ⊕○○○
4.6.2	CPP	Specific types or doses of antiandrogens cannot currently be recommended with inadequate evidence in PCOS.	
4.7		Inositol	
4.7.1	EBR	Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research.	❖ ⊕○○○
4.7.2	CPP	Women taking inositol and other complementary therapies are encouraged to advise their health professional.	

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
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 need to 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	CCR	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	CCR	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 clomiphene citrate is off label in many countries. Where off label use of ovulation induction agents is allowed, health professionals need to inform women and discuss the evidence, possible concerns and side effects.	
5.2.2	CPP	Pregnancy needs to be excluded prior to ovulation induction.	
5.2.3	CPP	Unsuccessful, prolonged use of ovulation induction agents needs to 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 or cost is prohibitive, health professionals can use other ovulation induction agents.	
5.3.3	CPP	Health professionals and women need to be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate.	

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
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 and pregnancy 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 is ≥ 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 and pregnancy 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	
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.	❖❖❖ ⊕⊕○○
5.5.2	EBR	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.	❖❖❖ ⊕⊕○○
5.5.3	EBR	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.	❖❖❖❖ ⊕⊕⊕○
5.5.4	EBR	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.	❖❖❖ ⊕⊕⊕○
5.5.5	EBR	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.	❖❖❖❖ ⊕⊕⊕○

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE
5.5.6	CPP	Where gonadotrophins are prescribed, considerations include: ● 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 optimise monofollicular development ● risk and implications of potential multiple pregnancy	
5.5.7	CPP	Gonadotrophin induced ovulation is only triggered when there are fewer than three mature follicles and needs to be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.	
5.6		Anti-obesity agents	
5.6.1	CCR	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.	❖
5.7		Laparoscopic surgery	
5.7.1	EBR	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.	❖❖❖ ⊕⊕○○
5.7.2	CCR	Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.	❖❖❖
5.7.3	CPP	Risks need to be explained to all women with PCOS considering laparoscopic ovarian surgery.	
5.7.4	CPP	Where laparoscopic ovarian surgery is to be recommended, the following need to 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.	

NO.	CATE-GORY	RECOMMENDATION	QUALITY## AND GRADE

5.8   Bariatric surgery

| 5.8.1 | CCR | Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having a 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 need to 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 need to 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 | CCR | In the absence of an absolute indication for IVF ± intracytoplasmic sperm injection (ICSI), women with PCOS and anovulatory infertility could be offered IVF as third line therapy where 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 need to be counselled prior to starting treatment including on: | |

- availability, cost and convenience
- increased risk of ovarian hyperstimulation syndrome
- options to reduce the risk of ovarian hyperstimulation.

| 5.9.4 | CCR | 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 follicle stimulating hormone (FSH) preparations. | ❖❖❖ |

| 5.9.5 | CCR | 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. | ❖❖❖ |

NO.	CATE-GORY	RECOMMENDATION	QUALITY[##] AND GRADE
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 is best 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 gonadotropin-releasing hormone (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 in women with PCOS, consideration needs to be given to an elective freeze of all embryos.	
5.9.10	EBR	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 GnRH agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS.	❖❖❖ ⊕⊕○○
5.9.11	CCR	In a GnRH 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 GnRH 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 (see 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 GnRH antagonist protocol to reduce risk of ovarian hyperstimulation syndrome (see above for metformin therapy considerations).	
5.9.13	CPP	The term in vitro maturation (IVM) treatment cycle is 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).	
5.9.14	CCR	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.	❖❖❖

[#] Off-label' prescribing occurs when a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the approved product information document for that drug by the regulatory body. Prescribing off label is often unavoidable and common and does not mean that the regulatory body has rejected the indication, more commonly there has not been a submission to request evaluation of the indication or that patient group for any given drug.

Chapter One

Screening, diagnostic assessment, risk assessment and life-stage

Diagnosis and treatment of polycystic ovary syndrome (PCOS) remain controversial with challenges defining individual components within the diagnostic criteria and significant clinical heterogeneity across the phenotypes, which is further varied by ethnic differences and changes in clinical features across the life course. The guideline addresses issues for all those affected with PCOS across the lifespan. Where recommendations differ by life stages or body mass index (BMI) status, this is clarified.

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 reflecting ovulatory dysfunction, as reflected in the Rotterdam criteria. Ovulatory dysfunction can occur with regular cycles. When anovulation needs to be confirmed, hormonal assessment is relevant if 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. Indeed, the greatest controversy in this diagnostic criteria is during the pubertal transition. 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 with potential concerns about over-diagnosis. Likewise, women internationally report under diagnosis and delayed diagnosis, dissatisfaction in diagnosis experience, with related anxiety and limited opportunity for education, prevention of complications and treatment of symptoms [13]. Young women may also be commenced on the combined oral contraceptive pill (COCP) 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 supplementary 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 [17]. The average adult menstrual cycle is 28 days, ranging from 24 - 35 days [18]. The majority of irregular cycles may be ovulatory two years post-menarche [18-21], with 80% of cycles being within 21 - 45 days [19, 21-23]. By the third post-menarcheal year, 95% of cycles fall into this range, however cycles can remain irregular until the fifth year [24, 25]. Regular ovulatory cycle onset is also related to age at menarche [26]. In those who begin menses before 12 years, between 12 - 13 years, and after 13 years of age, 50% of cycles are ovulatory by one year, three years, and 4.5 years, respectively [26]. At age 15, more than 50% of girls who are oligo-amenorrheic remain so at age 18 [27]. 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. With increasing gynaecologic age, fewer females experience cycles exceeding 45 days [28].

It is recognised that irregular menstrual cycles and other features of PCOS can overlap with those observed in the normal pubertal transition and it is important to define where these features are more likely to reflect PCOS. Overall the greatest controversy here relates to the past approaches of identifying the 95th centile of cycle duration as abnormal. If this percentile is used to define a single diagnostic feature (e.g. menstrual cycles) in a condition with a prevalence of around 10%, this is a simplistic and poorly informed approach. In fields such as diabetes and other conditions where diagnostic features represent a continuum, considerable refinement has occurred with alignment with other clinical features and health outcomes. This approach was applied here and the body of literature on normal menstrual cycles reviewed to identify the 85th to 90th percentile, pending more appropriate cluster analysis and longitudinal follow-up data.
This approach was approved by the Paediatric guideline development group (GDG) panel (Appendix III).

Recommendations

1.1.1	CCR	Irregular menstrual cycles are defined as:	❖❖❖❖

- normal in the first year post menarche as part of the pubertal transition
- > 1 to < 3 years post menarche: < 21 or > 45 days
- > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year
- > 1 year post menarche > 90 days for any one cycle
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)

When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.

1.1.2	CCR	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.	❖❖❖❖
1.1.3	CPP	For adolescents who have features of PCOS but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence.	
1.1.4	CPP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	

Justification

Whilst limited 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 GDG and the paediatric endocrine and gynecology expert panel from across the GDGs, carefully considered the available literature, the international feedback and the potential for both over diagnosis and delayed diagnosis when assessing this diagnostic feature in PCOS. They also considered 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 highlighting the need to identify those "at risk" and to emphasise reassessment. It is recognised these recommendations will change practice and deviate from past guidelines stipulating > 45 days for all adolescents. Here more specific cut-offs were provided aligned with gynaecological maturity.

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, alopecia and acne) and biochemical hyperandrogenism. Both features of hyperandrogenism 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 Vermeulen 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. Moving forward 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 definitive recommendations on the optimal hormone and method to measure biochemical diagnosis hyperandrogenism in PCOS, although data indicates that, as a single measure, free testosterone measures provide the most optimal accuracy to detect biochemical hyperandrogenism followed, in no specific order by total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione.

Summary of narrative review evidence

Given the limited evidence identified on systematic review, a narrative review was completed (see supplementary Technical Report). In summary, with few exceptions, 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 DHEAS 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. DHEAS 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. Current studies focus on different assays in women already diagnosed with PCOS. This approach has inherent bias as the diagnosis includes hyperandrogenism and further studies are needed to explore relationships between androgen levels and the various immediate and long term clinical features of PCOS.

Recommendations

1.2.1	EBR	Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS.	❖❖❖❖ ⊕⊕○○
1.2.2	EBR	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.	❖❖❖ ⊕⊕○○
1.2.3	EBR	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.	❖❖❖ ⊕⊕○○
1.2.4	CCR	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.	❖❖❖❖
1.2.5	CPP	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.	
1.2.6	CPP	Where assessment of biochemical hyperandrogenism is important in women on hormonal contraception, drug withdrawal is recommended for three months or longer before measurement, and contraception management with a non-hormonal alternative is needed during this time.	
1.2.7	CPP	Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent.	
1.2.8	CPP	Interpretation of androgen levels needs to be guided by the reference ranges of the laboratory used, acknowledging that ranges for different methods and laboratories vary widely. Normal values are ideally based on levels from a well phenotyped healthy control population or by cluster analysis of a large general population considering age and pubertal specific stages.	
1.2.9	CPP	Where androgen levels are markedly above laboratory reference ranges, other causes of biochemical hyperandrogenism need to 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.	

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%. Laboratory calculated values are recommended. High quality assays provide a more accurate diagnosis and the additional associated cost was deemed important and justified after considering all elements of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. Access issues were also acknowledged. 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 provided by the guideline is likely to be valued.

CONTENTS

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 androgen-related alopecia. The interrelationships of these clinical features remains unclear, varies by ethnicity, and requires 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 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 (mFG) [41, 42] to assess terminal hairs (hairs that would grow > 5mm in length if left unmolested, are usually pigmented, and are medullated). mFG 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].

Comedonal acne is common in adolescent girls, moderate or severe comedonal acne (i.e. 10 or more facial lesions) in early puberty or moderate inflammatory acne through the perimenarcheal years is uncommon (< 5% prevalence) [44, 45]. There are no studies evaluating alopecia in adolescents. For these reasons, mild acne and alopecia are not recommended as considerations in the diagnostic criteria for adolescents.

Defining 'abnormal' in hirsutism is controversial. The mFG cut-off score can be based on percentile with a score > 6 - 8 consistent with the 95th percentile of unselected women [41, 43, 46]). It can also be defined by a lower percentile 85 - 90th percentile or by cluster analysis where the score is analysed in relation to other features of PCOS. These approaches suggest that an mFG scores of > 3 in White and Black women [47], and > 5 in Mongoloid Asian (Han Chinese) women [48] represents true abnormality. As outlined above under irregular menstrual cycles, a simplistic cut off at the 95th centile is not appropriate and for this reason the GDG, after reviewing all available evidence, recommended the cut offs of ≥ 4 - 6 on mFG.

The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism and the severity of hirsutism varies by ethnicity. Overall, >50% of women with mFG scores of 3-5 have elevated androgens and/or PCOS [49], and >70-90% of women with scores >5 [42, 46]. Referral bias needs to be considered in reported populations [50, 51]. Hirsutism adversely impacts quality of life [52] and most women readily treat hirsutism complicating assessment, hence health professionals should be prepared to assess any woman who complains of excess hair [49, 53].

Acne is associated with biochemical hyperandrogenism [54, 55], yet the predictive value of acne alone is unclear [40, 54] and there is no accepted assessment tool [40]. Most studies of women with alopecia reveal a relatively low prevalence of hyperandrogenemia [40, 56] and the predictive value of alopecia alone remains unclear, in part as there are many causes that can contribute to alopecia aside from hyperandrogenism. Hair loss on the scalp is usually assessed visually using the Ludwig scale [40].

Recommendations

1.3.1	CCR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, alopecia and hirsutism and, in adolescents, severe acne and hirsutism.	❖❖❖❖
1.3.2	CCR	Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. Reported unwanted excess hair growth and/or alopecia should be considered important, regardless of apparent clinical severity.	❖❖❖❖
1.3.3	CCR	Standardised visual scales are preferred when assessing hirsutism, such as the modified Ferriman Gallwey score (mFG) with a level ≥ 4- 6 indicating hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment. (See recommendations on ethnic variation).	❖❖❖❖
1.3.4	CCR	The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.	❖❖❖❖
1.3.5	CPP	There are no universally accepted visual assessments for evaluating acne.	
1.3.6	CPP	The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism and the severity of hirsutism varies by ethnicity.	
1.3.7	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 need to be considered in pathological hirsutism, with terminal hairs clinically growing > 5mm in length if untreated, varying in shape and texture and generally being pigmented.	

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 mFG score for facial and terminal hair growth is the principal instrument for clinical assessment of hirsutism. 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

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 [57]. This introduced arguably milder phenotypes into PCOS with limited data on natural history, prompting calls for phenotype identification and more research [16]. 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 original criteria [58]. 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. Independent of diagnosis, if clinically indicated, ultrasound is useful to screen for other pathology. This clinical question was prioritised, with recognition that a reproducible technique and standard reporting to reliably estimate follicle number per ovary 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, 59-71]. Two of the fifteen studies were in adolescents [64, 71]. 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 per ovary. Other key challenges with the literature in this area included the variable populations (with and without women with PCOS) used to define cut off values and the use of the 95th percentile cut offs to define abnormality. 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 [72]. 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 [73-77]. 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 postmenarche, PCOM is common and not associated with reproductive dysfunction [58, 78]. Therefore, adult PCOM criteria are likely inaccurate for ultrasound diagnosis of PCOS in adolescence with substantive overlap between follicle numbers per ovary in normal adolescents and those with other features of PCOS.

Recommendations

1.4.1	CCR	Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage.	❖❖❖❖
1.4.2	CCR	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	CCR	The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.	❖❖❖❖
1.4.4	CCR	Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be on either ovary, a follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10ml, ensuring no corpora lutea, cysts or dominant follicles are present.	❖❖❖
1.4.5	CPP	If using older technology, the threshold for PCOM could be an ovarian volume ≥ 10ml on either ovary.	
1.4.6	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.	
1.4.7	CPP	In transabdominal ultrasound reporting is best focussed on ovarian volume with a threshold of ≥ 10ml, given the difficulty of reliably assessing follicle number with this approach.	

1.4.8	CPP	Clear protocols are recommended for reporting follicle number per ovary and ovarian volume on ultrasound. Recommended minimum reporting standards include:

- last menstrual period
- transducer bandwidth frequency
- approach/route assessed
- total follicle number per ovary measuring 2-9mm
- three dimensions and volume of each ovary
- Reporting of endometrial thickness and appearance is preferred – 3-layer endometrial assessment may be useful to screen for endometrial pathology
- other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles ≥ equal 10mm

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

Justification

It was recognised that the data in young women with a gynaecological age of < 8 years (< 8 years after menarche) is inadequate, that peak ovarian maturity has not yet been reached and that defining PCOM at this life stage is not currently possible with the high incidence of multi-follicular ovaries. There was recognition of the risk of over diagnosis in adolescents if ultrasound criteria were included in this age group. Limitations in performing transvaginal ultrasounds in those not yet sexually active was also recognised. These factors were deemed to make the use of ultrasound inappropriate for diagnosis of PCOS in those with a gynaecological age < 8 years at this time. Ultrasound may be indicated for other reasons at this life stage, hence 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 FNPO as the key diagnostic criteria for PCOM in adults was reconfirmed by the updated evidence review and expert deliberation. 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 significant advances were noted since the original Rotterdam recommendations. All relevant limitations of the evidence were considered by the GDG and co-opted experts, especially the limited relevance of the 95th centile cut offs in determining abnormal FNPO. These factors resulted in a FNPO recommendation between the original Rotterdam and more recent Androgen Excess and PCOS Society (AEPCOS) recommendations. These recommendations also 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. Importantly, they also limit use and costs of a somewhat invasive test, where it is not appropriate.

1.5 Anti-Müllerian Hormone (AMH)

Is Anti-Müllerian Hormone effective for diagnosis of PCOS?
Is Anti-Müllerian Hormone effective for diagnosis of PCOM?

Clinical need for the questions

Given the challenges with ultrasound in diagnosis of PCOS, including in the years after menarche, serum Anti-Müllerian Hormone (AMH) has been proposed as an alternative marker of ovulatory dysfunction in PCOS. AMH is a polypeptide of the transforming growth factor beta (TGF-β) 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 [79, 80]. 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 [62, 65, 81-107]. One of these was a systematic review [88] 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 [85, 86, 92, 98]; and one for PCOM only [103]. Six studies included adolescents and one of these addressed PCOS and PCOM [86]. The remaining 21 studies included adult participants for diagnosis of PCOS, with three addressing PCOS and PCOM [85, 92, 98], and the remaining 18 addressing PCOS [62, 65, 81-84, 87, 91, 93-97, 99, 102, 104, 105, 107]. In adolescents, one was in overweight and obese participants [89] and one had unclear BMI [106]. In adults, one [82] included lean and obese participants; and five [62, 81, 85, 91, 107] 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

| 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 | There is emerging evidence that 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 assays will be more accurate in the detection of PCOM. | |

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 [4] 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 [4, 108]. 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 in the cut off scores, with Middle Eastern and South Asian women having higher cut off scores for 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 [109]. 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

1.6.1	CCR	Health professionals should consider ethnic variation in the presentation and manifestations of PCOS, including:

- a relatively mild phenotype in Caucasians
- higher BMI in Caucasian women, especially in North America and Australia
- more severe hirsutism in Middle Eastern, Hispanic and Mediterranean women
- increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians
- lower BMI and milder hirsutism in East Asians
- higher BMI and metabolic features in Africans

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. In response to peer review feedback specific ethnic differences have been noted in the guideline to inform practice.

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 generally around the age of 51 years. The diagnosis of PCOS by Rotterdam criteria requires two of three criteria in women, including oligo- and/or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries by ultrasound [57]. However, these three criteria for diagnosis change naturally with age impacting on phenotype and presenting challenges in diagnosis. Overall it is acknowledged that there is inadequate evidence of the natural history of PCOS and the concept of whether PCOS resolves and/ or persists remains unclear pending better longitudinal studies. 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 [110-112]. 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 [60]. Androgens decline with age in women generally including those with PCOS [113-115] in longitudinal and cross-sectional studies [116]. Testosterone free androgen index (FAI), and calculated free testosterone are higher in women with PCOS aged 18–44 years compared to controls [116]. 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 [117] and PCOS has been independently associated with later menopause [118]. 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 [119] but little is known about acne and alopecia in these women. Postmenopausal women with PCOS have higher 17-hydroxyprogesterone, androstenedione, DHEAS, total Testosterone and FAI than women without PCOS [116, 119, 120]. However, androgen assays are unreliable in women especially with the lower levels generally observed postmenopause [121]. Postmenopausal women with PCOS have abnormal glucose metabolism [122] and higher triglycerides than controls [119]. 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] have been considered, as have insulin resistance [125].

Recommendations

1.7.1	CCR	Postmenopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism.	❖❖❖
1.7.2	CCR	A diagnosis of PCOS postmenopause could be considered if there is a past diagnosis of PCOS, 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, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.	

Justification

A 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 postmenopausal PCOS phenotypes and persistence of PCOS postmenopause. 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 also have adverse consequences (psychological etc), whilst making a diagnosis may prompt risk recognition and screening such as for glycaemic abnormalities.

CONTENTS

1.8 Cardiovascular disease

Are women with PCOS at increased risk for cardiovascular disease?

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

Clinical need for the questions

Cardiovascular disease (CVD) remains one of the leading causes of death in women and any condition further increasing CVD risk, will have significant public health impact. CVD primarily affects postmenopausal women in the later decades of life, however CVD development and risk factors are present in early adulthood. 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 and that cardiovascular health overall needs to be considered, 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 (6) and prospective cohort (1) 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, I^2 14%; CVD-related death (2 studies, 779 participants, I^2 0%); and coronary artery/heart disease (2 studies, 2152 participants, I^2 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. Furthermore the relatively young age of women included in most studies limits the interpretation of the available data.

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

1.8.1	CCR	All those with PCOS should be offered regular monitoring for weight changes and excess weight, in consultation with and where acceptable to the individual woman. Monitoring could be at each visit or at a minimum 6 - 12 monthly, with frequency planned and agreed between the health professional and the individual (see 3.5).	❖❖❖❖
1.8.2	CCR	Weight, height and ideally waist circumference should be measured and BMI calculated with the following considered: • BMI categories and waist circumference should follow World Health Organisation guidelines, also noting ethnic and adolescent ranges. • Consideration should be given for Asian and high-risk ethnic groups including recommended monitoring of waist circumference.	❖❖❖❖
1.8.3	CCR	All women with PCOS should be assessed for cardiovascular risk factors and global CVD risk.	❖❖❖❖
1.8.4	CCR	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	CCR	Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (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	CCR	All women with PCOS should have blood pressure measured annually, or more frequently based on global CVD risk.	❖❖❖❖
1.8.7	CPP	Health professionals need to be aware that CVD risk in women with PCOS, remains unclear pending high quality studies, however prevalence of CVD risk factors is increased, warranting consideration of screening.	
1.8.8	CPP	Consideration needs to be given to the significant differences in CVD risk across ethnicities (see 1.6.1) when determining frequency of risk assessment.	

Justification

Whilst it remains unclear as to whether women with PCOS have a higher risk of CVD, data remains limited and women have generally been studied at a relatively young age. The guidelines therefore emphasise the increase in CVD risk factors, rather than making a recommendation about CVD risk. 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.

CONTENTS

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 gestational diabetes (GDM), impaired glucose tolerance (IGT) and type II diabetes (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 [9] and underlying insulin resistance [142] 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. Ethnicity, BMI and other risk factors also influence risk of glycaemic abnormalities and as per the general populations, these need to be considered when determining screening type and frequency.

Hyperglycaemic 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 IGT (OR 2.48, 95% CI 1.63, 3.77; BMI-matched studies OR 2.54, 95% CI 1.44, 4.47), DM2 (OR 4.43, 95% CI 4.06, 4.82; BMI-matched studies OR 4.00, 95% CI 1.97, 8.10) [143]. Consistently, DM2 was four times higher in a recent Danish registry study and was diagnosed four years earlier in PCOS [144]. The prevalence differs by ethnicity and is higher in more obese study populations [144]. 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 [144]. 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 [145] 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 guidelines for case detection and diagnosis of DM2 [146].

Summary of narrative review evidence

Whilst guidelines consistently recommend screening for DM2 in PCOS, whether to target subgroups, which test to use (fasting glucose, OGTT or HbA1c) and optimal frequency, vary between guidelines [147] and remain controversial. Some recommend screening all women with PCOS [148], 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 of excess weight on DM2 risk in PCOS, presents challenges. In a low risk northern European ethnic group, lean women did not develop DM2 by 46 years, with risk increased in the majority who were overweight or obese [149]. 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 also 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 significantly impacts on DM2 incidence [150].

General guidelines recommend testing for prediabetes and DM2 in adolescents and adults at any age who are overweight or obese (BMI over 25 kg/m^2 or 23 kg/m^2 in Asians), with additional risk factors (e.g. PCOS) [151] . 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, screening was considered 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 [152], not yet demonstrated based on fasting glucose or HbA1c criteria [151]. HbA1c also brings cost, interference with other conditions and variation across ethnicities. The GDG 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) [153]. Population recommendations are to screen at antenatal booking and at 24 - 28 weeks in women with risk factors for DM2 [151], with many guidelines recommending universal screening at 24 - 28 weeks. In this context the GDG 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

1.9.1	CCR	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.	❖❖❖❖
1.9.2	CCR	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.	❖❖❖❖
1.9.3	CCR	An oral glucose tolerance test (OGTT), fasting plasma glucose or HbA1c should be performed to assess glycaemic status. In high-risk women with PCOS (including a BMI > 25kg/m^2 or in Asians > 23kg/m^2, history of impaired fasting glucose, impaired glucose tolerance or gestational diabetes, family history of diabetes mellitus type 2, hypertension or high-risk ethnicity), an OGTT is recommended.	❖❖❖❖
1.9.4	CCR	A 75-g OGTT should be offered in all women with PCOS preconception when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation.	❖❖❖❖

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 GDG 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 three 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 GDG members voted in favour of the final recommendations, however support for these recommendations were not unanimous (see supplementary Technical Report).

1.10 Obstructive sleep apnea

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

Clinical need for the question

Obstructive sleep apnea (OSA) 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 9 - 38% [154], 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 [155]. 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 this was reviewed narratively based on clinical expertise. Randomised controlled trials (RCTs) demonstrate benefits for symptoms, quality of life, mood and productivity [156]. Observational trials link OSA to adverse cardiovascular outcomes and death [157] and surrogate outcomes may improve with treatment [158]. Relationships to diabetes and glycaemic response to treatment remain controversial [159-163], whilst large RCTs have failed to show CVD benefits of OSA treatment [156, 164, 165]. Clinically, OSA screening is currently warranted in those with symptoms, where treatment benefit has been demonstrated in the general population [166]. In PCOS, several studies demonstrate high rates of OSA [167-170] and with matched controls [167], the high prevalence of OSA was not explained by obesity. Hyperandrogenism may contribute to OSA [171] and there are link to metabolic syndrome [172, 173], although treatment studies in PCOS are very limited [172].

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 [174]. 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 [175, 176] 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

1.10.1	CCR	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.	❖❖❖❖
1.10.2	CCR	A simple screening questionnaire, preferably the Berlin tool, could be applied and if positive, referral to a specialist considered.	❖❖❖
1.10.3	CPP	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, consideration can be given to referral to a specialist centre for further evaluation.	

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 inter-related 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 between 2 - 6 times higher in women with PCOS [177], with most adenocarcinomas (> 95%) including Type I and Type II cancers [178, 179], with type I increased in PCOS [180, 181]. The increased prevalence of endometrial cancer in PCOS [182], is related to prolonged endometrial exposure to unopposed estrogen in anovulation. Additionally, endometrium in PCOS may exhibit progesterone resistance [183]. 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 [181, 183].

Three meta-analyses, with overlapping studies, report increased risk of endometrial cancer in PCOS [184-186]. All include estimates from analyses that did not take into account BMI, relevant in both PCOS and endometrial cancer [177] with studies limited by few exposed cases. Where BMI was considered, associations with PCOS and endometrial cancer are less consistent [181]. 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 [187], yet others report contrasting results on BMI [180]. Another group reported a higher OR in premenopausal women [188]. Differences relate to variable adjustment for confounders and study population [181], with endometrial thickness and age significant predictors [189, 190].

Regarding PCOS treatments, metformin has no association or a protective association with endometrial cancer [181]. Clomiphene studies are limited by power, but a small non-significant increased risk of endometrial cancer has been shown [191]. 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 [181]. 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 [183].

Recommendations

1.11.1	CCR	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.

1.11.2	CPP	Health professionals require 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 risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. However, routine ultrasound screening of endometrial thickness in PCOS is not recommended.

1.11.3	CPP	Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.

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 wellbeing

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 [109]. This task force completed relevant systematic and narrative reviews, which informed this guideline development group (GDG). Here we expand the AEPCOS task force to include additional members and expertise from primary care. We considered additional questions and completed a full Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework evaluation.

2.1 Quality of life

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

In women with PCOS, what dimensions of quality of life 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 [109]. Assessment is self-reported and can be measured through a variety of tools. Generic tools include the Short Form -36 (SF-36) and World Health Organisation (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 polycystic ovary syndrome questionnaire (PCOSQ) has 26 items across emotions, body hair, weight, infertility and menstrual abnormalities and the modified polycystic ovary syndrome questionnaire (MPCOSQ) adds acne [109, 192]. 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 quality of life (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 [109].

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 MPCOSQ which includes an acne domain [193, 194]. 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 [7, 195]. A meta-analysis and recent update have showed that key domains were hirsutism, menstruation and infertility [196], yet this varied by population studied, life stage and cultural factors [109] and heterogeneity is to be expected.

In clinical care, the key consideration was determined by the GDG 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 applying relevant tools in clinical care to highlight patient priorities, with the caveat that clinically meaningful differences in scores need to be determined.

Recommendations

2.1.1	CCR	Health professionals and women should be aware of the adverse impact of PCOS on quality of life.	❖❖❖❖
2.1.2	CCR	Health professionals should capture and consider perceptions of symptoms, impact on quality of life and personal priorities for care to improve patient outcomes.	❖❖❖❖
2.1.3	CPP	The PCOS quality of life tool (PCOSQ), or the modified PCOSQ, may be useful clinically to highlight PCOS features causing greatest distress, and to evaluate treatment outcomes on women's subjective PCOS health concerns.	

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, however it may highlight clinical priorities for women. Primarily, 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.

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. Hormonal medications can influence mood in the general population, although literature in PCOS is limited [197]. 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 [13] 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 [109], with daily fatigue, sleep disturbances and diminished interest prominent [195]. 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) [198], which persisted in BMI matched studies. A meta-analysis of 910 women with PCOS and 1347 controls reported higher depression scores in PCOS [199], although these may not have been clinically significant. A meta-analysis of 26 studies including 4716 participants from 14 countries [200], 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 [201], 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 [202] 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%) [203]. Overall, women with PCOS have a higher prevalence of depressive symptoms and depression, independent of obesity.

Anxiety: Anxiety symptoms are increased in PCOS [109]. Meta-analyses of six studies and another of eleven studies reported higher anxiety scores in PCOS compared to controls [199, 200]. Another of four studies reported a sevenfold increase in abnormal anxiety scores in PCOS [204], however, heterogeneity existed in all meta-analysis. A recent rigorous meta-analysis of ten studies [201] 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, 52.0%) in PCOS and 8.5% (IQR: 3.3, 12.0%) in controls. A large population-based study of 24385 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) [202]. A large hospital database showed anxiety in PCOS at 14%, compared to 5.9% of those without a diagnosis of PCOS [203]. 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 [109] 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 [205-208]. Further potential contributors to depression and anxiety in PCOS include the chronic [209-213], complex and frustrating nature of PCOS [214, 215]. 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 GDG expertise and consumer perspectives, informed the recommendations. These included:

- The treatment of depression in adults with chronic physical health problems, NICE, 2009 [216].
- Common mental health problems: identification and pathways to care, NICE, 2011 [217].
- Antenatal and postnatal mental health: clinical management and service guidance, NICE, 2014 [218].
- Screening for Depression in Adults: US Preventive Services Task Force Recommendations, 2016 [219].
- Screening for Depression in Children and Adolescents: US Preventive Services Task Force Recommendations 2016 [220].
- Screening for and Treatment of Suicide Risk Relevant to Primary Care: A Systematic Review for the US Preventive Services Task Force, 2014 [221].
- Royal Australian NZ College of Psychiatrists Clinical Practice Guidelines for Mood Disorders 2015 [222].
- 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 [223].

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 [216-220]. US guidelines conclude moderate benefit of depression screening in the general adult population [219]. Australian guidelines for the general population do not recommend routine screening, except during the perinatal period [222, 224].

Overall in PCOS, where prevalence and severity is higher, the GDG 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 of clinical judgement considering an individual woman's risk factors, can inform if additional screening appears warranted. Screening during the antenatal and postnatal periods in PCOS is aligned with recommendations in the general population.

Recommendations

2.2.1	CCR	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.	❖❖❖❖
2.2.2	CCR	Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals, informed by regional guidelines.	❖❖❖❖
2.2.3	CCR	If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered in PCOS, informed by regional clinical practice guidelines.	❖❖❖❖
2.2.4	CPP	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.	
2.2.5	CPP	Assessment of anxiety and or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened according to regional guidelines, or by using the following stepped approach:	

2.2.5 (continued)

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 for anxiety and depression is offered in PCOS, the following need consideration:	

- 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 need to be informed by clinical regional practice guidelines.
- Use of agents that exacerbate PCOS symptoms, including weight gain, need careful consideration.

2.2.7	CPP	Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, as they may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	

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 [225] 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. Therapies used in PCOS, including hormonal contraceptives and ovulation induction agents, can affect psychosexual function in the general population although data in PCOS is limited [226]. 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 [227-230]. It appears that women with PCOS suffer from greater psychosexual dysfunction than women in the general population in most studies [207, 231-237]. Whilst there is limited quality research in this area, studies [207, 233, 234] do show a correlation between PCOS and reduced QoL, sexual satisfaction and feminine identity. A recent systematic review on psychosexual dysfunction in PCOS found that a satisfying sex life is important for women with PCOS, however, in women with PCOS sexual function, as well as feelings of sexual attractiveness, are compromised [238]. Women with PCOS judge their appearance and body hair to negatively impact on their sexuality and their ability to engage in relationships. This remains controversial with some studies suggesting the prevalence of psychosexual dysfunction in PCOS group is similar to the general population [229, 230]. A recent systematic review by GDG 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 [207, 233, 235]. 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 [232]. In considering screening tools the Female Sexual Function Index (FSFI) [229] and Arizona Sexual Experience Scale (ASEX) [230] are commonly used to evaluate psychosexual dysfunction.

Recommendations

| 2.3.1 | CCR | All health professionals should be aware of the increased prevalence of psychosexual dysfunction and should consider exploring how features of PCOS, including hirsutism and body image, impact on sex life and relationships in PCOS. | ❖❖❖❖ |
| 2.3.2 | CCR | If psychosexual dysfunction is suspected, tools such as the Female Sexual Function Index can be considered. | ❖❖❖❖ |

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 GDG, 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. Women with PCOS, compared with controls, had a negative body image on the validated Multidimensional Body-Self Relations Questionnaire (MBSRQ) [7]. Evidence is conflicting however, with some case-control studies not finding differences in body image satisfaction and self-esteem compared to women without PCOS [237, 239, 240]. Women with PCOS feel less physically attractive, healthy or physically fit and are less satisfied with their body size and appearance [241], and this negative body image predicts both depression and anxiety [242]. Infertile women with PCOS have lower body satisfaction than non-infertile women with PCOS [243]. Hirsute women experienced lower self-esteem than non-hirsute women [243]. Overall, PCOS features, in particular hirsutism and increased weight, impact negatively on body image and QoL [242, 244], and negative body image is strongly associated with depression in women with PCOS [245, 246], even after controlling for weight [8, 246].

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 GDG and key relevant sources of evidence-based information for the general population. Assessment of body image includes measures of body dissatisfaction and disordered eating [247], body size estimation [248] and weight [249, 250]. The National Institute for Health and Care Excellence (NICE) Guideline 31 – Obsessive Compulsive Disorder: Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder [251] and the Australian Medical Association Position Statement: Body Image and Health 2002 [252] informed the recommendations provided. The Female Sexual Function Index tool is the most commonly used in PCOS studies of psychosexual dysfunction.

Recommendations

| 2.4.1 | CCR | 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 according to regional guidelines or by 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. Approaches 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 disorders, 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. bingeing, 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 [109]. 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 [253], 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 [254] 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 [202]. Surveys in PCOS show mixed results across the different disorders [195, 255, 256], but overall suggest an increased prevalence of eating disorders and disordered eating. Women with PCOS also have more identified risk factors for eating disorders [257] across obesity, depression, anxiety, self-esteem and poor body image [195, 240, 256].

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.

Recommendations

2.5.1	CCR	All health professionals and women should be aware of the increased prevalence of eating disorders and disordered eating associated with PCOS. ❖❖
2.5.2	CCR	If eating disorders and disordered eating are suspected, further assessment, referral and treatment, including psychological therapy, could be offered by appropriately trained health professionals, informed by regional clinical practice guidelines. ❖❖
2.5.3	CPP	Eating disorders and disordered eating can be screened using the following stepped approach.

Step 1: The SCOFF (Sick, Control, One stone, Fat, Food) 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 breadth 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 increasingly 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 gap and compelling need for improved information provision [13, 260, 261]. Women internationally report inadequate information, delayed diagnosis and variation in care. 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, 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 [13, 266]. Women often see multiple health professionals before diagnosis [13, 260, 267, 268], flag symptoms multiple times [214, 269] and experience delays in diagnosis [13, 214, 260, 267]. Receiving a diagnosis is important to women [214]; yet may lead to anxiety and frustration without adequate information [267-269]. Reproductive and metabolic features are concerns [13, 270], 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 [13, 214, 260, 268, 269, 271, 272]. Women's initial source of information is their healthcare provider [214, 269, 270], yet if inadequate, inaccurate or conflicting, frustration is reported [13, 271]. The internet is accessed yet quality is often poor [214, 269, 271] or conflicted by commercial interests [271], 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 [13, 260, 267, 268, 273]. Women with PCOS are best supported by a range of information resources: respectful and empathetic healthcare providers, websites, leaflets and support groups [214, 264, 265]. Health professional research suggests variation in care by specialty including across rates of undiagnosed PCOS [274] and investigations [275]. Women with PCOS infrequently report seeing a dietitian or receiving dietary advice [276]. Educational programs improve knowledge and confidence in PCOS among doctors [277], 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 [278] 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 [278]. 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

2.6.1	CCR	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.	❖❖❖❖
2.6.2	CCR	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	CCR	PCOS information should be comprehensive, evidence-based and inclusive of the biopsychosocial dimensions of PCOS across the life-span.	❖❖❖❖
2.6.4	CCR	Women's needs, communication preferences, beliefs and culture should be considered and addressed through provision of culturally and linguistically appropriate co-designed resources and care.	❖❖❖❖
2.6.5	CCR	Interdisciplinary care needs to be considered for those with PCOS where appropriate and available. Primary care is generally well placed to diagnose, screen and coordinate interdisciplinary care.	❖❖❖❖
2.6.6	CCR	Care needs to be person centred, address women's priorities and be provided in partnership with those with PCOS and where appropriate, their families.	❖❖❖❖
2.6.7	CPP	Guideline dissemination and translation including multimodal education tools and resources is important, with consultation and engagement with stakeholders internationally.	

Justification

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 multi-faceted 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 affects 75% of lean women and 95% of overweight women [279]. It is independently exacerbated by excess weight [142, 280], increasing prevalence and severity of metabolic, reproductive and psychological features of PCOS [11, 281-283]. Benefits from lifestyle intervention and weight loss have been demonstrated in women with PCOS [284-287] and healthy lifestyle is important in preventing excess weight gain in PCOS and can offer benefits even without weight loss [288-292]. Women with PCOS internationally report that excess weight causes significant distress and concern and that there is inadequate information and support around lifestyle change [13]. 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 [284-287, 293-312]. 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 quality of life (QoL) factors in women with PCOS [313]. 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 body mass index (BMI), free androgen index (FAI), sex hormone-binding globulin (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

3.1.1	CCR	Healthy lifestyle behaviours encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to achieve and/or maintain healthy weight and to optimise hormonal outcomes, general health, and QoL across the life course.	❖❖❖❖
3.1.2	EBR	Lifestyle intervention (preferably multicomponent including diet, exercise and behavioural strategies) should be recommended in all those with PCOS and excess weight, for reductions in weight, central obesity and insulin resistance.	❖❖❖ ⊕⊕○○
3.1.3	CPP	Achievable goals such as 5% to 10% weight loss in those with excess weight 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.	
3.1.4	CPP	SMART (Specific Measurable, Achievable, Realistic and Timely) goal setting and self-monitoring can enable achievement of realistic lifestyle goals.	
3.1.5	CPP	Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating, need consideration and management to optimise engagement and adherence to lifestyle interventions.	
3.1.6	CPP	Health professional interactions around healthy lifestyle, including diet and exercise, need to be respectful, patient-centred and to value women's individualised healthy lifestyle preferences and cultural, socioeconomic and ethnic differences. Health professionals need to also consider personal sensitivities, marginalisation and potential weight-related stigma.	
3.1.7	CPP	Adolescent and ethnic-specific BMI and waist circumference categories need to be considered when optimising lifestyle and weight.	
3.1.8	CPP	Healthy lifestyle may contribute to health and QoL benefits in the absence of weight loss.	
3.1.9	CPP	Healthy lifestyle and optimal weight management appears equally effective in PCOS as in the general population and is the joint responsibility of all health professionals, partnering with women with PCOS. Where complex issues arise, referral to suitably trained allied health professionals needs to be considered.	
3.1.10	CPP	Ethnic groups with PCOS who are at high cardiometabolic risk as per 1.6.1 require greater consideration in terms of healthy lifestyle and lifestyle intervention.	

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. Women with PCOS prioritised weight management and also emphasised the need to optimise healthy lifestyle in lean women and in all women with PCOS, independent of weight loss goals. 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 area needed [314, 315]. 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 [314], 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 [316] 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 [317]. 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 [318, 319] 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 type 2 diabetes (DM2) or cardiovascular disease (CVD), summarised key success factors in lifestyle interventions [320]. Behavioural change techniques in combination with diet and exercise interventions, increased weight loss over diet and/or physical activity alone [320]. Self-management has positive impacts [320] and family support improves outcomes, [320]. Mode of delivery and trained intervention facilitator, setting and intensity didn't impact outcomes [320]. 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 [320, e.g., 321]. 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 [322-325].

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 [326]. In the general population, behavioural and cognitive behavioural interventions have strong empirical support and are recommended in international guidelines on the treatment of excess weight [e.g., 321, 327].

Recommendations

3.2.1	CCR	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.	❖❖❖❖
3.2.2	CPP	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.	

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 [308]; one RCT with a low risk of bias investigating the changes in anthropometric and metabolic outcomes by comparing a DASH (dietary approaches to stop hypertension) diet with a control diet [328, 329]; 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 [330]. 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. A systematic review [331] and more recent large scale studies [332] show that in the general population, there is no benefit of any one diet type and that hormone levels including insulin do not predict responses. Given the above evidence and other systematic reviews in the general population that reported similar or less weight loss and compliance for a low fat diet compared to other approaches [333, 334], and a large RCT reported similar changes in weight for a range of reduced energy diets with different macronutrient content over two years [335], the assertions that specific dietary composition has selective long term advantages at this stage appears to be unjustified.

Recommendations

| 3.3.1 | CCR | 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. | ❖❖❖❖ |

| 3.3.2 | CCR | General healthy eating principles should be followed for all women with PCOS across the life course, as per general population recommendations. | ❖❖❖❖ |

| 3.3.3 | CPP | To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 to 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight and physical activity levels. | |

| 3.3.4 | CPP | 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. | |

| 3.3.5 | CPP | 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. | |

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 [336, 337]. 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 sub-grouped by exercise intensity into light, moderate, vigorous or high-intensity [338] (Table 5). Two small RCTs are relevant in PCOS. Regular moderate intensity cycle exercise had greater metabolic benefit over 24 compared to 12 weeks, without impact on reproductive biomarkers [148, 339, 340]. Whilst 20 weeks of aerobic compared to combined exercise, superimposed on a high protein diet, showed similarly improved PCOS features [148, 287, 339, 341]. Small RCTs and high quality mechanistic studies (cohort and case control studies) show physical activity, including formal exercise (aerobic and muscle strengthening), improves body composition and clinical features [148, 206, 287, 290, 339, 341-349], compared to minimum or no interventions. These benefits occur independent of significant weight loss [290] and can occur with exercise alone [290, 350].

The mechanistic impacts of exercise and physical activity on cardiometabolic and reproductive features of PCOS are well described [339, 351-353]. While acknowledging the limitations in quality of evidence (sample size, study type, heterogeneity of interventions), improved glycaemic and reproductive outcomes, QoL and functional capacities have been shown [148, 287, 339, 349, 351-354]. Psychologically, limited community based/epidemiological studies show positive associations between self-reported physical activity and mental health status [206, 342] and vigorous exercise and better health outcomes in women with PCOS [355]. Conversely, there is an increase in sedentary behaviour documented in PCOS [356]. Mechanistically, insulin resistance, underpinned by insulin signalling pathway defects, is involved in the aetiology [336, 337] and clinical features of PCOS [336, 337, 357-359]. Moderate aerobic exercise improves insulin sensitivity short-term in PCOS [360].

Insulin resistance is also ameliorated in groups where exercise reduces DM2 risk [152, 361] and CVD factors [362, 363]. Similarly, resistance or weight-bearing exercise either alone or in combination with aerobic exercise improves health outcomes in groups [364-367]. In general populations, physical activity and structured exercise deliver metabolic, cardiovascular, and psychosocial benefits, whether alone or combined with diet changes [368-370]. Sedentary behaviours link to all-cause mortality and adverse health impacts [371, 372], whilst aerobic and resistance exercise reduce cardiometabolic risk factors [373]. Health impacts of exercise therapy may also reduce long-term healthcare costs [374]. Overall, current guidelines for the general population recommend 150 minutes of exercise per week, with 90 minutes at moderate to high intensity [338, 375-382] (Table 5).

Recommendations

3.4.1   CCR   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-minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.

3.4.2   CCR   Health professionals should encourage and advise the following for modest weight-loss,   ❖❖❖
prevention of weight-regain and greater health benefits:

- 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 involving major muscle groups on 2 non-consecutive days/week
- minimised sedentary, screen 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. Daily, 10000 steps is ideal, including activities of daily living and 30 minutes of structured physical activity or around 3000 steps. Structuring of recommended activities need to consider women's and family routines as well as cultural preferences

3.4.4   CPP   Realistic physical activity SMART goals could include 10-minute bouts, progressively increasing physical activity 5% weekly, up to and above recommendations.

3.4.5   CPP   Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be used as an adjunct to support and promote active lifestyles and minimise sedentary behaviours.

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 used. 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 Section 3.1 Lifestyle interventions.

Table 5: Physical activity intensity and examples.

INTENSITY AND MEASURE	DESCRIPTION	EXAMPLES OF ACTIVITIES AND ADL'S (ACTIVITIES OF DAILY LIVING)
LIGHT 1.6 - 3 †METs 40 - 55% *HRmax	• Aerobic activity that does not cause noticeable changes in breathing rate. • An intensity that can be sustained for at least 60 minutes.	Casual walking, cycling < 8km/hr (5mph), stretching, light weight training, dancing slowly, leisurely sports (playing catch) golf (using cart), light yard/house work.
MODERATE 3 - 6 †METs 55 - 70% *HRmax	• Aerobic activity that can be conducted whilst having an uninterrupted conversation. • An intensity that may last between 30 to 60 minutes.	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.
VIGOROUS 6 - 9 †METs 70 - 90% *HRmax	• Aerobic activity where an uninterrupted conversation generally can't be maintained • Intensity that may last up to 30 minutes	Race walking, jogging/running, mountain climbing, cycling (> 16km/hr, 10mph), 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-motorised lawn mowing, occupations with heavy lifting or rapid movement.

* Predicted maximal heart rate (HRmax) = 208 – (0.7 X AGE[years]);

† metabolic equivalent (MET) where 1 MET is the O_2/kg body weight/min required to sustain ones resting metabolic rate [3.5 mL/kg/min])[338] and [383].

CONTENTS

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, increases 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 [384]. Rates of weight gain appear higher in PCOS, and BMI increases of one, are associated with a 9% higher prevalence of PCOS [315]. Women with PCOS also appear to have higher genetic susceptibility to obesity [385]. The temporal trends of obesity prevalence in PCOS show an increase from 51% in the 90s to 74% in the following decades [386]. 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 in PCOS. 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) [387]. 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 [115]. 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 [388]. Overall rates of weight gain and excess weight are increased in PCOS.

Obesity influences the phenotypic expression of PCOS, exacerbating metabolic, reproductive, and psychological features [279, 389]. Lipid abnormalities are increased independently in PCOS and are exacerbated by excess weight [386, 389, 390]. Central obesity is associated with more severe metabolic disturbance [389]. The prevalence of impaired glucose tolerance (IGT) and DM2 is further increased in women with PCOS with excess weight, especially in high-risk ethnic groups [391]. Conversely, weight loss reduces abdominal fat and insulin resistance and improves clinical features of PCOS (see Chapter 3) [294, 392].

Obesity impacts on ovulatory dysfunction, irregular menstrual cycles, time to conception, infertility and response to ovulation induction and is associated with increased miscarriage, hyperglycaemia, pre-eclampsia, perinatal morbidity, fetal macrosomia and greater potential for trans-generational transmission of obesity and adverse metabolic features [294, 386, 390, 393]. When combined with insulin resistance, DM2 and PCOS, the adverse outcomes can be more than additive [386, 390]. Expert opinion recommends that obese women with PCOS delay infertility therapy and pursue lifestyle modification, where possible [384, 387].

Psychological comorbidities of PCOS with overweight/obesity include anxiety, depression, low health-related QoL, sexual dissatisfaction, poor self-esteem and psychological distress [384, 390, 392]. 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.

Overall, healthy lifestyle is recommended in all women with PCOS 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 (especially in high-risk ethnic groups) waist circumference.

Recommendations

3.5.1	CCR	Health professionals and women should be aware that women with PCOS have a higher prevalence of weight gain and obesity, presenting significant concerns for women, impacting on health and emotional wellbeing, with a clear need for prevention.	❖❖❖
3.5.2	CCR	All those with PCOS should be offered regular monitoring for weight changes and excess weight as per 1.8.1 and 1.8.2.	❖❖❖❖
3.5.3	CPP	When assessing weight, related stigma, negative body image and/or low self-esteem need to be considered and assessment needs to be respectful and considerate. Beforehand, explanations on the purpose and how the information will be used and the opportunity for questions and preferences needs to be provided, permission sought and scales and tape measures adequate. Implications of results need to be explained and where this impacts on emotional wellbeing, support provided.	
3.5.4	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 causes 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, consistent with international public health recommendations. Awareness, respectful monitoring and early intervention are important considerations from adolescence. The GDG recognised the need for adequate training of health professionals in the empathetic partnering with women to enable weight management.

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 guideline.

Recommendations

4.1.1	CPP	Consideration of the individual's personal characteristics, preferences and values is important in recommending pharmacological treatment.
4.1.2	CPP	When prescribing pharmacological therapy in PCOS, benefits, adverse effects and contraindications in PCOS and general populations need to be considered and discussed before commencement.
4.1.3	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 need to inform women and discuss the evidence, possible concerns and side effects of treatment.
4.1.4	CPP	Holistic approaches are required and pharmacological therapy in PCOS needs to be considered alongside education, lifestyle and other options including cosmetic therapy and counselling.

'Off label' prescribing occurs when a drug is prescribed for an indication, a route of administration, or a patient group that is not included in the approved product information document for that drug by the relevant regulatory body. Prescribing off label is often unavoidable and common and does not mean that the regulatory body has rejected the indication; more commonly there has not been a submission to request evaluation of the indication or that patient group for any given drug.

4.2 and 4.3 Combined Oral Contraceptive Pills and combined oral contraceptive pills in combination with other agents

Is the combined oral contraceptive pill (COCP) 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, are commonly prescribed for adults and adolescents with PCOS to ameliorate the clinical symptoms and associated hormonal disturbances. The effects of 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 COCP 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 ethinyloestradiol (EE) with benefits and contraindications considered similar.

Summary of systematic review evidence – COCP alone

Research evidence - ADOLESCENTS

COCP versus placebo

One randomised controlled trial (RCT) was identified to address this comparison in adolescents [319]. There was a statistically significant improvement with COCP (compared to placebo) for high-density lipoprotein (HDL) in this very low quality study with low certainty. No statistically significant differences were found for outcomes: body mass index (BMI) (kg/m^2); Waist (cm); Total testosterone (ng/dl); sex hormone-binding globulin (SHBG) (nmol/liter); free androgen index (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 [319]. There was a statistically significant improvement with lifestyle (compared to COCP) for low-density lipoprotein (LDL) in this very low quality study with very low certainty. No statistically significant differences were found for: BMI (kg/m^2); 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 [394]. 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); HDL (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 is adolescents [395]. 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 <u>very low quality study with very low certainty</u> for outcomes: BMI (kg/m^2); 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 [396-404]. 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); homeostatic model assessment (HOMA) (change from baseline); BMI (kg/m^2); waist-hip-ratio (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 <u>low to very low certainty</u> 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 [402, 404-408]. 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/m^2); 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 <u>low to very low certainty</u> 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 [395]. 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 <u>very low quality study with very low certainty</u> for outcomes: BMI (kg/m^2); 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 [409]. 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 – COCP combined with other agents

Research evidence - ADOLESCENTS

COCP + metformin+ lifestyle versus COCP + lifestyle + placebo

One RCT was identified to address this comparison is adolescents [319]. 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/m^2); 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 in adolescents [410]. 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/m^2); 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 [402, 404-408]. 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 [395]. 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/m^2); 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 [411-414]. 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 [415]. 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. Consideration of adverse effects is needed before prescribing COCPs. Absolute contraindications for COCP use according to world health organisation (WHO) include 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 [416]. Other risk factors for DVT need consideration including postpartum immobility, transfusion at delivery, BMI > 30 kg/m^2, 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, WHO recommends that COCPs with 35 micrograms of EE and cyproterone acetate should only be used when treating moderate to severe hirsutism or acne due to higher DVT risk. For contraception, irregular menstrual cycles and mild to moderate hirsutism, other lower risk preparations are recommended first line [417].

Recommendations – COCP alone

4.2.1	EBR	The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and/or 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/or 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 in adults and adolescents with PCOS and practice should be informed by general population guidelines.	❖❖❖ ⊕⊕○○
4.2.5	CCR	The 35 microgram ethinyloestradiol plus cyproterone acetate preparations should not be considered first line in PCOS as per general population guidelines, due to adverse effects including venous thromboembolic risks.	❖
4.2.6	CPP	When prescribing COCPs in adults and adolescents with PCOS: • various COCP preparations have similar efficacy in treating hirsutism • the lowest effective estrogen doses (such as 20-30 micrograms of ethinyloestradiol or equivalent), and natural estrogen preparations need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability • the generally limited evidence on effects of COCPs in PCOS needs to be appreciated with practice informed by general population guidelines (WHO Guidelines) • the relative and absolute contraindications and side effects of COCPs need to be considered and to be the subject of individualised discussion • PCOS specific risk factors such as high BMI, hyperlipidemia and hypertension need to be considered.	

Recommendations – COCP in combination with other agents

4.3.1	EBR	In combination with the COCP, metformin should be considered in women with PCOS for management of metabolic features where COCP and lifestyle changes do not achieve desired goals.	❖❖❖❖ ⊕⊕○○
4.3.2	EBR	In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI ≥ 25kg/m^2 where COCP and lifestyle changes do not achieve desired goals.	❖❖❖❖ ⊕⊕○○
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 considered in PCOS to treat hirsutism, after six months or more of COCP and cosmetic therapy have failed to adequately improve symptoms.	❖❖ ⊕⊕○○
4.3.5	CCR	In combination with the COCP, antiandrogens could be considered for the treatment of androgen-related alopecia 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.	

Justification

Although relatively safe, COCPs have absolute and relative contraindications and risks and benefits in the general population that need consideration by health professionals and women. Although combined metformin and COCP offers additional benefits, these did not surpass the impact of COCP plus lifestyle intervention. Hence the combination is indicated where COCP and lifestyle have failed to meet goals. A combination regime may also 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 off label treatments specifically for treatment of PCOS. 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 and the regulation status of relevant medications. The combination of off label treatments 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. Insulin resistance is documented on clamp studies in 75% of lean women and 95% of overweight women [279] and addressing this has underpinned the use of metformin in PCOS. Metformin is currently widely used by women with PCOS, yet there is variability in recommendations across health professional specialties, with endocrinologists familiar with metformin and more likely to prescribe this therapy. Also the efficacy of metformin in terms of improving clinical outcomes remains uncertain. Mild side effects do 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. A multitude of studies have been completed in PCOS for a range of clinical outcomes and synthesis of the literature and recommendations on metformin use was prioritised.

Summary of systematic review evidence

Metformin versus placebo

Twenty RCTs that address outcomes for this comparison were identified [318, 319, 418-435], of which 19 RCTs were in adults [318, 418-435], and 1 was in adolescents [319].

Weight: When 5 RCTs were combined in meta-analysis, there was no statistically significant difference between metformin and placebo [418, 424, 427, 433, 434]. When three of the studies in those with BMI > 25kg/m2 were subgrouped [424, 427, 433], metformin was better than placebo.

BMI: When 15 RCTs were combined in meta-analysis [318, 319, 418-422, 424, 425, 428-432, 435], and when 11 of the RCTs in those with BMI > 25kg/m2 was subgrouped [318, 319, 419-422, 424, 425, 429, 432, 435], 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) [418, 419, 421, 424, 427, 429, 431, 434]. When 3 of the RCTs in those with BMI < 25kg/m2 were subgrouped [418, 429, 431], 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 [319, 423, 425, 429-431].

SHBG: When 13 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [318, 319, 418-421, 423-425, 428, 430, 431, 434]. In one very small RCT (n=20), where BMI was not reported, there was a statistically significant difference in favour of metformin [423].

FAI: When 6 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo, regardless of BMI subgroups [318, 319, 423, 424, 430, 431].

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 [318, 319, 418-421, 423-425, 428, 430, 431, 433-435].

Fasting insulin: When 9 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo [318, 419-421, 424, 425, 429, 433, 434]. In one small RCT (n=60) of those with BMI <or> 25kg/m2, there was a statistically significant difference in favour of metformin [434].

Fasting glucose: When 13 RCTs were combined in meta-analysis there was no statistically significant difference between metformin and placebo [318, 319, 418-421, 424, 425, 428, 429, 433-435]. In one small RCT (n=58) of those with BMI <or> 25kg/m^2, there was a statistically significant difference in favour of metformin [434].

Cholesterol: When 10 RCTs were combined in meta-analysis [319, 419, 421, 422, 424, 425, 428, 429, 431, 434], and when 6 of the RCTs in those with BMI > 25kg/m2 was subgrouped [319, 419, 421, 424, 425, 429], 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 [319, 419, 424, 425, 429-431, 433, 434].

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) [319, 419, 423-425, 429-431, 434]. When 6 of the RCTs in those with BMI > 25kg/m^2 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 [319, 419, 421, 423-425, 428, 429, 431, 434].

There were no statistically significant differences between metformin and placebo for HOMA, menstrual cycles, CRP (C-reactive protein) or PAI-1 (plasminogen activator inhibitor-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. 10 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 [402, 404, 436]. 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].

Side effects were not reported.

Metformin versus lifestyle

Three RCTs that address this comparison in adolescents and adults were identified [318, 319, 437]. 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 [438]. 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 [439]. 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 850mg twice a day.

Metformin versus anti-androgen + COCP

One study was identified to address this comparison in adults [440]. 500mg of metformin was better for fasting glucose; and 850mg 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 [441-444]. While a statistically significant improvement was found in cycles per year and HOMA-IR (homeopathic model assessment of insulin resistance) 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 diarrhoea 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 [441, 442, 444, 445]. 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. Overall there was 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. Side effects are usually mild, self-limiting and may be minimised 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 [446]. It is known in other populations to prevent weight gain and appears to assist with weight loss, to prevent and manage DM2, gestational diabetes (GDM), and to reduce microvascular and cardiovascular disease in DM2 [446, 447]. 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 [446]. Concerns on Vitamin B12 deficiency with longer term metformin use have also emerged [448], however more research is needed. Data from other populations suggests that side effects can be minimised with lower metformin starting dose, extended release preparations and/or administration with food [449].

Recommendations

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.	❖❖❖ ⊕⊕○○
4.4.2	EBR	Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI ≥ 25kg/m^2 for management of weight and metabolic outcomes.	❖❖❖ ⊕⊕○○
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.	❖❖❖ ⊕⊕○○
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 (see 1.6.1).	
4.4.5	CPP	Where metformin is prescribed the following need to be considered:	

- adverse effects, including gastrointestinal side-effects that are generally dose dependent and self-limiting, need to be the subject of individualised discussion
- starting at a low dose, with 500mg increments 1-2 weekly and extended release preparations may minimise side effects
- metformin use appears safe long-term, based on use in other populations, however ongoing requirement needs to be considered and use may be associated with low vitamin B12 levels
- use is generally off label and health professionals need to 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 also has clear benefits in other relevant populations including those with DM2, which also informed GDG recommendations. In PCOS, evidence indicated that metformin is effective overall and /or in specified subgroups, in improving weight, BMI, WHR ratio, testosterone and TG in women with PCOS including those defined by Rotterdam criteria. In providing these recommendations, the GDG considered the very high rating that women with PCOS credited to BMI as an outcome of importance and value. 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 this guideline. Gastrointestinal side effects were noted, but appear to be mild, self-limiting and could be minimised 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 guidelines, systematic and Cochrane reviews 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 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 [450]. However, in PCOS and in reproductive-aged women generally, the role of anti-obesity pharmacological agents remains unclear. Anti-obesity agents reviewed here were sibutramine and orlistat.

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 [451]. 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 [452]. 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 [450], systematic and Cochrane reviews [453] 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 [450]. It was noted that cost effectiveness of these agents is yet to be established [454].

Recommendations

4.5.1	CCR	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	For anti-obesity medications, cost, contraindications, side effects, variable availability and regulatory status need to be considered and pregnancy needs to be avoided whilst taking these medications.	

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 and in reproductive aged women generally, the GDG 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 considered and monitored. Concerns about cost effectiveness was also considered by the group, based on evidence in the general population.

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 androgen-related alopecia (see Chapter 1: Screening, diagnostic assessment, risk assessment and life-stage). Given the adverse impact of clinical hyperandrogenism on emotional wellbeing and QoL (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. 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, 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. Pure anti-androgens were prioritised and reviewed here across flutamide, finasteride and sprironolactone. Other agents such as synthetic progestin with anti-androgenic properties were not prioritised for review in this guideline.

Summary of systematic review evidence

Anti-androgen versus placebo

One study of adolescents was identified to address this comparison [455]. 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/m^2); Modified Ferriman-Gallwey score (mFG); 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 [442]. 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/m^2); Number of cycles in previous 6 months; Hirsutism (FG 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 [456, 457]. 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 [441, 442, 444]. 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 [?IU/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 randomised controlled studies.

As the undesirable effect of antiandrogens is mostly related to mild hepatotoxicity, lifestyle does not seem 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 GDG considered it is mandatory to use concomitant contraception with anti-androgens in order to avoid foetal male under virilisation in the event of unplanned pregnancy [458]. Consistent with the Endocrine Society guidelines we recommend against antiandrogen monotherapy unless adequate contraception is used and note that cosmetic and COCP therapy are first line treatments for hirsutism in women including in PCOS [459]. 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 [458].

Recommendations

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 androgen-related alopecia.	❖❖❖ ⊕○○○
4.6.2	CPP	Specific types or doses of antiandrogens cannot currently be recommended with inadequate evidence in PCOS.	

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. It was also acknowledged that the various anti androgens have different efficacy and side effects. However, evidence to inform use of these agents alone was poor for all identified agents. 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 sensitising 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 [460]. Previous studies have focused on insulin resistance and hormonal profiles and gestational diabetes in women with PCOS.

Summary of systematic review evidence

A Cochrane systematic review [461] 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 GDG meeting, ovulation rate and menstrual cycles appear to improve with inositol in women with PCOS [460, 462]. Furthermore, some data also suggests inositol may be effective in decreasing risk for GDM [463]. The literature however is limited, many key questions remain [460] and research is prioritised. Many of the included studies focused on combinations of therapy such as inositol and folate and adequate studies of inositol alone were not available.

Recommendations

4.7.1	EBR	Inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research.	❖ ⊕○○○
4.7.2	CPP	Women taking inositol and other complementary therapies are encouraged to advise their health professional.	

Justification

Whilst the evidence at this time on the benefit of inositol (in all forms) was inadequate to make an evidence-based recommendation, there is some emerging 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.

Chapter Five

Assessment and treatment of infertility

The evidence synthesis team, guideline lead and guideline development group (GDG) members were involved in the original Australian evidenced-based guideline in PCOS, and in 2014 the World Health Organisation (WHO) commissioned evidence synthesis update and development of guidelines for the management of anovulatory infertility in women with PCOS [464]. Here we expand the prioritised questions aligned with international consultation, extend the GDG, update and expand evidence synthesis, and complete a full Grading of Recommendations, Assessment, Development, and Evaluation (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). The prevalence of miscarriage appears increased in PCOS with more research needed. 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/m^2, waist to hip ratio (WHR – central adiposity), smoking status, alcohol consumption, prescribed and recreational drug use, untreated sexually transmitted infections, nutritional status, supplementation with folate, vitamin D and dental health have 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 (QoL). These factors should be optimised, aligned with WHO guidance, and priority areas and recommendations for the general population [465].

Pregnancy and fertility complications: Women with PCOS are at an increased risk of gestational diabetes (GDM), 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/m^2 (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 with associated adverse outcomes including cycle cancellation and decrease in fertilisation, implantation, ongoing pregnancy and live birth (17). Bariatric surgery is generally considered second-line to improve fertility outcomes in PCOS with anovulation and significant obesity (BMI ≥35kg/m^2) resistant to intensive lifestyle modification and/or pharmacotherapy (17).

Prospective randomised studies of preconception interventions that evaluate broad screening and lifestyle intervention are lacking in the general population and in PCOS [466], 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 [467, 468]. In antenatal care, there was no evidence to guide screening for GDM 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

5.1.1	CPP	Factors such as blood glucose, weight, blood pressure, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health need to 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.

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. Recommendations here are expected to improve efficacy 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 intervention 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, potentially affecting around 30% of infertile women [469]. The diagnostic assessment of infertility often includes tubal testing by hysterosalpingography or laparoscopy as outlined in the WHO 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 the need for 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 this 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 [470]. Yet the assessment of tubal patency is considered in infertility workup, as outlined in the WHO evidence report 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 [471]. In this context, consideration of risks for tubal pathology are clinically appropriate, including:

a. Previous abdominal or pelvic sepsis,
b. Previous pelvic and/or abdominal surgery
c. Cases of recurrent acute pelvic pain [472],
d. History of sexual transmitted diseases or pelvic inflammatory disease or
e. Endometriosis

Recommendations

5.1.3	CCR	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	CCR	Tubal patency testing should be considered prior to ovulation induction in women with PCOS where there is suspected tubal infertility.	❖❖❖

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, where other risk factors are present.

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. In addition, duration of ovulation induction was considered under general principles.

5.2.1	CPP	The use of ovulation induction agents, including letrozole, metformin and clomiphene citrate is off label in many countries. Where off label use of ovulation induction agents is allowed, health professionals need to inform women and discuss the evidence, possible concerns and side effects.
5.2.2	CPP	Pregnancy needs to be excluded prior to ovulation induction.
5.2.3	CPP	Unsuccessful, prolonged use of ovulation induction agents needs to be avoided, due to poor success rates.

5.3 Letrozole

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

Clinical need for the question

Aromatase inhibitors (AI) are effective as ovulation-inducing agents, including letrozole and anastrozole, with letrozole being the most widely used [473, 474]. These agents prevent the aromatase-induced conversion of androgens to oestrogens, including in the ovary. Yet their mechanisms of ovulation induction are unknown, however they increase secretion of follicle-stimulating hormone (FSH) stimulating ovarian follicle development and maturation [475]. The efficacy, adverse effects and overall role of letrozole in oral ovulation induction have remained controversial.

Summary of systematic review evidence

AIs versus placebo

One small RCT [476] with a low risk of bias compared letrozole to placebo in women with clomiphene citrate (CC) 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 [477] and Misso 2012 [478], however since there is only one study, the meta-analyses do not provide additional evidence.

AIs versus CC

Thirteen RCTs compared letrozole with CC. Seven of these RCTs had a high risk of bias [479-485], two had a moderate risk of bias [486, 487] and four had a low risk of bias [488-491]. Upon meta-analysis, we found that letrozole was better than CC for ovulation rate per patient; pregnancy rate per patient; and live birth rate per patient. There was no difference between letrozole and CC 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 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 I^2 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 CC plus metformin for ovulation rate per cycle, pregnancy rate per cycle, miscarriage rate per pregnancy and multiple pregnancy rate per pregnancy in CC-resistant women with PCOS [492]. This study was included in a meta-analysis by Franik 2014 [477] and Misso 2012 [478], however since there is only one study, the meta-analysis does not provide additional evidence.

AI versus laparoscopic ovarian surgery

Three RCTs with low risk of bias [493-495] compared letrozole to laparoscopic ovarian surgery (LOS) and found that there was insufficient evidence of a difference between letrozole and LOS. One of the RCTs in 147 women with CC resistance found that letrozole was better than LOS for ovulation rate per cycle [493], however the evidence is of low certainty. The systematic review by Farquhar 2012 [496] 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 catalyses the conversion of androgens to oestrogens, including in the ovary and increase FSH secretion [475], stimulating ovarian follicle development and maturation. AIs prevent this conversion. These agents were originally used to improve pregnancy rates and limit adverse effects [497, 498], especially with clomiphene resistance and failure [498-501]. Letrozole has side effects include gastrointestinal disturbances, hot flushes, headache and back pain [502, 503] and concerns have been raised on potential teratogenic effects [504] in an abstract, as yet unconfirmed in peer-reviewed publications, yet this has sparked a series of warnings to avoid use of AI in infertility. Multiple subsequent case series [486, 505-508], multi-centre RCTs [503, 509] and a recent systematic review and meta-analysis [510], 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% [511]).

Recommendations

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.	❖❖❖❖ ⊕⊕〇〇
5.3.2	CPP	Where letrozole is not available or use is not permitted or cost is prohibitive, health professionals can use other ovulation induction agents.	
5.3.3	CPP	Health professionals and women need to 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, failure to ovulate (letrozole resistance) is lower with letrozole versus clomiphene. Multiple pregnancy rates appear 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 was considered to currently outweigh the adverse effects of relatively increased fatigue and dizziness, multiple pregnancy, and unconfirmed concerns about higher congenital anomalies.

5.4 Clomiphene citrate and/or 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 (CC) is a selective oestrogen receptor modulator with both oestrogenic and anti-oestrogenic properties [512]. It was first approved for use in women with anovulation in 1967 [513] and acts as an anti-oestrogen [475]. CC resistance and failure is well documented [514] and a discrepancy is noted between good ovulation rates and lower pregnancy rates, due to the anti-oestrogenic effects of CC on the endometrium and cervical mucus. Twin pregnancy and triplets with CC are 5–7% and 0.3%, respectively and OHSS is less than 1% [515]. The potential for borderline increased risk of ovarian tumours with 12 cycles or more has been noted [516].

Insulin resistance is common in PCOS [517, 518], driving ovarian androgen biosynthesis and increased bioavailability of free androgens. Excess local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation [519]. This has led to insulin-sensitising drugs use in ovulation induction. Metformin has been most widely studied in PCOS and has the most reassuring safety profile [520]. Efficacy has been controversial and therapeutic regimens are not well standardised in clinical practice, with variable doses in use [319].

Summary of systematic review evidence

Metformin versus placebo

One systematic review [521] with up to fourteen studies; and one RCT [522] 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). Gastrointestinal upsets 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 [464].

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 CC 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 [521] with up to seven 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, CC was better than metformin for live birth rate, pregnancy rate and ovulation rate in BMI > 30kg/m^2; and metformin was better than CC 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 [523] and two RCTs (one medium quality RCT with moderate risk of bias [524] and one low quality RCT with high risk of bias [525] were identified by the search. Metformin plus CC was better than metformin alone for ovulation rate, pregnancy rate and live birth rate. There was no statistically significant difference between metformin plus CC and metformin alone for miscarriage rate or adverse events.

Clomiphene citrate versus metformin + clomiphene citrate

One systematic review [521] with up to twenty-one studies; and one RCT [526] were identified to address this comparison. Metformin plus CC was statistically significantly better than CC alone for pregnancy rate per participant and ovulation rate per participant, including when subgrouped by BMI (BMI < 30kg/m^2 and BMI > 30 subgroups). Adverse events were statistically significantly better with CC alone than with metformin plus CC. There was no statistically significant difference between metformin plus CC and CC 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 [526] was insufficient evidence to supplement the findings of Morley 2017 [521].

Clomiphene citrate versus aromatase inhibitors (letrozole)

Thirteen RCTs (level II) compared letrozole with CC. Seven of these RCTs had a high risk of bias [479-485], two had a moderate risk of bias [486, 487] and four had a low risk of bias [488-491]. Upon meta-analysis, we found that letrozole was better than CC for ovulation rate per patient [479, 480, 482, 484, 486, 487, 490, 491]; pregnancy rate per patient [479-491]; and per cycle [482, 483, 491]; and live birth rate per patient [480, 486, 488, 490, 491]. There was no difference between letrozole and CC for ovulation rate per cycle [482, 483, 488, 489, 491]; multiple pregnancy rate per patient [479, 481, 482, 485, 486, 489-491]; and miscarriage rate per patient [480-482, 486-491]. 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)

Two RCTs were identified by the search to address this comparison. One RCT was low quality with high risk of bias [527] compared recombinant FSH with CC 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 [528] comparing CC 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 CC. Brown 2016 [529] meta-analysed these same two RCTs combining data for live birth rate and ongoing pregnancy rate and found that gonadotrophins were better than CC (OR 0.64 [0.41, 0.98] p=0.041, I2=0%). Meta-analysis of the two studies for clinical pregnancy rate found that CC 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)

Two RCTs were identified to address this comparison, however there was insufficient evidence to determine whether one intervention was better than the other [530, 531].

Recommendations

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 and pregnancy 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 is ≥ 30 kg/m^2) 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/m^2) 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 and pregnancy rates.	❖❖❖ ⊕⊕○○
5.4.6	CPP	The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered.	

Justification

CC 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 CC, given efficacy on systematic review. Usual doses of metformin range from 1500mg (most commonly) to 1700mg per day for non-fertility studies. A change in usual care may result 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 luteinizing hormone (LH), or an anti-estrogenic endometrial effects). To prevent overstimulation and multiple pregnancy, the traditional standard step-up regimens [532] were replaced by either low-dose step-up regimens [533, 534] or step-down regimens [535] with gonadotropins used alone and different gonadotropin preparations appearing to work equally well [536]. 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 laparoscopic surgery remains unclear.

Summary of systematic review evidence

Gonadotrophin versus clomiphene citrate

Two RCTs were identified by the search to address this comparison. One RCT was low quality with high risk of bias [527] compared recombinant FSH with CC 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 [528] comparing CC 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 CC. Brown [529] meta-analysed these same two RCTs combining data for live birth rate and ongoing pregnancy rate and found that gonadotrophins were better than CC (OR 0.64 [0.41, 0.98] p=0.041, I2=0%). Meta-analysis of the two studies for clinical pregnancy rate found that CC 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 CC plus metformin [537, 538]. The RCTs found that FSH was better than CC 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 gastrointestinal (GI) side effects or adverse events. A systematic review by Abu Hashim [539] conducted meta-analysis including studies that do not meet our PICO (patient, intervention, comparison, outcome), 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 [538]. 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

One high quality systematic review of RCTs (level I) with low risk of bias compared LOS 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 LOS was better than gonadotrophins for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] I2 = 0%, 4 studies, 303 participants) [496].

Gonadotrophins versus gonadotrophins + clomiphene citrate

One RCT [540] with moderate risk of bias found that FSH plus CC was better than FSH alone for ovulation rate per woman randomised and per protocol, total FSH dose used per woman randomised and per protocol, and duration of stimulation per woman randomised and per protocol. There was no statistical difference between the two interventions for pregnancy rate and live birth rate per woman randomised and per protocol.

Recommendations

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.	❖❖❖ ⊕⊕○○
5.5.2	EBR	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.	❖❖❖ ⊕⊕○○
5.5.3	EBR	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.	❖❖❖❖ ⊕⊕⊕○
5.5.4	EBR	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.	❖❖❖ ⊕⊕⊕○
5.5.5	EBR	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.	❖❖❖❖ ⊕⊕⊕○
5.5.6	CPP	Where gonadotrophins are prescribed, considerations include: • 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 optimise monofollicular development • risk and implications of potential multiple pregnancy	
5.5.7	CPP	Gonadotrophin induced ovulation is only triggered when there are fewer than three mature follicles and needs to be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.	

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 [541], 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 [294, 301]. 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 as pharmacological agents commenced in the 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 [542]. 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 in a three-arm trial, with no control group, no meaningful conclusions can be inferred. 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 COCP 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 lacking.

Recommendations

| 5.6.1 | CCR | 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. | ❖ |

Justification

With inadequate evidence in both PCOS and infertility generally, the risk/benefit ratio is currently too uncertain 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

Observations that women with PCOS resumed regular ovulation following ovarian biopsies, led to development of surgical wedge resection via laparotomy [543]. Observational data looked promising, but surgery was surpassed by ovulation induction agents, until less invasive laparoscopic surgery [544], with potential for less adhesions and lower cost. Minor methodological 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 clarification of the role of LOS, particularly in comparison to other treatments, is needed 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 LOS to metformin and found that there was insufficient evidence to make a recommendation about LOS 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 [545-547] largely because the evidence was conflicting. One RCT reported that LOS 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) [545] and the other study reported that metformin was better than LOS 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) [546, 547]. 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 clomiphene cirtrate

Two high quality RCTs (level II) with a low risk of bias compared LOS to CC [548, 549] and found that there was no difference between LOS and CC for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy [548, 549]. There was insufficient evidence to support or refute the use of LOS over CC for multiple pregnancies [548, 549].

Laparoscopic ovarian surgery versus clomiphene critrate + metformin

Three low to moderate quality RCTs with low to moderate risk of bias compared LOS to CC plus metformin (all three studies reported in Farquhar 2012 systematic review [496]). Meta-analyses found that CC plus metformin (CC+M) was better than LOS for live birth rate, but there was no difference for pregnancy rate per patient, multiple pregnancy rate, or miscarriage rate per pregnancy [496]. There was insufficient evidence to support or refute the use of LOS over CC plus metformin for ovulation rate per patient, and OHSS [496].

Laparoscopic ovarian surgery versus aromatase inhibitors

Three RCTs with low risk of bias [493-495] compared letrozole to LOS and found that there was insufficient evidence of a difference between letrozole and LOS. One of the RCTs in 147 women with CC resistance found that letrozole was better than LOS for ovulation rate per cycle [493], however the evidence is of low certainty. The systematic review by Farquhar 2012 [496] 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 LOS 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 [550].

Laparoscopic ovarian surgery versus gonadotrophins

One high quality systematic review of RCTs (level I) with low risk of bias compared LOS to FSHs 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 LOS was better than FSH for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] I^2 = 0%, 4 studies, 303 participants) [496].

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% [551]. This was considered along with the RCT data.

Recommendations

5.7.1	EBR	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.	❖❖❖ ⊕⊕◯◯
5.7.2	CCR	Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.	❖❖❖
5.7.3	CPP	Risks need to be explained to all women with PCOS considering laparoscopic ovarian surgery.	
5.7.4	CPP	Where laparoscopic ovarian surgery is to be recommended, the following need to 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
- ere may be a small associated risk of lower ovarian reserve or loss of ovarian function
- periadnexal adhesion formation may be an associated risk.

Justification

LOS is an 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 LOS 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/m^2) [552]. Women with PCOS have higher rates of weight gain and of obesity, adversely affecting fertility. 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 severely obese women. Potential benefits 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 [553] recommend considering bariatric surgery with a BMI ≥35kg/m^2 with one or more severe complications, expected to improve with weight loss and failure of structured lifestyle intervention [553]. Obesity surgery can be considered after non-surgical treatment has failed with a BMI ≥40kg/m^2 and obesity surgery can be first line treatment with a BMI ≥50kg/m^2 [554]. Other guidelines recommend lower barriers to surgery [555]. 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 [556]. Adjustable gastric banding, once the choice for women planning pregnancy is now less common given complications and overall lower long-term weight loss [556].

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 [557, 558]. Yet these studies are absent in PCOS for fertility and pregnancy outcomes, with current PCOS studies poorly designed [559], 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 [560], as is the optimal type of bariatric surgery.

Bariatric surgery can cause malabsorption and psychological issues including disordered eating [254] and may adversely affect 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 especially for pregnant women, there are reports of poor compliance [561] and challenges tolerating fortified foods such as bread. National registries (surgery, pregnancy, infants) 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 [562], with similar findings in retrospective studies [563]. Benefits have included less GDM and large for gestational age babies.

Recommendations

5.8.1	CCR	Bariatric surgery should be considered an experimental therapy in women with PCOS, for the purpose of having a 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 needs to 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 need to 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.

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 and 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 and pregnancy outcomes in women with PCOS.

5.9a In-vitro fertilisation

In women with PCOS, is stimulated In-vitro fertilisation/Intracytoplasmic Sperm Injection effective for improving fertility outcomes?

Clinical need for the question

Ovulation induction therapies are first and second line in infertility management 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 In-vitro fertilisation (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. 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 include indications, timing and comparative efficacy with other treatments, yet 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 GDG in making their recommendations [464]. 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, QoL, OHSS risk, multiple pregnancy, miscarriage and livebirth rates should be investigated.

Recommendations

5.9.1	CCR	In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory ❖❖❖ infertility could be offered IVF as third line therapy where 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 need to be counselled prior to starting treatment including on: • availability, cost and convenience • increased risk of ovarian hyperstimulation syndrome • options to reduce the risk of ovarian hyperstimulation.

Justification

The GDG deemed IVF should be considered after failed ovulation induction treatment with high pregnancy rates per cycle, especially in younger women. Given the risks and the high costs that can be prohibitive for many patients, IVF should be considered third line medical therapy. It was noted that conception and delivery 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 Gonadotropin releasing hormone protocol

In women with PCOS undergoing IVF/ICSI treatment, is the gonadotropin releasing hormone antagonist protocol or gonadotropin releasing hormone 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 gonadotropin releasing hormone (GnRH) and other options including in-vitro maturation (see below) [564]. One of the proposed methods to reduce the risk of OHSS is to use a GnRH antagonist (as opposed to an agonist) [565-568]. 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 luteinising hormone (LH) secretion.

Summary of systematic review evidence

In the eight included studies of low [569-571], moderate [572-575], and high risk of bias [576] 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) [569-571, 574, 576], in the duration of gonadotropin use (6 studies in favour of the antagonist protocol) [570-574, 576], in OHSS rates (2 studies in favour of the antagonist protocol) [571, 573]. 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

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 is best 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 gonadotropin-releasing hormone (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 in women with PCOS, consideration needs to be given to an elective freeze of all embryos.	

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 agonist 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 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 [577]. 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 human menopausal gonadotropin (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 [578]. 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 [579]. 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.

Recommendation

5.9.4	CCR	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 follicle stimulating hormone (FSH) preparations.	❖❖❖

Justification

Only one small study in PCOS has been identified investigating uFSH versus rFSH in PCOS during ovarian stimulation for IVF/ICSI [578]. 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 luteinizing hormone (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

Options have been explored to reduce OHSS risk in IVF/ICSI in PCOS. 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 [580-582]. 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 [282]. 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 [581]. 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 [579, 583]. 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 [584]. 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.

Recommendation

| 5.9.5 | CCR | 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. | ❖❖❖ |

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.

CONTENTS

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 third-line (after failed ovulation induction) or in those with other infertility factors such as tubal damage, severe endometriosis or male factors [585]. IVF ± ICSI treatment in PCOS poses challenges, including OHSS [586]. Metformin has been studied to restore ovulation and enhance pregnancy rates in PCOS [587], through a range of mechanisms [522, 588, 589]. 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 hypothesised that metformin may reduce the production of vascular endothelial growth factor, both of which are important factors involved in the pathophysiology of OHSS [590]. 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 [588, 591, 592], moderate [522], and high risk of bias [593, 594] 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 [595] was identified by the search, however it included studies that did not meet the selection criteria for this question. The guideline development group (GDG) 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 OHSS reduced. Mild generally self-limiting side-effects were noted with adjunct metformin, as outlined in Chapter 4.

Recommendations

5.9.10	EBR	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 GnRH agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS.	❖❖❖ ⊕⊕◯◯
5.9.11	CCR	In a GnRH 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 GnRH 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 (see 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 GnRH antagonist protocol to reduce risk of ovarian hyperstimulation syndrome (see above for metformin therapy considerations).	

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, explanation is required for use.

5.9g In-vitro maturation

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. IVM of oocytes limits or omits ovarian stimulation prior to oocyte retrieval, with maturation of oocytes post retrieval, avoiding OHSS risk [564]. The definition of an IVM cycle requires clarification [596], as cycles employing an hCG trigger injection are generally associated with asynchronous oocyte maturation rates, poor embryo implantation rates and lower pregnancy rates [597, 598]. 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 [599]. Given that IVM is used in practice and has theoretical benefits, 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

With an absence of relevant RCTs [600], retrospective studies suggest IVM is similarly successful for live birth with frozen embryos generated with IVM as embryo transfers generated by standard IVF treatment [564]. However, pregnancy rates are reduced and miscarriage rates are higher if a fresh embryo transfer is performed with IVM [564]. Embryo development appears slower with a greater degree of embryo arrest in IVM [601, 602].

Recommendations

5.9.13	CPP	The term in vitro maturation (IVM) treatment cycle is 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).
5.9.14	CCR	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. ❖❖❖

Justification

The GDG 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 live birth 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 National Health and Medical Research Council (NHMRC) standards and procedures for rigorously developed external guidelines [603] and according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [15]. These methods were aligned with European Society of Human Reproduction and Embryology (ESHRE) approaches to guideline development [605].

The work builds on the original Australian guideline in PCOS [148], the update in 2014 as well as the World Health Organisation (WHO) guideline in infertility management [464] and Androgen Excess and PCOS Society (AEPCOS) Statement on improving emotional wellbeing in PCOS [109].

The International evidence–based guideline for the assessment and management of PCOS underpins 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. Thirty-seven organisations were engaged with formal partnership with ESHRE and American Society for Reproductive Medicine (ASRM). Guideline development groups (GDGs) included members nominated by the engaged international societies. Society-nominated panel members included women with PCOS, paediatricians, endocrinologists, gynaecologists, primary care physicians, reproductive endocrinologists, psychiatrists, psychologists, dietitians, exercise physiologist, public health experts, researchers and other co-opted experts as required. They were supported by an experienced project management, 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 and process

Governance included an international advisory board from six continents, a project board, five GDGs, a paediatric advisory panel, advisors and a translation committee (See Figure 1). The Australian Centre for Research Excellence in PCOS (CREPCOS) and the NHMRC partnered with the ESHRE and ASRM to deliver the guideline. The majority of the funding was provided by the Australian government, with contributions from ESHRE and ASRM. Four advisory, five project board and fifteen GDG 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 the thirty-seven engaged societies and their convened special interest groups of experts and consumers as well as public consultation have informed the final guideline.

Multidisciplinary international guideline development groups

GDGs were convened to address each of the five key clinical areas. Expertise was sought through PCOS networks to ensure multidisciplinary participation within each GDG. Each GDG 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 GDG), a consumer representative, evidence officers and representative to consider cultural aspects. See Appendix III. Co-opted experts were also included as needed.

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 women with PCOS, 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: The National Fertility Association (United States), and Victorian Assisted Reproductive Treatment Authority (VARTA) (Australia), who were actively engaged throughout the guideline process.

An 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 GDGs. 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 GDGs. Consumer representatives are also extensively engaged and are partnering in the guideline translation activities.

Indigenous representation and CALD (culturally and linguistically diverse)

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 GDGs 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 [603]. All members of the GDGs have provided signed declarations of interest and a confidentiality agreement. Additionally, declarations of interest were a standing agenda item at each monthly meeting and GDG 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 (MCHRI-PCOS-Guideline-Group-l@monash.edu).

Training of GDGs in evidence review and guideline development methods

All GDG 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 GDG 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 clinical questions to be addressed. A further prioritisation exercise was conducted within the topic specific GDGs 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 a) where recent or concurrent systematic reviews were being completed by GDG members that could be captured on narrative review; b) where questions were less well suited to a PICO systematic review format; c) for lower prioritised questions or d) where there was insufficient evidence identified for a question where a systematic review was conducted.

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

The clinical questions addressed by each GDG are as follows:

GDG 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 anti-mullerian hormone (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 CVD?
- Are women with PCOS at increased risk for impaired glucose tolerance (IGT), gestational diabetes (GDM) and type 2 diabetes mellitus (T2DM)?
- In women with PCOS, what is the most effective tool/method to assess risk of T2DM?
- Are women with PCOS at increased risk for sleep apnoea?
- What is the method/tool most effective to screen for sleep apnoea 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)?

GDG 2 - Prevalence, screening, diagnostic assessment and management of emotional wellbeing

- In women with PCOS: 1) What is the prevalence and severity of reduced quality of life (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?

GDG 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, QoL 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, QoL 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, QoL 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?

GDG 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?

GDG 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 intrauterine insemination (IUI) treatment or delayed tubal patency testing?
- In women with PCOS, is clomiphene citrate (CC) 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 CC for improving fertility outcomes?
- In women with PCOS, are aromatase inhibitors (AIs) 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 (In-vitro fertilisation/Intra-cytoplasmic sperm injection), does the choice of follicle-stimulating hormone (FSH) effect fertility outcomes?
- In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous luteinizing hormone (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 gonadotropin-releasing hormone (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 human chorionic gonadotropin (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?

* Not all questions resulted in a recommendation. Where evidence was inadequate only research recommendations were made and are captured in a separate document.

Outcome prioritisation using the GRADE method

The most relevant outcomes were prioritised by ranking their importance by health professionals and consumers to help 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 [15]. GDG members, including consumers also participated in this exercise.

Table 6: Steps for considering the relative importance of outcomes

What	Assessment and prioritisation of outcomes as critical, important but not critical, or low importance.
	Requires judgement of the balance between the desirable and undesirable health outcomes of an intervention.
Why	To focus attention on those outcomes that are considered most important when conducting evidence review and to resolve or clarify disagreements.
	To support making a recommendation and to determine the strength of the recommendation.
How	Scoping the relevant literature.
	By asking GDG members, including consumers to prioritise outcomes in light of the considerations for 'what' and 'why'.
Evidence	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.
	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.
	Additionally, the collective experience of the GDG members, including consumers, will be used using transparent methods for documenting and considering them, such as a Delphi process.

To facilitate ranking of outcomes according to their importance the following scale was be used [15].

RATING SCALE:

1	2	3	4	5	6	7	8	9

of **least** importance   of **most** importance

Of limited importance for making a decision (not included in evidence profile)	Important, but not critical for making a decision (included in evidence profile)	Critical for making a decision (included in evidence profile)

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 (Population, Intervention, Comparison, Outcome) 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 AGREE II (Appraisal of Guidelines for Research and Evaluation) 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 GDGs were able to develop guideline recommendations. The evidence reviews for each question can be found in the supplementary 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 framework was used by the GDGs 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 supplementary 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 randomised controlled trials (RCT(s)) that met the selection criteria and were not included in the systematic reviews were also 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; and
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 GDG. 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. Furthermore, while a formal analysis of cost effectiveness was not performed in this guideline, any study addressing a clinical question (PICO) that also reported cost effectiveness would be captured and addressed in the GRADE process. 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 (Cumulative Index to Nursing and Allied Health Literature)
- 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)
- EMBASE
- EBM Reviews (OVID)
- Medline (OVID)
- Medline in-process and other non-indexed citations (OVID)
- PsycINFO (OVID)

The bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analysis were also searched for identification of additional studies. Details of the search strategies and search results for each evidence review can be found in the supplementary Technical report.

Inclusion of studies

To determine the literature to be assessed further, a reviewer scanned the titles, abstracts 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 (i.e. quality appraisal criteria used for an RCT is different to that used for a cohort study) [604]. Individual quality items were investigated using a descriptive component approach. Any disagreement or uncertainty was resolved by discussion among the GDG 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 [604]

RATING	DESCRIPTION
Low	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.
Moderate	Some of the criteria have been fulfilled and those criteria that have not been fulfilled may affect the conclusions of the study.
High	Few or no criteria fulfilled or the conclusions of the study are likely or very likely to be affected.
Insufficient information	Not enough information provided on methodological quality to be able to determine risk of bias.

Data extraction

Data, according to the selection criteria, were extracted from included studies using a specially developed data extraction form [604]. 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 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 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 or duration of treatment. These can be found in the supporting 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; and
- 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; and
- 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 [15].

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 [15]).

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 [15]. Evidence profiles can be found in the Technical report.

Formulation of recommendations using the GRADE evidence to decision framework

The Evidence to Decision (EtD) 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 [15]. 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 10. Recommendation types

EBR	Evidence sufficient to inform an evidence-based recommendation (EBR)
CCR	In the absence of adequate evidence in PCOS, a clinical consensus recommendation (CCR) was made
CPP	Evidence not sought. A clinical practice point (CPP) was made where important issues arose from discussion of evidence-based or clinical consensus recommendations

The strength of the recommendations can be identified throughout the guideline by the following (adapted from ESHRE manual for guideline development [605] and the GRADE approach [15]):

Table 11: Strength of recommendations (adapted from GRADE [15] and ESHRE Manual [605])

TARGET GROUP	STRONG RECOMMENDATIONS*	CONDITIONAL (WEAK) RECOMMENDATIONS FOR THE OPTION (TEST OR TREATMENT)	CONDITIONAL (WEAK) RECOMMENDATION FOR EITHER THE OPTION OR THE COMPARISON	RESEARCH ONLY RECOMMENDATIONS	CLINICAL PRACTICE POINTS (CPP)**
CONSUMERS	Most people in your situation would want the recommended course of action and only a small proportion would not.	The majority of people in your situation would want the recommended course of action, but some would not.	There is considerable lack of clarity over whether the majority of people in your situation would want the recommended course of action or not.	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.	Clinicians, patients and policy makers are informed on the clinical implications relevant to implementation of recommendations.
HEALTH PROFESSIONALS	Most patients should receive the recommended course of action.	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.		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.	
POLICY MAKERS	The recommendation can be adopted as policy in most situations.	Policy making needs to consider perspectives and involvement of diverse stakeholders.	Policy decisions remain unclear.	Policy makers need to be aware of the need for evidence gaps and health professional and consumer prioritised research gaps.	

* 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

CONTENTS

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 GDG on the practical application of the recommendation, balancing benefits and harms. Where the word "should" is used in the recommendations, the GDG 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 GDGs 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 GDGs 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 [606].

Public consultation

Public and targeted consultation will be conducted for a period of thirty days commencing 10th February to 12th March 2018 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) [603]. The public consultation strategy is available upon request, email MCHRI-PCOS-Guideline-Group-l@monash.edu.

External review

This guideline was reviewed by the International Advisory Group, independently by relevant professional colleges and societies and through public consultation.

Scheduled review and update of the guideline

The GDGs 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 regulatory bodies 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

After five years the societies and organisations will be reengaged, the guideline panels revised and reconvened and the guideline updated as per NHMRC processes.

Dissemination and implementation

A comprehensive, international dissemination and implementation program is underway to amplify the impact of the international guideline for the assessment and treatment of PCOS. 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; and
- orientate international health policy towards an evidence-based, best practice approach.

Significant outcomes of the 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 the program is the active engagement of thirty-seven international collaborators and 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 have leveraged 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 Syndrome 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) in Australia. Guideline leads are involved in the establishment of a core outcome set in PCOS, to be implemented into clinical data sets to evaluate alignment with evidence-based care. Finally, the translation and dissemination plan is supported by a comprehensive evaluation framework, measuring international impacts and outcomes.

See practice algorithms in Appendix VIII.

Algorithm I: Screening, diagnostic assessment, risk assessment and life-stage

Algorithm II: Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

Algorithm III: Lifestyle

Algorithm IV: Pharmacological treatment for non-fertility indications

Algorithm V: Assessment and management of infertility

	TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
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.				
CONSUMERS	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.	PCOS APP (AskPCOS)	• Monash University • PCOS-CRE • PCOS consumers	• Apple itunes • Social media channels (Dedicated facebook page, twitter) • Range of conventional media	• A low cost, internationally accessible PCOS APP • Self-diagnosis function • Interactive personalised functionality tailoring information provision to individual consumer needs • Referral information to appropriate health professionals • Peer support access • Secondary data to inform PCOS research • Google analytics to enhance PCOS APP
	Provision of translated, e-health, evidence-informed PCOS information, informed by consumer needs and preferences.	e-health PCOS information accessible to a range of consumer groups	• Jean Hailes for Women's Health • VARTA • Women's Health Vic • (POSAA) • International organisations and consumer groups	• PCOS Centre for Research Excellence • International organisations and consumer groups	Accessible, translated PCOS e-health information informed by the highest quality evidence and consumer needs and preferences
	Co-develop and deliver a PCOS Lifestyle Education Program for women with PCOS	PCOS Lifestyle Education Program	• Victorian Government • International organisations	• Health services • International organisations	• Provision of an evidence-based, tailored lifestyle education program
	Co-develop and deliver an accessible, interactive, no cost, internationally available online PCOS course for consumers.	PCOS learning course	• Monash University • PCOS-CRE • MCHRI	• Monash University • MHCRI	• Accessible, online, interactive, no cost, internationally available PCOS course for consumers

TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
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.				

	TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
CONSUMERS	Co-develop PCOS Model of Care with a sustainable, psychosocial multidisciplinary approach, incorporating a comprehensive PCOS translation platform.	PCOS Clinical Model of Care	• Australian Health Services • Victorian Government	• Australian Health Services • International scale up	Sustainable, evidence-based, psychosocial-multidisciplinary PCOS services • 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.	• National and International engaged societies and organisations • CaLD and Aboriginal and Torres Strait Islanders	• National and International engaged societies and organisations	A range of translated, accessible PCOS written materials that are tailored to the needs of consumers. • Fact sheets, booklets for different consumer groups, language translated health materials

TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
Aim: Increase the uptake of PCOS evidence-based practice among health professionals internationally.				

	TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
HEALTH PROFESSIONALS	Implement an extensive publication plan targeting international journals, discipline specific publications and in the general medical media domain.	16 publications published in high impact journals and discipline specific publications	Experts from international engaged organisations	High impact international journals Discipline specific publications Medical media	16 publications published in high impact journals and discipline specific publications
	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 international engaged organisations	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

TRANSLATION STRATEGY	DELIVERABLE/S	COLLABORATOR/S	DISSEMINATION	OUTCOMES
Aim: Increase the uptake of PCOS evidence-based practice among health professionals internationally.				
HEALTH PROFESSIONALS — Develop a range of PCOS educational resources with high utility with health professionals.	Webinars Face-to-face events Flexible learning opportunities	International and national engaged organisations Peak bodies	International and national engaged organisations Peak body learning portals	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.	PCOS accredited CPD for-fee online course	• Monash University • PCOS-CRE • MHCRI International and national engaged organisations	• Monash University • Futurelearn FOOC (For-fee online course) • International and national engaged organisations	• Accessible, accredited, online, interactive, for-fee, internationally available PCOS course for health professionals
GOVERNMENT — To influence international/national health policy leveraging high level health professional expertise and informed by the highest quality evidence and consumer needs and preferences.	PCOS health policy is based on the highest quality evidence and consumer needs and preferences	International and national Governments, health organisations. Health professional experts PCOS health consumers		PCOS health policy based on the highest quality evidence and informed by health professional expertise and consumer needs and preferences

References

1. Azziz, R., et al., *Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline*. Journal of Clinical Endocrinology & Metabolism, 2006. **91**(11): p. 4237-45.

2. Diamanti-Kandarakis, E., H. Kandarakis, and R. Legro, *The role of genes and environment in the etiology of PCOS*. Endocrine, 2006. **30**(1): p. 19-26.

3. March, W., et al., *The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria*. Human Reproduction, 2010. **25**(2): p. 544-51.

4. Bozdag, G., et al., *The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis*. Hum Reprod, 2016. **31**(12): p. 2841-2855.

5. Davis, S., et al., *Preliminary indication of a high prevalence of polycystic ovary syndrome in indigenous Australian women*. Gynecological Endocrinology, 2002. **16**(6): p. 443-6.

6. Teede, H., A. Deeks, and L. Moran, *Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan*. BMC Medicine, 2010. **8**: p. 41.

7. Deeks, A., M. Gibson-Helm, and H. Teede, *Is having polycystic ovary syndrome (PCOS) a predictor of poor psychological function including depression and anxiety*. Human Reproduction, 2011. **Advance access published March 23, 2011**.

8. Moran, L., et al., *Polycystic ovary syndrome: a biopsychosocial understanding in young women to improve knowledge and treatment options*. Journal of Psychosomatic Obstetrics & Gynecology, 2010. **31**(1): p. 24-31.

9. Boomsma, C., et al., *A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome*. Human Reproduction Update, 2006. **12**(6): p. 673-83.

10. Apridonidze, T., et al., *Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2005. **90**(4): p. 1929-35.

11. Legro, R., et al., *Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women*. Journal of Clinical Endocrinology & Metabolism, 1999. **84**(1): p. 165-168.

12. Saini, S., et al., *Gaps in knowledge in diagnosis and management of polycystic ovary syndrome*. Fertility and Sterility, 2016. **106**(3): p. e100.

13. Gibson-Helm, M., et al., *Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome*. Journal of Clinical Endocrinology and Metabolism, 2017. **102**(2): p. 604-612.

14. Brakta, S., et al., *Perspectives on Polycystic Ovary Syndrome: Is Polycystic Ovary Syndrome Research Underfunded?* J Clin Endocrinol Metab, 2017. **102**(12): p. 4421-4427.

15. The GRADE Working Group, GRADE handbook for grading quality of evidence and strength of recommendation. Vol. Version 3.2 [updated March 2009]. 2009

16. NIH Evidence based workshop panel, *NIH Evidence based workshop on Polycystic Ovary Syndrome*. http://prevention.nih.gov/workshops/2012/pcos/resources.aspx., 2012.

17. Lemarchand-Béraud, T., et al., *Maturation of the hypothalamo-pituitary-ovarian axis in adolescent girls*. Journal of Clinical Endocrinology & Metabolism, 1982. **54**(2): p. 241-6.

18. Treloar, A., et al., *Variation of the human menstrual cycle through reproductive life*. International Journal of Fertility, 1967. **12**: p. 77.

19. Flug, D., R. Largo, and A. Prader, *Menstrual patterns in adolescent Swiss girls: a longitudinal study*. Annals of Human Biology 1984. **11**(6): p. 495-508.

20. Pena, A.S., et al., *The majority of irregular menstrual cycles in adolescence are ovulatory: results of a prospective study*. Arch Dis Child, 2018. **103**(3): p. 235-239.

21. Widholm, O. and R. Kantero, *A statistical analysis of the menstrual patterns of 8,000 Finnish girls and their mothers*. Acta Obstet Gynecol Scand Suppl, 1971. **14**(Suppl).

22. Adams Hillard, P., *Menstruation in young girls: a clinical perspective* Obstetrics & Gynecology, 2002. **99**(4): p. 655-62.

23. Slap, G., *Menstrual disorders in adolescence*. Best Practice & Research Clinical Obstetrics & Gynaecology 2003. **17**(1): p. 75-92.

24. Apter, D., *Endocrine and metabolic abnormalities in adolescents with a PCOS-like condition: consequences for adult reproduction*. Trends Endocrinol Metab, 1998. **9**(2): p. 58-61.

25. Metcalf, M.G., et al., *Incidence of ovulation in the years after the menarche*. J Endocrinol, 1983. **97**(2): p. 213-9.

26. Apter, D. and R. Vihko, *Early menarche, a risk factor for breast cancer, indicates early onset of ovulatory cycles*. Journal of Clinical Endocrinology & Metabolism, 1983. **57**(1): p. 82-6.

27. van Hooff, M.H., et al., *Predictive value of menstrual cycle pattern, body mass index, hormone levels and polycystic ovaries at age 15 years for oligo-amenorrhoea at age 18 years*. Hum Reprod, 2004. **19**(2): p. 383-92.

28. Witchel, S.F., et al., *The Diagnosis of Polycystic Ovary Syndrome during Adolescence*. Horm Res Paediatr, 2015.

29. Vermeulen, A., L. Verdonck, and J. Kaufman, *A critical evaluation of simple methods for the estimation of free testosterone in serum*. Journal of Clinical Endocrinology & Metabolism, 1999. **84**(10): p. 3666-3672.

30. Rosner, W. and H. Vesper, *Toward excellence in testosterone testing: A consensus statement*. Journal of Clinical Endocrinology & Metabolism, 2010. **95**(10): p. 4542-4548.

31. Taieb, J., B. Mathian, and F. Millot, et al,, *Testosterone measured by 10 immunoassays and by radio-isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children*. Clinical Chemistry, 2003. **49**: p. 1381-1395.

32. Bili, A.E., et al., *The combination of ovarian volume and outline has better diagnostic accuracy than prostate-specific antigen (PSA) concentrations in women with polycystic ovarian syndrome (PCOS)*. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2014. **179**: p. 32-35.

33. Escobar-Morreale, H., et al., *Receiver operating characteristic analysis of the performance of basal serum hormone profiles for the diagnosis of polycystic ovary syndrome in epidemiological studies*. European Journal of Endocrinology, 2001. **145**(5): p. 619-624.

34. Koskinen, P., et al., *Optimal use of hormone determinations in the biochemical diagnosis of the polycystic ovary syndrome*. Fertility & Sterility, 1996. **65**(3): p. 517-22.

35. Rudnicka, E., S. Radowicki, and K. Suchta, *Prostate specific antigen (PSA) in diagnosis of polycystic ovarian syndrome - a new insight*. Gynecological Endocrinology, 2016. **32**(11): p. 931-935.

36. Stener-Victorin, E., et al., *Are there any sensitive and specific sex steroid markers for polycystic ovary syndrome?* J Clin Endocrinol Metab, 2010. **95**(2): p. 810-9.

37. Villarroel, C., et al., *Hirsutism and oligomenorrhea are appropriate screening criteria for polycystic ovary syndrome in adolescents*. Gynecological Endocrinology, 2015. **31**(8): p. 625-9.

38. Salameh, W.A., et al., *Specificity and predictive value of circulating testosterone assessed by tandem mass spectrometry for the diagnosis of polycystic ovary syndrome by the National Institutes of Health 1990 criteria*. Fertil Steril, 2014. **101**(4): p. 1135-1141.e2.

39.   Hahn, S., et al., *Diagnostic value of calculated testosterone indices in the assessment of polycystic ovary syndrome*. Clin Chem Lab Med, 2007. **45**(2): p. 202-7.

40.   Lizneva, D., et al., *Androgen excess: Investigations and management*. Best Pract Res Clin Obstet Gynaecol, 2016. **37**: p. 98-118.

41.   Ferriman, D. and J.D. Gallwey, *Clinical assessment of body hair growth in women*. J Clin Endocrinol Metab, 1961. **21**: p. 1440-7.

42.   Yildiz, B.O., et al., *Visually scoring hirsutism*. Hum Reprod Update, 2010. **16**(1): p. 51-64.

43.   Hatch, R., et al., *Hirsutism: implications, etiology, and management*. Am J Obstet Gynecol, 1981. **140**(7): p. 815-30.

44.   Eichenfield, L.F., et al., *Evidence-based recommendations for the diagnosis and treatment of pediatric acne*. Pediatrics, 2013. **131 Suppl 3**: p. S163-86.

45.   Lucky, A.W., et al., *Predictors of severity of acne vulgaris in young adolescent girls: results of a five-year longitudinal study*. J Pediatr, 1997. **130**(1): p. 30-9.

46.   Knochenhauer, E.S., et al., *Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study*. J Clin Endocrinol Metab, 1998. **83**(9): p. 3078-82.

47.   DeUgarte, C.M., et al., *Degree of facial and body terminal hair growth in unselected black and white women: toward a populational definition of hirsutism*. J Clin Endocrinol Metab, 2006. **91**(4): p. 1345-50.

48.   Zhao, X., et al., *Defining hirsutism in Chinese women: a cross-sectional study*. Fertil Steril, 2011. **96**(3): p. 792-6.

49.   Souter, I., et al., *The prevalence of androgen excess among patients with minimal unwanted hair growth*. American Journal of Obstetrics and Gynecology, 2004. **191**(6): p. 1914-1920.

50.   Ezeh, U., B.O. Yildiz, and R. Azziz, *Referral bias in defining the phenotype and prevalence of obesity in polycystic ovary syndrome*. J Clin Endocrinol Metab, 2013. **98**(6): p. E1088-96.

51.   Lizneva, D., et al., *Phenotypes and body mass in women with polycystic ovary syndrome identified in referral versus unselected populations: systematic review and meta-analysis*. Fertil Steril, 2016. **106**(6): p. 1510-1520 e2.

52.   Jones, G.L., et al., *Health-related quality of life measurement in women with polycystic ovary syndrome: a systematic review*. Hum Reprod Update, 2008. **14**(1): p. 15-25.

53.   Kazemi, H., et al., *Women self-perception of excess hair growth, as a predictor of clinical hirsutism: a population-based study*. Journal of Endocrinological Investigation, 2015. **38**(8): p. 923-928.

54.   Uysal, G., et al., *Is acne a sign of androgen excess disorder or not?* Eur J Obstet Gynecol Reprod Biol, 2017. **211**: p. 21-25.

55.   Slayden, S.M., et al., *Hyperandrogenemia in patients presenting with acne*. Fertil Steril, 2001. **75**(5): p. 889-92.

56.   Olsen, E.A., et al., *Evaluation and treatment of male and female pattern hair loss*. J Am Acad Dermatol, 2005. **52**(2): p. 301-11.

57.   The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, *Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome: The Rotterdam ESHRE/ASRM- Sponsered PCOS Consensus Workshop Group*. Fertility & Sterility, 2004. **81**(1): p. 19-25.

58.   Kristensen, S., et al., *A very large proportion of young Danish women have polycystic ovaries: is a revision of the Rotterdam criteria needed?* Human Reproduction, 2010. **25**(12): p. 3117–3122.

59.   Allemand, M.C., et al., *Diagnosis of polycystic ovaries by three-dimensional transvaginal ultrasound*. Fertil Steril, 2006. **85**(1): p. 214-9.

60.   Alsamarai, S., et al., *Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age*. J Clin Endocrinol Metab, 2009. **94**(12): p. 4961-70.

61. Atiomo, W.U., et al., *Ultrasound criteria in the diagnosis of polycystic ovary syndrome (PCOS).* Ultrasound Med Biol, 2000. **26**(6): p. 977-80.

62. Carmina, E., et al., *Amh Measurement Versus Ovarian Ultrasound in the Diagnosis of Polycystic Ovary Syndrome in Different Phenotypes*. Endocrine Practice, 2016. **22**(3): p. 287-93.

63. Chen, Y., et al., *Ovarian volume and follicle number in the diagnosis of polycystic ovary syndrome in Chinese women*. Ultrasound Obstet Gynecol, 2008. **32**(5): p. 700-3.

64. Chen, Y., et al., *The role of ovarian volume as a diagnostic criterion for chinese adolescents with polycystic ovary syndrome*. Journal of Pediatric & Adolescent Gynecology, 2008. **21**(6): p. 347-350.

65. Dewailly, D., et al., *Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries*. Hum Reprod, 2011. **26**(11): p. 3123-9.

66. Jonard, S., et al., *Ultrasound examination of polycystic ovaries: is it worth counting the follicles?* Hum Reprod, 2003. **18**(3): p. 598-603.

67. Jonard, S., Y. Robert, and D. Dewailly, *Revisiting the ovarian volume as a diagnostic criterion for polycystic ovaries*. Hum Reprod, 2005. **20**(10): p. 2893-8.

68. Kosus, N., et al., *Do threshold values of ovarian volume and follicle number for diagnosing polycystic ovarian syndrome in Turkish women differ from western countries?* Eur J Obstet Gynecol Reprod Biol, 2011. **154**(2): p. 177-81.

69. Lujan, M.E., et al., *Updated ultrasound criteria for polycystic ovary syndrome: reliable thresholds for elevated follicle population and ovarian volume*. Hum Reprod, 2013. **28**(5): p. 1361-8.

70. Pache, T.D., et al., *How to discriminate between normal and polycystic ovaries: transvaginal US study*. Radiology, 1992. **183**(2): p. 421-3.

71. Villa, P., et al., *Ovarian volume and gluco-insulinaemic markers in the diagnosis of PCOS during adolescence*. Clin Endocrinol (Oxf), 2013. **78**(2): p. 285-90.

72. Hansen, K.R., et al., *A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause*. Hum Reprod, 2008. **23**(3): p. 699-708.

73. Badouraki, M., et al., *Evaluation of pelvic ultrasonography in the diagnosis and differentiation of various forms of sexual precocity in girls*. Ultrasound Obstet Gynecol, 2008. **32**(6): p. 819-27.

74. Razzaghy-Azar, M., et al., *Sonographic measurement of uterus and ovaries in premenarcheal healthy girls between 6 and 13 years old: correlation with age and pubertal status*. J Clin Ultrasound, 2011. **39**(2): p. 64-73.

75. Herter, L.D., et al., *Ovarian and uterine findings in pelvic sonography: comparison between prepubertal girls, girls with isolated thelarche, and girls with central precocious puberty*. J Ultrasound Med, 2002. **21**(11): p. 1237-46; quiz 1247-8.

76. Badouraki, M., et al., *Sonographic assessment of uterine and ovarian development in normal girls aged 1 to 12 years*. J Clin Ultrasound, 2008. **36**(9): p. 539-44.

77. Kelsey, T.W., et al., *Ovarian volume throughout life: a validated normative model*. PLoS One, 2013. **8**(9): p. e71465.

78. Codner, E., et al., *Polycystic ovarian morphology in postmenarchal adolescents*. Fertil Steril, 2011. **95**(2): p. 702-6 e1-2.

79. Cook, C.L., et al., *Relationship between serum mullerian-inhibiting substance and other reproductive hormones in untreated women with polycystic ovary syndrome and normal women*. Fertil Steril, 2002. **77**(1): p. 141-6.

80. Seifer, D.B. and D.T. MacLaughlin, *Mullerian Inhibiting Substance is an ovarian growth factor of emerging clinical significance*. Fertility and Sterility. **88**(3): p. 539-546.

81. Casadei, L., et al., *The role of serum anti-Mullerian hormone (AMH) in the hormonal diagnosis of polycystic ovary syndrome*. Gynecological Endocrinology, 2013. **29**(6): p. 545-50.

82. Cassar, S., et al., *Polycystic ovary syndrome and anti-Mullerian hormone: role of insulin resistance, androgens, obesity and gonadotrophins*. Clinical Endocrinology, 2014. **81**(6): p. 899-906.

83. Chao, K.C., et al., *Anti-Mullerian hormone serum level as a predictive marker of ovarian function in Taiwanese women*. Journal of the Chinese Medical Association: JCMA, 2012. **75**(2): p. 70-4.

84. Dewailly, D., et al., *Using cluster analysis to identify a homogeneous subpopulation of women with polycystic ovarian morphology in a population of non-hyperandrogenic women with regular menstrual cycles*. Human Reproduction, 2014. **29**(11): p. 2536-43.

85. Eilertsen, T.B., E. Vanky, and S.M. Carlsen, *Anti-Mullerian hormone in the diagnosis of polycystic ovary syndrome: can morphologic description be replaced?* Human Reproduction, 2012. **27**(8): p. 2494-502.

86. Hart, R., et al., *Serum antimullerian hormone (AMH) levels are elevated in adolescent girls with polycystic ovaries and the polycystic ovarian syndrome (PCOS)*. Fertility & Sterility, 2010. **94**(3): p. 1118-21.

87. Homburg, R., et al., *The relationship of serum anti-Mullerian hormone with polycystic ovarian morphology and polycystic ovary syndrome: a prospective cohort study*. Human Reproduction, 2013. **28**(4): p. 1077-83.

88. Iliodromiti, S., et al., *Can anti-Mullerian hormone predict the diagnosis of polycystic ovary syndrome? A systematic review and meta-analysis of extracted data*. Journal of Clinical Endocrinology & Metabolism, 2013. **98**(8): p. 3332-40.

89. Kim, J.Y., et al., *Anti-Mullerian hormone in obese adolescent girls with polycystic ovary syndrome*. Journal of Adolescent Health, 2017. **60**(3): p. 333-339.

90. Kim, J.Y., et al., *Anti-mullerian hormone (AMH) in obese adolescent girls with polycystic ovary syndrome (PCOS): cross-sectional and treatment-associated longitudinal changes*. Endocrine reviews. Conference: 98th annual meeting and expo of the endocrine society, ENDO, 2016. 37(2 Supplement 1).

91. Koninger, A., et al., *Anti-Mullerian Hormone: an indicator for the severity of polycystic ovarian syndrome*. Archives of Gynecology & Obstetrics, 2014. **290**(5): p. 1023-30.

92. Lauritsen, M.P., et al., *The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Mullerian hormone*. Human Reproduction, 2014. **29**(4): p. 791-801.

93. Li, L., et al., *Elevated serum anti-mullerian hormone in adolescent and young adult Chinese patients with polycystic ovary syndrome*. Wiener Klinische Wochenschrift, 2010. **122**(17-18): p. 519-24.

94. Li, Y., et al., *Different diagnostic power of anti-Mullerian hormone in evaluating women with polycystic ovaries with and without hyperandrogenism*. Journal of Assisted Reproduction & Genetics, 2012. **29**(10): p. 1147-51.

95. Pigny, P., et al., *Comparative assessment of five serum antimullerian hormone assays for the diagnosis of polycystic ovary syndrome*. Fertility & Sterility, 2016. **105**(4): p. 1063-1069.e3.

96. Pigny, P., et al., *Serum anti-Mullerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2006. **91**(3): p. 941-5.

97. Sahmay, S., et al., *Elevated serum levels of anti-Mullerian hormone can be introduced as a new diagnostic marker for polycystic ovary syndrome*. Acta Obstetricia et Gynecologica Scandinavica, 2013. **92**(12): p. 1369-74.

98. Sahmay, S., et al., *Diagnosis of Polycystic Ovary Syndrome: AMH in combination with clinical symptoms*. Journal of Assisted Reproduction & Genetics, 2014. **31**(2): p. 213-20.

99. Saikumar, P., et al., *Anti mullerian hormone: A potential marker for recruited non growing follicle of ovarian pool in women with polycystic ovarian syndrome*. Journal of Clinical and Diagnostic Research, 2013. **7**(9): p. 1866-1869.

100. Sopher, A.B., et al., *Anti-Mullerian hormone may be a useful adjunct in the diagnosis of polycystic ovary syndrome in nonobese adolescents*. Journal of Pediatric Endocrinology & Metabolism, 2014. **27**(11-12): p. 1175-9.

101. Tokmak, A., et al., *Is anti-mullerian hormone a good diagnostic marker for adolescent and young adult patients with polycystic ovary syndrome?Anti-mullerian hormon polikistik over sendromlu adolesan ve genc eriskinlerde iyi bir tanisal belirtec midir?* Turk Jinekoloji ve Obstetrik Dernegi Dergisi, 2015. **12**(4): p. 199-204.

102. Tremellen, K. and D. Zander-Fox, *Serum anti-Mullerian hormone assessment of ovarian reserve and polycystic ovary syndrome status over the reproductive lifespa*n. Australian & New Zealand Journal of Obstetrics & Gynaecology, 2015. **55**(4): p. 384-9.

103. Villarroel, C., et al., *Polycystic ovarian morphology in adolescents with regular menstrual cycles is associated with elevated anti-Mullerian hormone*. Human Reproduction, 2011. **26**(10): p. 2861-8.

104. Wiweko, B., et al., *Anti-mullerian hormone as a diagnostic and prognostic tool for PCOS patients*. Journal of Assisted Reproduction & Genetics, 2014. **31**(10): p. 1311-6.

105. Woo, H.Y., et al., *Differences of the association of anti-Mullerian hormone with clinical or biochemical characteristics between women with and without polycystic ovary syndrome*. Endocrine Journal, 2012. **59**(9): p. 781-90.

106. Yetim, A., et al., *Anti-Mullerian Hormone and Inhibin-A, but not Inhibin-B or Insulin-Like Peptide-3, may be Used as Surrogates in the Diagnosis of Polycystic Ovary Syndrome in Adolescents: Preliminary Results*. Journal of clinical research in pediatric endocrinology, 2016. **8**(3): p. 288-97.

107. Zadehmodarres, S., et al., *Anti-mullerian hormon level and polycystic ovarian syndrome diagnosis.* Iranian Journal of Reproductive Medicine, 2015. **13**(4): p. 227-230.

108. Boyle, J., Cunningham J, O'Dea K, Dunbar T, Norman RJ., *Prevalence of polycystic ovary syndrome in a sample of Indigenous women in Darwin, Australia.* Med J Aust, 2012. **196**(1): p. 62-6.

109. Dokras, A., et al., *Androgen Excess-Polycystic Ovary Syndrome Society Position Statement on Depression, Anxiety, Quality of Life and Eating Disorders in Polycystic Ovary Syndrome*. Fertility and Sterility, 2018. **In Press**.

110. Elting, M.W., et al., *Women with polycystic ovary syndrome gain regular menstrual cycles when ageing.* Hum Reprod, 2000. **15**(1): p. 24-8.

111. Vulpoi, C., et al., *Ageing and reproduction: is polycystic ovary syndrome an exception?* Ann Endocrinol (Paris), 2007. **68**(1): p. 45-50.

112. Brown, Z.A., et al., *The phenotype of polycystic ovary syndrome ameliorates with aging*. Fertil Steril, 2011. **96**(5): p. 1259-65.

113. Liang, S.J., et al., *Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40.* Human reproduction, 2011. **26**(12): p. 3443-3449.

114. Winters, S.J., et al., *Serum testosterone levels decrease in middle age in women with the polycystic ovary syndrome*. Fertil Steril, 2000. **73**(4): p. 724-9.

115. Carmina, E., A.M. Campagna, and R.A. Lobo, *A 20-year follow-up of young women with polycystic ovary syndrome*. Obstet Gynecol, 2012. **119**(2 Pt 1): p. 263-9.

116. Pinola, P., et al., *Androgen Profile Through Life in Women With Polycystic Ovary Syndrome: A Nordic Multicenter Collaboration Study*. J Clin Endocrinol Metab, 2015. **100**(9): p. 3400-7.

117. Tehrani, F.R., et al., *Is polycystic ovary syndrome an exception for reproductive aging?* Hum Reprod, 2010. **25**(7): p. 1775-81.

118. Li, J., et al., *Common diseases as determinants of menopausal age*. Human Reproduction, 2016. **31**(12): p. 2856-2864.

CONTENTS

119. Schmidt, J., et al., *Reproductive hormone levels and anthropometry in postmenopausal women with polycystic ovary syndrome (PCOS): a 21-year follow-up study of women diagnosed with PCOS around 50 years ago and their age-matched controls*. J Clin Endocrinol Metab, 2011. **96**(7): p. 2178-85.

120. Markopoulos, M.C., et al., *Hyperandrogenism in women with polycystic ovary syndrome persists after menopause*. J Clin Endocrinol Metab, 2011. **96**(3): p. 623-31.

121. Legro, R.S., et al., *Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism*. J Clin Endocrinol Metab, 2010. **95**(12): p. 5305-13.

122. Puurunen, J., et al., *Unfavorable hormonal, metabolic, and inflammatory alterations persist after menopause in women with PCOS*. J Clin Endocrinol Metab, 2011. **96**(6): p. 1827-34.

123. Krentz, A., D. von Mühlen, and E. Barrett Connor, *Searching for polycystic ovary syndrome in postmenopausal women: evidence of a dose-effect association with prevalent cardiovascular disease*. Menopause, 2007. **14**(2): p. 284-292.

124. Merz, C.N., et al., *Cardiovascular Disease and 10-Year Mortality in Postmenopausal Women with Clinical Features of Polycystic Ovary Syndrome*. J Womens Health (Larchmt), 2016. **25**(9): p. 875-81.

125. Gabrielli, L., C. de Almeida Mda, and E.M. Aquino, *Proposed criteria for the identification of polycystic ovary syndrome following menopause: An ancillary study of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)*. Maturitas, 2015. **81**(3): p. 398-405.

126. de Groot, P.C., et al., *PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis*. Human Reproduction Update, 2011. **17**(4): p. 495-500.

127. Heida, K.Y., et al., *Cardiovascular risk management after reproductive and pregnancy-related disorders: A Dutch multidisciplinary evidence-based guideline*. Eur J Prev Cardiol, 2016. **23**(17): p. 1863-1879.

128. Calderon-Margalit, R., et al., *Prospective association of polycystic ovary syndrome with coronary artery calcification and carotid-intima-media thickness: the Coronary Artery Risk Development in Young Adults Women's study*. Arteriosclerosis, Thrombosis & Vascular Biology, 2014. **34**(12): p. 2688-94.

129. Cibula, D., et al., *Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome*. Human Reproduction, 2000. **15**(4): p. 785-9.

130. Iftikhar, S., et al., *Risk of cardiovascular events in patients with polycystic ovary syndrome*. Netherlands Journal of Medicine, 2012. **70**(2): p. 74-80.

131. Lunde, O. and T. Tanbo, *Polycystic ovary syndrome: a follow-up study on diabetes mellitus, cardiovascular disease and malignancy 15-25 years after ovarian wedge resection*. Gynecological Endocrinology, 2007. **23**(12): p. 704-9.

132. Mani, H., et al., *Diabetes and cardiovascular events in women with polycystic ovary syndrome: a 20-year retrospective cohort study*. Clinical Endocrinology, 2013. **78**(6): p. 926-34.

133. Morgan, C.L., et al., *Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched, reference controls: a retrospective, observational study.* Journal of Clinical Endocrinology & Metabolism, 2012. **97**(9): p. 3251-60.

134. Schmidt, J., et al., *Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study*. J Clin Endocrinol Metab, 2011. **96**(12): p. 3794-803.

135. Wild, S., et al., *Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study*. Clinical Endocrinology, 2000. **52**(5): p. 595-600.

136. Wild, R., et al., *Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: A consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society*. Journal of Clinical Endocrinology & Metabolism, 2010. **95**(5): p. 2038–2049.

137. National Vascular Disease Prevention Alliance, *Guidelines for the assessment of absolute cardiovascular disease risk*, National Heart Foundation of Australia, Editor. 2009.

138. National Health and Medical Research Council, *Clinical Practice Guidelines for the Management of Overweight and Obesity in Adults*. 2003.

139. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, *Lipid Management Guidelines 2001 - summary paper*. Medical Journal of Australia, 2001. **175**(5 November): p. S57-S88.

140. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, *Position statement of lipid management*. Heart, Lung & Circulation, 2005: p. 275-291.

141. National Heart Foundation of Australia (National Blood Pressure and Vascular Disease Advisory Committee), *Guide to management of hypertension 2008*, updated 2010. 2010: Australia.

142. Cassar, S., et al., *Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic–hyperinsulinaemic clamp studies*. Human Reproduction, 2016. **31**(11): p. 2619-2631.

143. Moran, L., et al., *Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis*. Human Reproduction Update, 2010. **16**(4): p. 347-63.

144. Rubin, K.H., et al., *Development and Risk Factors of Type 2 Diabetes in a Nationwide Population of Women With Polycystic Ovary Syndrome*. J Clin Endocrinol Metab, 2017. **102**(10): p. 3848-3857.

145. Tomlinson, J., et al., *Type 2 diabetes and cardiovascular disease in polycystic ovary syndrome: what are the risks and can they be reduced?* Diabetic Medicine, 2010. **27**(5): p. 498-515.

146. Colagiuri, S., et al., *National Evidence Based Guideline for Case Detection and Diagnosis of Type 2 Diabetes,* Diabetes Australia and the NHMRC, Editor. 2009: Canberra, Australia.

147. Pelanis, R., et al., *The prevalence of Type 2 diabetes is not increased in normal-weight women with PCOS*. Human reproduction (Oxford, England), 2017. **32**(11): p. 1-8.

148. Teede, H.J., et al., *Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline*. Medical Journal of Australia, 2011. **195**(6): p. S65-S112.

149. Ollila, M.E., et al., *Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus-a prospective, population-based cohort study*. Hum Reprod, 2017. **32**(2): p. 423-431.

150. Kakoly, N.S., et al., *Ethnicity, obesity and the prevalence of impaired glucose tolerance and type 2 diabetes in PCOS: a systematic review and meta-regression*. Human Reproduction Update, 2018.

151. American Diabetes Association, *Standards of Medical Care in Diabetes-2017*. Diabetes Care, 2017. **40**(Suppl 1).

152. Knowler, W.C., et al., *Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin*. N Engl J Med, 2002. **346**(6): p. 393-403.

153. Bodmer-Roy, S., et al., *Pregnancy outcomes in women with and without gestational diabetes mellitus according to the International Association of the Diabetes and Pregnancy Study Groups criteria*. Obstet Gynecol, 2012. **120**(4): p. 746-52.

154. Senaratna, C.V., et al., *Prevalence of obstructive sleep apnea in the general population: A systematic review*. Sleep Med Rev, 2017. **34**: p. 70-81.

155. Mansfield, D.R., N.A. Antic, and R.D. McEvoy, *How to assess, diagnose, refer and treat adult obstructive sleep apnoea: a commentary on the choices*. Med J Aust, 2013. **199**(8): p. S21-6.

156. McEvoy, R.D., et al., *CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea*. N Engl J Med, 2016. **375**(10): p. 919-31.

CONTENTS

157. Marin, J.M., et al., *Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study*. Lancet, 2005. **365**(9464): p. 1046-53.

158. Hu, X., et al., *The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: a meta-analysis of randomized controlled trials*. J Clin Hypertens (Greenwich), 2015. **17**(3): p. 215-22.

159. Lam, J.C., et al., *A randomised controlled trial of nasal continuous positive airway pressure on insulin sensitivity in obstructive sleep apnoea*. Eur Respir J, 2010. **35**(1): p. 138-45.

160. Coughlin, S.R., et al., *Cardiovascular and metabolic effects of CPAP in obese males with OSA*. Eur Respir J, 2007. **29**(4): p. 720-7.

161. Comondore, V.R., et al., *The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: a pilot feasibility randomized crossover trial*. Lung, 2009. **187**(1): p. 17-22.

162. West, S.D., et al., *Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes*. Thorax, 2007. **62**(11): p. 969-74.

163. Shaw, J.E., et al., *The Effect of Treatment of Obstructive Sleep Apnea on Glycemic Control in Type 2 Diabetes*. Am J Respir Crit Care Med, 2016. **194**(4): p. 486-92.

164. Peker, Y., et al., *Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea. The RICCADSA Randomized Controlled Trial*. Am J Respir Crit Care Med, 2016. **194**(5): p. 613-20.

165. Parra, O., et al., *Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial*. Eur Respir J, 2011. **37**(5): p. 1128-36.

166. Jonas, D.E., et al., *Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force*. Jama, 2017. **317**(4): p. 415-433.

167. Fogel, R.B., et al., *Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome*. J Clin Endocrinol Metab, 2001. **86**(3): p. 1175-80.

168. Vgontzas, A.N., et al., *Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance*. J Clin Endocrinol Metab, 2001. **86**(2): p. 517-20.

169. Gopal, M., et al., *The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome*. Sleep Med, 2002. **3**(5): p. 401-4.

170. Mokhlesi, B., et al., *Risk of obstructive sleep apnea in obese and nonobese women with polycystic ovary syndrome and healthy reproductively normal women*. Fertil Steril, 2012. **97**(3): p. 786-91.

171. Andersen, M.L. and S. Tufik, *The effects of testosterone on sleep and sleep-disordered breathing in men: its bidirectional interaction with erectile function*. Sleep Med Rev, 2008. **12**(5): p. 365-79.

172. Tasali, E., et al., *Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome*. J Clin Endocrinol Metab, 2011. **96**(2): p. 365-74.

173. Tasali, E., E. Van Cauter, and D.A. Ehrmann, *Relationships between sleep disordered breathing and glucose metabolism in polycystic ovary syndrome*. J Clin Endocrinol Metab, 2006. **91**(1): p. 36-42.

174. Subramanian, S., et al., *Practice patterns of screening for sleep apnea in physicians treating PCOS patients. Sleep Breath*, 2007. **11**(4): p. 233-7.

175. Chung, F., et al., *STOP questionnaire: a tool to screen patients for obstructive sleep apnea*. Anesthesiology, 2008. **108**(5): p. 812-21.

176. Chai-Coetzer, C.L., et al., *A simplified model of screening questionnaire and home monitoring for obstructive sleep apnoea in primary care*. Thorax, 2011. **66**(3): p. 213-9.

177. Charalampakis, V., et al., *Polycystic ovary syndrome and endometrial hyperplasia: an overview of the role of bariatric surgery in female fertility*. Eur J Obstet Gynecol Reprod Biol, 2016. **207**: p. 220-226.

178. Bokhman, J.V., *Two pathogenetic types of endometrial carcinoma*. Gynecol Oncol, 1983. **15**(1): p. 10-7.

179. Deligdisch, L. and C.F. Holinka, *Endometrial carcinoma: two diseases?* Cancer Detect Prev, 1987. **10**(3-4): p. 237-46.

180. Fearnley, E.J., et al., *Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case-control study*. Cancer Causes Control, 2010. **21**(12): p. 2303-8.

181. Harris, H.R. and K.L. Terry, *Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review*. Fertil Res Pract, 2016. **2**: p. 14.

182. Hardiman, P., O.C. Pillay, and W. Atiomo, *Polycystic ovary syndrome and endometrial carcinoma*. Lancet, 2003. **361**(9371): p. 1810-2.

183. Dumesic, D.A. and R.A. Lobo, *Cancer risk and PCOS*. Steroids, 2013. **78**(8): p. 782-5.

184. Barry, J.A., M.M. Azizia, and P.J. Hardiman, *Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis*. Hum Reprod Update, 2014. **20**(5): p. 748-58.

185. Chittenden, B.G., et al., *Polycystic ovary syndrome and the risk of gynaecological cancer: a systematic review*. Reprod Biomed Online, 2009. **19**(3): p. 398-405.

186. Haoula, Z., M. Salman, and W. Atiomo, *Evaluating the association between endometrial cancer and polycystic ovary syndrome*. Hum Reprod, 2012. **27**(5): p. 1327-31.

187. Wild, S., et al., *Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study*. Hum Fertil (Camb), 2000. **3**(2): p. 101-105.

188. Zucchetto, A., et al., *Hormone-related factors and gynecological conditions in relation to endometrial cancer risk*. Eur J Cancer Prev, 2009. **18**(4): p. 316-21.

189. Park, J.C., et al., *Endometrial histology and predictable clinical factors for endometrial disease in women with polycystic ovary syndrome*. Clin Exp Reprod Med, 2011. **38**(1): p. 42-6.

190. Cheung, A.P., *Ultrasound and menstrual history in predicting endometrial hyperplasia in polycystic ovary syndrome*. Obstet Gynecol, 2001. **98**(2): p. 325-31.

191. Brinton, L.A., et al., *Fertility drugs and endometrial cancer risk: results from an extended follow-up of a large infertility cohort*. Hum Reprod, 2013. **28**(10): p. 2813-21.

192. Jones, G.L., et al., *The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (PCOSQ)*: a validation. Hum Reprod, 2004. **19**(2): p. 371-7.

193. Malik-Aslam, A., M.D. Reaney, and J. Speight, *The suitability of polycystic ovary syndrome-specific questionnaires for measuring the impact of PCOS on quality of life in clinical trials*. Value Health, 2010. **13**(4): p. 440-6.

194. Taghavi, S.A., et al., *Health-related quality of life in polycystic ovary syndrome patients: A systematic review*. Iran J Reprod Med, 2015. **13**(8): p. 473-82.

195. Hollinrake, E., et al., *Increased risk of depressive disorders in women with polycystic ovary syndrome*. Fertil Steril, 2007. **87**(6): p. 1369-76.

196. Bazarganipour, F., et al., *The impact of polycystic ovary syndrome on the health-related quality of life: A systematic review and meta-analysis*. Iran J Reprod Med, 2015. **13**(2): p. 61-70.

197. Skovlund, C., et al., *Association of hormonal contraception with depression*. JAMA Psychiatry, 2016. **73**(11): p. 1154-1162.

198. Dokras, A., et al., *Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis*. Obstet Gynecol, 2011. **117**(1): p. 145-52.

199. Barry, J.A., A.R. Kuczmierczyk, and P.J. Hardiman, *Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis*. Hum Reprod, 2011. **26**(9): p. 2442-51.

200. Veltman-Verhulst, S.M., et al., *Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies*. Hum Reprod Update, 2012. **18**(6): p. 638-51.

201. Cooney, L.G., et al., *High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis*. Hum Reprod, 2017. **32**(5): p. 1075-1091.

202. Cesta, C.E., et al., *Polycystic ovary syndrome and psychiatric disorders: Co-morbidity and heritability in a nationwide Swedish cohort*. Psychoneuroendocrinology, 2016. **73**: p. 196-203.

203. Hart, R. and D.A. Doherty, *The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage*. J Clin Endocrinol Metab, 2015. **100**(3): p. 911-9.

204. Dokras, A., et al., *Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis*. Fertil Steril, 2012. **97**(1): p. 225-30.e2.

205. Benson, S., et al., *Prevalence and implications of anxiety in polycystic ovary syndrome: results of an internet-based survey in Germany*. Human Reproduction, 2009. **24**(6): p. 1446-51.

206. Deeks, A., M. Gibson-Helm, and H. Teede, *Anxiety and depression in polycystic ovary syndrome: a comprehensive investigation*. Fertility & Sterility, 2010. **93**(7): p. 2421-3.

207. Hahn, S., et al., *Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome*. European Journal of Endocrinology, 2005. **153**(6): p. 853-60.

208. Kerchner, A., et al., *Risk of depression and other mental health disorders in women with polycystic ovary syndrome: a longitudinal study*. Fertility & Sterility, 2009. **91**(1): p. 207-12.

209. Brydon, L., K. Magid, and A. Steptoe, *Platelets, coronary heart disease, and stress*. Behav Imm Brainun., 2006. **20**(2): p. 113-9.

210. Gold, P., W. Drevets, and D. Charney, *New insights into the role of cortisol and the glucocorticoid receptor in severe depression*. Biology & Psychiatry, 2002. **52**(5): p. 381-5.

211. Lustman, P., et al., *Depression and poor glycemic control: a meta-analytic review of the literature*. Diabetes Care, 2000. **23**(7): p. 934-42.

212. Roy-Byrne, P., et al., *Anxiety disorders and comorbid medical illness*. General Hospital Psychiatry 2008. **30**(3): p. 208-25.

213. Wilhelm, K., et al., *Prevalence and correlates of DSM-IV major depression in an Australian national survey*. Journal of Affective Disorders, 2003. **75**(2): p. 155-62.

214. Avery, J. and A. Braunack-Mayer, *The information needs of women diagnosed with Polycystic Ovarian Syndrome--implications for treatment and health outcomes*. BMC Womens Health 2007. **20**(7): p. 9.

215. Kitzinger, C. and J. Willmott, *'The thief of womanhood': women's experience of polycystic ovarian syndrome*. Social Science Medicine, 2002. **54**(3): p. 349-61.

216. National Institute for Health and Care Excellence. *Depression in adults with a chronic physical health problem: recognition and managemen*t. 2009 Noember 2015 10 March 2017]; Available from: https://www.nice.org.uk/guidance/cg91/resources/depression-in-adults-with-a-chronic-physical-health-problem-recognition-and-management-975744316357.

217. National Institute for Health and Care Excellence. *Common mental health problems: identification and pathways to care*. 2011 February 2014 10 March 2017]; Available from: https://www.nice.org.uk/guidance/cg123/resources/common-mental-health-problems-identification-and-pathways-to-care-35109448223173.

218. National Institute for Health and Care Excellence. *Antenatal and postnatal mental health: clinical management and service guidance*. 2014 10 March 2017]; Available from: https://www.nice.org.uk/guidance/cg192/resources/antenatal-and-postnatal-mental-health-clinical-management-and-service-guidance-35109869806789.

219. Siu, A.L. and U.S.P.S.T.F. and the, *Screening for depression in adults: US preventive services task force recommendation statement*. JAMA, 2016. **315**(4): p. 380-387.

220. Siu, A.L. and U.S.P.S.T.F. on behalf of the, *Screening for depression in children and adolescents: U.S. preventive services task force recommendation statement*. Annals of Internal Medicine, 2016. **164**(5): p. 360-366.

221. LeFevre, M.L. and U.S.P.S.T.F. on behalf of the, *Screening for suicide risk in adolescents, adults, and older adults in primary care: U.S. preventive services task force recommendation statement*. Annals of Internal Medicine, 2014. **160**(10): p. 719-726.

222. Malhi, G.S., et al., *Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders*. Australian & New Zealand Journal of Psychiatry, 2015. **49**(12): p. 1087-1206.

223. Adams, Y., N. Drew, and R. Walker, *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 (2nd edition)*, Pat Dudgeon, Helen Milroy, and R. Walker, Editors. 2014, Department of The Prime Minister and Cabinet: Canberra.

224. National Health and Medical Research Council, *Clinical Practice Guideline for the Management of Borderline Personality Disorder*. 2012: Melbourne.

225. Watson, J. and T. Davies, *ABC of mental health: psychosexual problems*. British Medical Journal, 1997. **315**: p. 239.

226. Clayton, A.H., et al., *The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women*. Mayo Clinic Proceedings. **93**(4): p. 467-487.

227. Dashti, S., et al., *Sexual Dysfunction in Patients with Polycystic Ovary Syndrome in Malaysia*. Asian Pac J Cancer Prev, 2016. **17**(8): p. 3747-51.

228. Eftekhar, T., et al., *Sexual dysfunction in patients with polycystic ovary syndrome and its affected domains*. Iran J Reprod Med, 2014. **12**(8): p. 539-46.

229. Ercan, C.M., et al., *Sexual dysfunction assessment and hormonal correlations in patients with polycystic ovary syndrome*. Int J Impot Res, 2013. **25**(4): p. 127-32.

230. Veras, A.B., et al., *Sexual dysfunction in patients with polycystic ovary syndrome: clinical and hormonal correlations*. Compr Psychiatry, 2011. **52**(5): p. 486-9.

231. Chen, C.H., et al., *Sexual orientations of women with polycystic ovary syndrome: clinical observation in Taiwan*. Taiwan J Obstet Gynecol, 2014. **53**(4): p. 542-6.

232. Drosdzol, A., et al., *Quality of life and marital sexual satisfaction in women with polycystic ovary syndrome*. Folia Histochemistry and Cytobiology, 2007(45; Suppl 1): p. S93-7.

233. Elsenbruch, S., et al., *Quality of life, psychosocial well-being, and sexual satisfaction in women with polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2003. **88**(12): p. 5801-5807.

234. Hahn, S., et al., *Metformin treatment of polycystic ovary syndrome improves health-related quality-of-life, emotional distress and sexuality Human Reproduction*, 2006. **21**(7): p. 1925-1934.

235. Janssen, O., et al., *Mood and sexual function in polycystic ovary syndrome*. Seminars in Reproductive Medicine, 2008. **26**(1): p. 45-52.

236. Manlove, H.A., C. Guillermo, and P.B. Gray, *Do women with polycystic ovary syndrome (PCOS) report differences in sex-typed behavior as children and adolescents?*: Results of a pilot study. Ann Hum Biol, 2008. **35**(6): p. 584-95.

237. Morotti, E., et al., *Body imaging and sexual behavior in lean women with polycystic ovary syndrome*. J Sex Med, 2013. **10**(11): p. 2752-60.

238. Pastoor, H., et al., *Sexual function in women with Polycystic Ovary Syndrome: a systematic review and meta-analysis*. RBM online, 2018. **In press**.

239. Annagur, B.B., A. Tazegul, and N. Akbaba, *Body Image, Self-Esteem and Depressive Symptomatology in Women with Polycystic Ovary Syndrome*. Noro Psikiyatr Ars, 2014. **51**(2): p. 129-132.

240. Karacan, E., et al., *Body Satisfaction and Eating Attitudes among Girls and Young Women with and without Polycystic Ovary Syndrome.* Journal of Pediatric and Adolescent Gynecology, 2014. **27**(2): p. 72-77.

241. Deeks, A., M. Gibson-Helm, and H. Teede. *Negative body image and lower self-efficacy in women with polycystic ovary syndrome. in Australian Society for Health and Behavioural Medicin*e. 2010. Brisbain.

242. Dawber, R., *Guidance for the management of hirsutism*. Current Medical Research & Opinion, 2005. **21**(8): p. 1227-1234.

243. Bazarganipour, F., et al., *Body image satisfaction and self-esteem status among the patients with polycystic ovary syndrome*. Iran J Reprod Med, 2013. **11**(10): p. 829-36.

244. Trent, M., et al., *Overweight status of adolescent girls with polycystic ovary syndrome: body mass index as mediator of quality of life*. Ambul Pediatr, 2005. **5**(2): p. 107-11.

245. Himelein, M.J. and S.S. Thatcher, *Depression and body image among women with polycystic ovary syndrome*. J Health Psychol, 2006. **11**(4): p. 613-25.

246. Pastore, L.M., et al., *Depression symptoms and body dissatisfaction association among polycystic ovary syndrome women*. J Psychosom Res, 2011. **71**(4): p. 270-6.

247. Strauman, T., et al., *Self-discrepancies and vulnerability to body dissatisfaction and disordered eating*. Journal of Personality & Social Psychology, 1991. **61**(6): p. 946-956.

248. Strauman, T. and A. Glenberg, *Self-concept and body-image disturbance: which self-beliefs predict body size overestimation?* Cognitive Therapy & Research, 1994. **18**(2105-125).

249. Andersen, B. and J. LeGrand, *Body image for women: conceptualization, assessment, and a test of its importance to sexual dysfunction and medical illness*. The Journal of Sex Research, 1991. **28**(3): p. 457-477.

250. Pliner, P., S. Chaiken, and G. Flett, *Gender differences in concern with body weight and physical appearance over the life span*. Personality & Social Psychology Bulletin, 1990. **16**(2): p. 263-272.

251. National Collaborating Centre for Mental Health, Obsessive compulsive disorder: *Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder*, National Institute for Health and Clinical Excellence, Editor. 2006, The British Psychological Society and The Royal College of Psychiatrists, UK.

252. Australian Medical Association, *Body Image and Health: AMA Position Statement*. 2002.

253. Hay PJ, et al., *Eating disorder behaviors are increasing: findings from two sequential community surveys in South Australia*. PLoS ONE, 2008. **3**(2).

254. Månsson, M., et al., *Women with polycystic ovary syndrome are often depressed or anxious—A case control study*. Psychoneuroendocrinology, 2008. **33**(8): p. 1132-1138.

255. Larsson, I., et al., *Dietary intake, resting energy expenditure, and eating behavior in women with and without polycystic ovary syndrome*. Clinical Nutrition, 2016. **35**(1): p. 213-218.

256. Lee, I., et al., *Increased risk of disordered eating in polycystic ovary syndrome.* Fertility and Sterility, 2017. **107**(3): p. 796-802.

257. Fairburn CG and Harrison PJ, *Eating disorders*. The Lancet, 2003. **36**: p. 407-15.

258. National Guideline Alliance, *NICE Guideline. Eating Disorders: recognition and treatment. Methods, evidence and recommendations*. Draft. . 2016, National Institute for Health and Care Excellence: London.

259. Pedersen, O. and P. Gaede, *Intensified multifactorial intervention and cardiovascular outcome in type 2 diabetes: the Steno-2 study*. Metabolism, 2003. **52**(8 Suppl 1): p. 19-23.

260. Gibson-Helm, M.E., et al., *Women's experiences of polycystic ovary syndrome diagnosis*. Family Practice, 2014. **31**(5): p. 545-9.

261. Teede, H., et al., *Polycystic Ovary Syndrome: Perceptions and Attitudes of Women and Primary Health Care Physicians on Features of PCOS and Renaming the Syndrome*. Journal of Clinical Endocrinology & Metabolism, 2014. **99**(1): p. E107-11.

262. Boyle, J., et al., *Process evaluation of a pilot evidence-based Polycystic Ovary Syndrome clinic in the Torres Strait*. Aust J Rural Health, 2017. **25**(3): p. 175-181.

263. Colwell, K., et al., *Women's perceptions of polycystic ovary syndrome following participation in a clinical research study: implications for knowledge, feelings, and daily health practices*. J Obstet Gynaecol Can, 2010. **32**(5): p. 453-9.

264. Holbrey, S. and N.S. Coulson, *A qualitative investigation of the impact of peer to peer online support for women living with polycystic ovary syndrome*. BMC Womens Health, 2013. **13**: p. 51.

265. Percy, C.A., et al., *Nurse-led peer support group: experiences of women with polycystic ovary syndrome*. J Adv Nurs, 2009. **65**(10): p. 2046-55.

266. Ching, H.L., V. Burke, and B.G.A. Stuckey, *Quality of life and psychological morbidity in women with polycystic ovary syndrome: Body mass index, age and the provision of patient information are significant modifiers.* Clinical Endocrinology, 2007. **66**(3): p. 373-379.

267. Crete, J. and P. Adamshick, *Managing polycystic ovary syndrome: what our patients are telling us*. Journal of Holistic Nursing, 2011. **29**(4): p. 256-269.

268. Snyder, B.S., *The Lived Experience of Women Diagnosed With Polycystic Ovary Syndrome*. Journal of Obstetric, Gynecologic, & Neonatal Nursing: Clinical Scholarship for the Care of Women, Childbearing Families, & Newborns, 2006. **35**(3): p. 385-392.

269. Jones, G.L., et al., *Health-Related Quality of Life Among Adolescents with Polycystic Ovary Syndrome*. Journal of Obstetric, Gynecologic, and Neonatal Nursing : JOGNN, 2011. **40**(5): p. 577.

270. Sills, E.S., et al., *Diagnostic and treatment characteristics of polycystic ovary syndrome: descriptive measurements of patient perception and awareness from 657 confidential self-reports.* BMC Womens Health, 2001. **1**(1): p. 3.

271. Tomlinson, J., et al., *Raising awareness of polycystic ovary syndrome*. Nursing Standard (through 2013), 2013. **27**(40): p. 35-9.

272. Kozica, S.L., et al., *Assessing self-efficacy and self-help methods in women with and without Polycystic Ovary Syndrome*. Behavioral Medicine, 2013. **39**(3): p. 90-6.

273. Abdolvahab Taghavi, S., et al., *Health-related quality of life in Iranian women with polycystic ovary syndrome: a qualitative study*. BMC Women's Health, 2015. **15**: p. 1-8.

274. Sivayoganathan, D., et al., *Full investigation of patients with polycystic ovary syndrome (PCOS) presenting to four different clinical specialties reveals significant differences and undiagnosed morbidity*. Human Fertility, 2011. **14**(4): p. 261-265.

275. Cussons, A.J., et al., *Polycystic ovarian syndrome: marked differences between endocrinologists and gynaecologists in diagnosis and management*. Clinical Endocrinology, 2005. **62**(3): p. 289-95.

CONTENTS

276. Jeanes, Y.M., et al., *Dietary management of women with polycystic ovary syndrome in the United Kingdom: The role of dietitians*. Journal of Human Nutrition and Dietetics, 2009. **22**(6): p. 551-558.

277. Spencer, A.L., J.E. Bost, and M. McNeil, *Do women's health internal medicine residency tracks make a difference?* Journal of Women's Health, 2007. **16**(8): p. 1219-1223.

278. Boyle, J., et al., *Process evaluation of a pilot evidence-based Polycystic Ovary Syndrome clinic in the Torres Strait*. Aust J Rural Health, 2016.

279. Stepto, N.K., et al., *Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp*. Hum Reprod, 2013. **28**(3): p. 777-84.

280. Acien, P., et al., *Insulin, androgens, and obesity in women with and without polycystic ovary syndrome: a heterogeneous group of disorders*. Fertility & Sterility, 1999. **72**(1): p. 32-40.

281. Balen, A., et al., *Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients.* Human Reproduction, 1995. **10**(8): p. 2107-11.

282. Kiddy, D., et al., *Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: an analysis of 263 consecutive cases*. Clinical Endocrinology, 1990. **32**(2): p. 213-20.

283. Ehrmann, D., et al., *Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2006. **91**(1): p. 48-53.

284. Clark, A., et al., *Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment*. Human Reproduction, 1998. **13**(6): p. 1502 - 1505.

285. Huber-Buchholz, M., D. Carey, and R. Norman, *Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: Role of insulin sensitivity and luteinizing hormone*. Journal of Clinical Endocrinology & Metabolism, 1999. **84**(4): p. 1470-1474.

286. Moran, L., et al., *Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2003. **88**(2): p. 812-819.

287. Thomson, R., et al., *Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome*. Fertility & Sterility, 2010. **94**(5): p. 1812-1816.

288. Glueck, C., et al., *Obesity and extreme obesity, manifest by ages 20-24 years, continuing through 32-41 years in women, should alert physicians to the diagnostic likelihood of polycystic ovary syndrome as a reversible underlying endocrinopathy*. European Journal of Obstetrics & Gynecological Reproductive Biology, 2005. **122**(2): p. 206-12.

289. Teede, H., et al., *Body mass index as a predictor of polycystic ovary syndrome risk: Results of a longitudinal cohort study*. US Endocrine Society abstract #246, 2010.

290. Hutchison, S., et al., *Effects of exercise on insulin resistance and body composition in overweight and obese women with and without polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2011. **96**(1): p. E48-56.

291. Poehlman, E., et al., *Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: A controlled randomized trial*. Journal of Clinical Endocrinology & Metabolism, 2000. **85**(7): p. 2463-2468.

292. Ross, R., et al., *Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men*. Annals of Internal Medicine, 2000. **133**: p. 92-103.

293. Andersen, P., et al., *Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome*. Metabolism, 1995. **44**(5): p. 611-616.

294. Clark, A., et al., *Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women*. Human Reproduction, 1995. **10**(10): p. 2705-2712.

295. Crave, J., et al., *Effects of diet and metformin administration on sex hormone-binding globulin, androgens, and insulin in hirsute and obese women*. Journal of Clinical Endocrinology & Metabolism, 1995. **80**(7): p. 2057-2062.

296. Crosignani, P., et al., *Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet*. Human Reproduction, 2003. **18**(9): p. 1928-1932.

297. Gambineri, A., et al., *Effect of flutamide and metformin administered alone or in combination in dieting obese women with polycystic ovary syndrome*. Clinical Endocrinology, 2004. **60**(2): p. 241-9.

298. Guzick, D., et al., *Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women*. Fertility & Sterility, 1994. **61**(4): p. 598-604.

299. Holte, J., et al., *Restored insulin sensitivity but persistently increased early insulin secretion after weight loss in obese women with polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 1995. **80**(9): p. 2586-2593.

300. Jakubowicz, D. and J. Nestler, *17 alpha-Hydroxyprogesterone responses to leuprolide and serum androgens in obese women with and without polycystic ovary syndrome offer dietary weight loss*. Journal of Clinical Endocrinology & Metabolism, 1997. **82**(2): p. 556-560.

301. Kiddy, D., et al., *Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome*. Clinical Endocrinology, 1992. **36**(1): p. 105-111.

302. Kiddy, D., et al., *Diet-induced changes in sex hormone binding globulin and free testosterone in women with normal or polycystic ovaries: correlation with serum insulin and insulin-like growth factor-I*. Clinical Endocrinology, 1989. **31**(6): p. 757-763.

303. Moran, L., et al., *C-reactive protein before and after weight loss in overweight women with and without polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2007. **92**(8): p. 2944-2951.

304. Moran, L., et al., *Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome*. American Journal of Clinical Nutrition, 2006. **84**(1): p. 77-87.

305. Pasquali, R., et al., *Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss*. Journal of Clinical Endocrinology & Metabolism, 1989. **68**(1): p. 173-179.

306. Pasquali, R., et al., *Effect of long-term treatment with metformin added to hypocaloric diet on body composition, fat distribution, and androgen and insulin levels in abdominally obese women with and without the polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2000. **85**(8): p. 2767-2774.

307. Qublan, H., et al., *Dietary intervention versus metformin to improve the reproductive outcome in women with polycystic ovary syndrome. A prospective comparative study*. Saudi Medical Journal, 2007. **28**(11): p. 1694-9.

308. Stamets K, et al., *A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome*. Fertility & Sterility, 2004. **81**(3): p. 630-637.

309. Tang, T., et al., *Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study*. Human Reproduction, 2006. **21**(1): p. 80-9.

310. Van Dam, E., et al., *Increase in daily LH secretion in response to short-term calorie restriction in obese women with PCOS*. American Journal of Physiology - Endocrinology & Metabolism, 2002. **282**(4): p. E865-872.

311. Wahrenberg, H., et al., *Divergent effects of weight reduction and oral anticonception treatment on adrenergic lipolysis regulation in obese women with the polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 1999. **84**(6): p. 2182-2187.

312. Kataoka, J., et al., *Weight Management Interventions in Women with and without PCOS: A Systematic Review*. Nutrients, 2017. **9**(9).

313. Moran, L., et al., *Lifestyle changes in women with polycystic ovary syndrome*. Cochrane Database of Systematic Reviews, 2011(2).

314. Moran, L.J., et al., *Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society*. Fertil Steril, 2009. **92**(6): p. 1966-82.

315. Teede, H.J., et al., *Longitudinal weight gain in women identified with Polycystic Ovary Syndrome: Results of an observational study in young women*. Obesity, 2013. **21**(8): p. 1526-1532.

316. Brennan, L. and K. Murphy, *The role of psychology in overweight and obesity management, in Applied topics in health psychology*, M. Caltabiano, & Ricciadelli, L., Editor. 2012, John Wiley & Sons: Oxford UK. p. 303.

317. Geier, L.M., M.T. Bekx, and E.L. Connor, *Factors Contributing to Initial Weight Loss Among Adolescents with Polycystic Ovary Syndrome*. Journal of Pediatric and Adolescent Gynecology. **25**(6): p. 367-370.

318. Hoeger, K.M., et al., *A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study*. Fertility & Sterility, 2004. **82**(2): p. 421-9.

319. Hoeger, K., et al., *The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials*. Journal of Clinical Endocrinology & Metabolism, 2008. **93**(11): p. 4299-306.

320. Greaves, C.J., Sheppard KE, Abraham C, Hardeman W, Roden M, Evans PH et al, *Intervention components associated with increased effectiveness in dietary and physical activity interventions*. BMC Public Health, 2011. **11**(119).

321. National Health and Medical Research Council, *Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia*. 2013, National Health and Medical Research Council: Melbourne.

322. Foster, G.D., A.P. Makris, and B.A. Bailer, *Behavioral treatment of obesity*. The American Journal of Clinical Nutrition, 2005. **82**(1): p. 230S-235S.

323. Wadden, T.A., C.E. Crerand, and J. Brock, *Behavioral treatment of obesity*. Psychiatric Clinics of North America, 2005. **28**: p. 151-170.

324. Wing, R., Papandonatos, G., Fava, J. L., Gorin, A. A., Phelan, S., McCaffery, J., & Tate, D. F, *Maintaining Large Weight Losses: The Role of Behavioral and Psychological Factors*. Journal of Consulting and Clinical Psychology, 2008. **76**(6): p. 1015-1021.

325. Wing, R.R., *Behavioural approaches to the treatment of obesity, in Handbook of obesity*. Clinical applications., G.A. Bray and C. Bouchard, Editors. 2008, Informa Healthcare: New York. p. 227-248.

326. Shaw, K., et al., *Psychological interventions for overweight or obesity*. Cochrane Database of Systematic Reviews, 2005(Issue 2. Art. No.: CD003818. DOI: 10.1002/14651858.CD003818.pub2.).

327. Jensen MD, et al., *Guidelines (2013) for managing overweight and obesity in adults*. Obesity, 2014. **22**(S2): p. S1-S410. .

328. Asemi, Z. and A. Esmaillzadeh, *DASH diet, insulin resistance, and serum hs-CRP in polycystic ovary syndrome: a randomized controlled clinical trial*. Hormone & Metabolic Research, 2015. **47**(3): p. 232-8.

329. Asemi, Z., et al., *Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized clinical trial*. Nutrition, 2014. **30**(11-12): p. 1287-93.

330. Toscani, M.K., et al., *Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study*. Gynecological Endocrinology, 2011. **27**(11): p. 925-30.

CONTENTS

331. Johnston, B.C., et al., *Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis*. JAMA, 2014. **312**(9): p. 923-33.

332. Gardner, C.D., et al., *Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The dietfits randomized clinical trial*. JAMA, 2018. **319**(7): p. 667-679.

333. Hession, M., et al., *Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities*. Obesity Reviews, 2009. **10**: p. 36–50.

334. Pirozzo, S., et al., *Advice on low-fat diets for obesity*. Cochrane Database of Systematic Reviews, 2002 (Issue 2 Art. No.: CD003640. DOI: 10.1002/14651858.CD003640.).

335. Sacks, F., et al., *Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates*. New England Journal of Medicine, 2009. **360**(9): p. 859-73.

336. Corbould, A., et al., *Insulin resistance in the skeletal muscle of women with polycystic ovary syndrome involves both intrinsic and acquired defects in insulin signaling*. American Journal of Physiology, Endocrinology & Metabolism, 2005. **288**(5): p. E1047 -E1054.

337. Diamanti-Kandarakis, E. and A. Papavassiliou, *Molecular mechanisms of insulin resistance in polycystic ovary syndrome*. Trends in Molecular Medicine, 2006. **12**(7): p. 324-32.

338. Norton, K., L. Norton, and D. Sadgrove, *Position statement on physical activity and exercise intensity terminology*. Journal of Science & Medicine in Sport, 2010. **13**(5): p. 496–502.

339. Jean Hailes for Women's Health on behalf of the PCOS Australian Alliance, *Evidence-based guidelines for the assessment and management of polycystic ovary syndrome*. 2015, Jean Hailes for Women's Health on behalf of the PCOS Australian Alliance: Melbourne.

340. Orio, F., et al., *Metabolic and cardiopulmonary effects of detraining after a structured exercise training programme in young PCOS women*. Clin Endocrinol (Oxf), 2008. **68**(6): p. 976-81.

341. Thomson, R.L., et al., *The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome*. J Clin Endocrinol Metab, 2008. **93**(9): p. 3373-80.

342. Banting, L.K., et al., *Physical activity and mental health in women with Polycystic Ovary Syndrome*. BMC Women's Health, 2014. **14**(51).

343. Harrison, C.L., et al., *The impact of intensified exercise training on insulin resistance and fitness in overweight and obese women with and without polycystic ovary syndrome*. Clin Endocrinol (Oxf), 2012. **76**(3): p. 351-7.

344. Moran, L.J., et al., *Exercise decreases anti-mullerian hormone in anovulatory overweight women with polycystic ovary syndrome: a pilot study*. Horm Metab Res, 2011. **43**(13): p. 977-9.

345. Nybacka, Å., *Serum anti-Müllerian hormone in response to randomized dietary management and/or physical exercise in overweight/obese women with polycystic ovary syndrome*. Fertil Steril, 2013. **100**: p. 1096 - 1102.

346. Nybacka, Å., et al., *Randomized comparison of the influence of dietary management and/or physical exercise on ovarian function and metabolic parameters in overweight women with polycystic ovary syndrome*. Fertility and Sterility, 2011. **96**(6): p. 1508-1513.

347. Kogure, G.S., et al., *Resistance Exercise Impacts Lean Muscle Mass in Women with Polycystic Ovary Syndrome*. Med Sci Sports Exerc, 2016. **48**(4): p. 589-98.

348. Miranda-Furtado, C.L., et al., *A Nonrandomized Trial of Progressive Resistance Training Intervention in Women With Polycystic Ovary Syndrome and Its Implications in Telomere Content*. Reprod Sci, 2016. **23**(5): p. 644-54.

349. Vizza, L., et al., *The feasibility of progressive resistance training in women with polycystic ovary syndrome: a pilot randomized controlled trial*. BMC Sports Sci Med Rehabil, 2016. **8**: p. 14.

350. Ross, R. and A. Bradshaw, *The future of obesity reduction: beyond weight loss.* Nature Reviews in Endocrinology, 2009. **5**(6): p. 319-25.

351. Haqq, L., et al., *Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: a systematic review and meta-analysis.* Endocrine Connections, 2014. **3**(1): p. 36-46.

352. Haqq, L., et al., *The Effect of Lifestyle Intervention on Body Composition, Glycemic Control, and Cardiorespiratory Fitness in Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis.* Int J Sport Nutr Exerc Metab, 2015. **25**(6): p. 533-40.

353. Harrison, C.L., et al., *Exercise therapy in polycystic ovary syndrome: a systematic review.* Hum Reprod Update, 2011. **17**(2): p. 171-83.

354. Ramos, F.K.P., et al., *Quality of Life in Women with Polycystic Ovary Syndrome after a Program of Resistance Exercise Training.* Rev Bras Ginecol Obstet, 2016. **38**(07): p. 340-347.

355. Greenwood, E.A., et al., *Vigorous exercise is associated with superior metabolic profiles in polycystic ovary syndrome independent of total exercise expenditure.* Fertility and Sterility, 2016. **2016**(2): p. 486-93.

356. Moran, L.J., et al., *The contribution of diet, physical activity and sedentary behaviour to body mass index in women with and without polycystic ovary syndrome.* Hum Reprod, 2013. **28**(8): p. 2276-83.

357. Corbould, A., et al., *Enhanced mitogenic signaling in skeletal muscle of women with polycystic ovary syndrome.* Diabetes, 2006. **55**(3): p. 751-9.

358. Teede, H., S. Hutchison, and S. Zoungas, *The management of insulin resistance in polycystic ovary syndrome.* Trends in Endocrinology & Metabolism, 2007. **18**(7): p. 273-9.

359. Teede, H., et al., *Insulin resistance, metabolic syndrome, diabetes and cardiovascular disease in polycystic ovary syndrome.* Endocrine, 2006. **30** (1): p. 45-53.

360. Richter, E., et al., *Effect of exercise on insulin action in human skeletal muscle.* Journal of Applied Physiology, 1989. **66**(2): p. 876-885.

361. Tuomilehto, J., et al., *Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance.* New England Journal of Medicine, 2001. **344**(18): p. 1343-1350.

362. Goodyear, L. and B. Kahn, *Exercise, glucose transport, and insulin sensitivity.* Annual Review of Medicine, 1998. **49**: p. 235-261.

363. Shephard, R. and G. Balady, *Exercise as cardiovascular therapy.* Circulation, 1999. **99**(7): p. 963-972.

364. Cuff, D., et al., *Effective exercise modality to reduce insulin resistance in women with type 2 diabetes.* Diabetes Care, 2003. **26**(11): p. 2977-82.

365. Maiorana, A., et al., *Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes.* Diabetes Research & Clinical Practice, 2002. **56**(2): p. 115-123.

366. Park, S., et al., *The effect of combined aerobic and resistance exercise training on abdominal fat in obese middle-aged women.* Journal of Physiological Anthropology & Applied Human Science, 2003. **22**(3): p. 129-135.

367. Sigal, R., et al., *Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial.* Annals of Internal Medicine, 2007. **147**(6): p. 357-69.

368. Barry, V.W., et al., *Fitness vs. Fatness on All-Cause Mortality: A Meta-Analysis.* Progress in Cardiovascular Diseases, 2014. **56**(4): p. 382-390.

369. Koivula, R.W., A.B. Tornberg, and P.W. Franks, *Exercise and diabetes-related cardiovascular disease: systematic review of published evidence from observational studies and clinical trials.* Curr Diab Rep., 2013. **13**(3): p. 372-80.

370. Nicolucci, A., *Relationship of exercise volume to improvements of quality of life with supervised exercise training in patients with type 2 diabetes in a randomised controlled trial: the Italian Diabetes and Exercise Study (IDES). 2012. 55(3): p. 579-88.* Diabetologia., 2012. **55**(3): p. 579-88.

371. Biddle, S.J.H., et al., *Too much sitting and all-cause mortality:is there a causal link?* BMC Public Health 2016. **16**: p. 635.

372. Ekelund, U., et al., *Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women.* The Lancet. **388**(10051): p. 1302-1310.

373. Snowling, N.J. and W.G. Hopkins, *Effects of Different Modes of Exercise Training on Glucose Control and Risk Factors for Complications in Type 2 Diabetic Patients: A meta-analysis*. Diabetes Care, 2006. **29**(11): p. 2518-2527.

374. Economics, D.A., *Value of Accredited Exercise Physiologists in Australia*. 2015, Exercise & Sports Science Australia: Australia.

375. American College of Sports Medicine American Heart Association, *Physical activity and public health guidelines*. 2007: USA.

376. Briffa, T., et al., *National Heart Foundation of Australia physical activity recommendations for people with cardiovascular disease*, National Heart Foundation of Australia, Editor. 2006: Sydney, Australia.

377. Department of Health and Ageing, *National physical activity guidelines*, Department of Health and Ageing Australian Government, Editor.

378. Haskell, W., et al., *Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association*. Circulation, 2007. **116**: p. 1081-1093.

379. Nelson, M., et al., *Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association*. Circulation, 2007. **116**: p. 1094-1105.

380. Physical Activity Guidelines Advisory Committee, *Physical Activity Guidelines Advisory Committee Report* Department of Health and Human Services, Editor. 2008: Washington DC, USA.

381. World Health Organisation, *Global strategy on diet, physical activity and health*. 2004: Geneva.

382. World Health Organisation, *A guide for population-based approaches to increasing levels of physical activity: Implementation of the WHO global strategy on diet, physical activity and health*. 2007: Geneva.

383. Centre for Disease Control, *Promoting Physical Activity-2nd Edition A Guide for Community Action*. 2010: Human Kinetics. 280.

384. Moran, L.J., et al., *Effects of lifestyle modification in polycystic ovarian syndrome*. Reprod Biomed Online, 2006. **12**(5): p. 569-78.

385. Day, F.R., et al., *Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome*. Nat Commun, 2015. **6**: p. 8464.

386. Yildiz, B.O., E.S. Knochenhauer, and R. Azziz, *Impact of obesity on the risk for polycystic ovary syndrome*. J Clin Endocrinol Metab, 2008. **93**(1): p. 162-8.

387. Brennan, L., et al., *Lifestyle and Behavioral Management of Polycystic Ovary Syndrome*. J Womens Health (Larchmt), 2017.

388. Ollila, M.M., et al., *Weight Gain and Dyslipidemia in Early Adulthood Associate With Polycystic Ovary Syndrome: Prospective Cohort Study*. J Clin Endocrinol Metab, 2016. **101**(2): p. 739-47.

389. Pasquali, R., *Obesity and androgens: facts and perspectives*. Fertil Steril, 2006. **85**(5): p. 1319-40.

390. Lim, S.S., et al., *The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis*. Obes Rev, 2013. **14**(2): p. 95-109.

391. Diamanti-Kandarakis, E., *Role of obesity and adiposity in polycystic ovary syndrome*. Int J Obes (Lond), 2007. **31 Suppl 2**: p. S8-13; discussion S31-2.

392. Gambineri, A., et al., *Obesity and the polycystic ovary syndrome*. Int J Obes Relat Metab Disord, 2002. **26**(7): p. 883-96.

393. Legro, R.S., *Obesity and PCOS: implications for diagnosis and treatment*. Semin Reprod Med, 2012. **30**(6): p. 496-506.

394. Al Khalifah, R.A., et al., *Metformin or Oral Contraceptives for Adolescents With Polycystic Ovarian Syndrome: A Meta-analysis*. Pediatrics, 2016. **137**(5): p. 1-12.

395. Ibanez, L. and F. de Zegher, *Ethinylestradiol-drospirenone, flutamide-metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity*. Journal of Clinical Endocrinology & Metabolism, 2004. **89**(4): p. 1592-7.

396. Dardzinska, J.A., et al., *Effects of metformin or an oral contraceptive containing cyproterone acetate on serum c-reactive protein, interleukin-6 and soluble vascular cell adhesion molecule-1 concentrations in women with polycystic ovary syndrome*. Experimental & Clinical Endocrinology & Diabetes, 2014. **122**(2): p. 118-25.

397. Harborne, L., et al., *Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2003. **88**(9): p. 4116-23.

398. Kilic, S., et al., *Inflammatory-metabolic parameters in obese and nonobese normoandrogenemic polycystic ovary syndrome during metformin and oral contraceptive treatment*. Gynecological Endocrinology, 2011. **27**(9): p. 622-9.

399. Meyer, C., B.P. McGrath, and H.J. Teede, *Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome*. Diabetes Care, 2007. **30**(3): p. 471-8.

400. Morin-Papunen, L., et al., *Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study.* Journal of Clinical Endocrinology & Metabolism, 2003. **88**(1): p. 148-56.

401. Morin-Papunen, L.C., et al., *Endocrine and metabolic effects of metformin versus ethinyl estradiol-cyproterone acetate in obese women with polycystic ovary syndrome: a randomized study*. Journal of Clinical Endocrinology & Metabolism, 2000. **85**(9): p. 3161-8.

402. Moro, F., et al., *Effects of drospirenone-ethinylestradiol and/or metformin on CD4(+)CD28(null) T lymphocytes frequency in women with hyperinsulinemia having polycystic ovary syndrome: a randomized clinical trial*. Reproductive Sciences, 2013. **20**(12): p. 1508-17.

403. Rautio, K., et al., *Effects of metformin and ethinyl estradiol-cyproterone acetate on lipid levels in obese and non-obese women with polycystic ovary syndrome*. European Journal of Endocrinology, 2005. **152**(2): p. 269-75.

404. Wu, J., et al., *Effects of metformin and ethinyl estradiol-cyproterone acetate on clinical, endocrine and metabolic factors in women with polycystic ovary syndrome*. Gynecological Endocrinology, 2008. **24**(7): p. 392-8.

405. Cibula, D., et al., *The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenaemia, SHBG and lipids in PCOS patients*. Human Reproduction, 2005. **20**(1): p. 180-4.

406. Elter, K., G. Imir, and F. Durmusoglu, *Clinical, endocrine and metabolic effects of metformin added to ethinyl estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study*. Human Reproduction, 2002. **17**(7): p. 1729-37.

407. Essah, P.A., et al., *Effect of combined metformin and oral contraceptive therapy on metabolic factors and endothelial function in overweight and obese women with polycystic ovary syndrome*. Fertility & Sterility, 2011. **96**(2): p. 501-504.e2.

408. Feng, W., et al., *Management of polycystic ovarian syndrome with Diane-35 or Diane-35 plus metformin*. Gynecological Endocrinology, 2016. **32**(2): p. 147-50.

409. Spritzer, P.M., et al., *Spironolactone as a single agent for long-term therapy of hirsute patients*. Clinical Endocrinology, 2000. **52**(5): p. 587-94.

410. Ibanez, L. and F. de Zegher, *Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of metformin at the start and after more than one year of therapy*. Journal of Clinical Endocrinology & Metabolism, 2005. **90**(1): p. 39-43.

411. Hagag, P., M. Steinschneider, and M. Weiss, *Role of the combination spironolactone-norgestimate-estrogen in Hirsute women with polycystic ovary syndrome*. Journal of Reproductive Medicine, 2014. **59**(9-10): p. 455-63.

412. Leelaphiwat, S., et al., *Comparison of desogestrel/ethinyl estradiol plus spironolactone versus cyproterone acetate/ethinyl estradiol in the treatment of polycystic ovary syndrome: a randomized controlled trial*. Journal of Obstetrics & Gynaecology Research, 2015. **41**(3): p. 402-10.

413. Tartagni, M., et al., *Comparison of Diane 35 and Diane 35 plus finasteride in the treatment of hirsutism*. Fertility & Sterility, 2000. **73**(4): p. 718-23.

414. Vieira, C.S., et al., *The effects of 2 mg chlormadinone acetate/30 mcg ethinylestradiol, alone or combined with spironolactone, on cardiovascular risk markers in women with polycystic ovary syndrome*. Contraception, 2012. **86**(3): p. 268-75.

415. Wang, Q.Y., et al., *Comparison of drospirenone-with cyproterone acetate-containing oral contraceptives, combined with metformin and lifestyle modifications in women with polycystic ovary syndrome and metabolic disorders: A prospective randomized control trial*. Chinese medical journal, 2016. **129**(8): p. 883-90.

416. World Health Organization. *2015 Quick Reference Chart for the WHO Medical Eligibility Criteria for Contraceptive Use*. Adapted from Medical Eligibility Criteria for Contraceptive Use, 5th Edition 2015; Available from: https://www.fhi360.org/sites/default/files/media/documents/chart-medical-eligibility-contraceptives-english.pdf.

417. World Health Organization. *Combined hormonal oral contraception and risk of venous thromboembolism (VTE)*. Sexual and reproductive health 2018; Available from: http://www.who.int/reproductivehealth/topics/family_planning/coc/en/.

418. Baillargeon, J.P., et al., *Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity*. Fertility & Sterility, 2004. **82**(4): p. 893-902.

419. Chou, K.H., et al., *Clinical, metabolic and endocrine parameters in response to metformin in obese women with polycystic ovary syndrome: a randomized, double-blind and placebo-controlled trial*. Hormone & Metabolic Research, 2003. **35**(2): p. 86-91.

420. Eisenhardt, S., et al., *Early effects of metformin in women with polycystic ovary syndrome: a prospective randomized, double-blind, placebo-controlled trial*. Journal of Clinical Endocrinology & Metabolism, 2006. **91**(3): p. 946-52.

421. Fleming, R., et al., *Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial.* Journal of Clinical Endocrinology & Metabolism, 2002. **87**(2): p. 569-74.

422. Karimzadeh, M.A., et al., *The effect of administration of metformin on lipid profile changes and insulin resistance in patients with polycystic ovary syndrome*. Middle East Fertility Society Journal, 2007. **12**(3): p. 174-8.

423. Kelly, C.J. and D. Gordon, *The effect of metformin on hirsutism in polycystic ovary syndrome*. European Journal of Endocrinology, 2002. **147**(2): p. 217-21.

424. Lord, J., et al., *The effect of metformin on fat distribution and the metabolic syndrome in women with polycystic ovary syndrome--a randomised, double-blind, placebo-controlled trial*. BJOG: An International Journal of Obstetrics & Gynaecology, 2006. **113**(7): p. 817-24.

425. Maciel, G.A., et al., *Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin*. Fertility & Sterility, 2004. **81**(2): p. 355-60.

426. Moghetti, P., et al., *Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation*. Journal of Clinical Endocrinology & Metabolism, 2000. **85**(1): p. 139-46.

427. Morin-Papunen, L., et al., *Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial*. Journal of Clinical Endocrinology & Metabolism, 2012. **97**(5): p. 1492-500.

428. Ng, E.H., N.M. Wat, and P.C. Ho, *Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial*. Human Reproduction, 2001. **16**(8): p. 1625-31.

429. Onalan, G., et al., *Predictive value of glucose-insulin ratio in PCOS and profile of women who will benefit from metformin therapy: obese, lean, hyper or normoinsulinemic?* European Journal of Obstetrics, Gynecology, & Reproductive Biology, 2005. **123**(2): p. 204-11.

430. Palomba, S., et al., *Insulin sensitivity after metformin suspension in normal-weight women with polycystic ovary syndrome*. Journal of Clinical Endocrinology & Metabolism, 2007. **92**(8): p. 3128-35.

431. Romualdi, D., et al., *Metformin effects on ovarian ultrasound appearance and steroidogenic function in normal-weight normoinsulinemic women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial*. Fertility & Sterility, 2010. **93**(7): p. 2303-10.

432. Tehrani, H.G., F. Mostajeran, and S. Shahsavari, *The effect of calcium and vitamin D supplementation on menstrual cycle, body mass index and hyperandrogenism state of women with polycystic ovarian syndrome*. Journal of Research in Medical Sciences, 2014. **19**(9): p. 875-880.

433. Trolle, B., et al., *Efficacy of metformin in obese and non-obese women with polycystic ovary syndrome: a randomized, double-blinded, placebo-controlled cross-over trial*. Human Reproduction, 2007. **22**(11): p. 2967-73.

434. Trolle, B., et al., *Adiponectin levels in women with polycystic ovary syndrome: impact of metformin treatment in a randomized controlled study*. Fertility & Sterility, 2010. **94**(6): p. 2234-8.

435. Vanky, E., et al., *Breast size increment during pregnancy and breastfeeding in mothers with polycystic ovary syndrome: a follow-up study of a randomised controlled trial on metformin versus placebo*. BJOG: An International Journal of Obstetrics & Gynaecology, 2012. **119**(11): p. 1403-9.

436. Haydardedeoglu, B., et al., *Metabolic and endocrine effects of metformin and metformin plus cyclic medroxyprogesterone acetate in women with polycystic ovary syndrome*. International Journal of Gynaecology & Obstetrics, 2009. **105**(1): p. 32-5.

437. Esfahanian, F., et al., *Effect of metformin compared with hypocaloric diet on serum C-reactive protein level and insulin resistance in obese and overweight women with polycystic ovary syndrome*. Journal of Obstetrics & Gynaecology Research, 2013. **39**(4): p. 806-13.

438. Fux Otta, C., et al., *Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial*. Gynecological Endocrinology, 2010. **26**(3): p. 173-8.

439. Harborne, L.R., et al., *Metformin and weight loss in obese women with polycystic ovary syndrome: comparison of doses*. Journal of Clinical Endocrinology & Metabolism, 2005. **90**(8): p. 4593-8.

440. Mehrabian, F., et al., *Comparison of the effects of metformin, flutamide plus oral contraceptives, and simvastatinj on the metabolic consequences of polycystic ovary syndrome*. Journal of Research in Medical Sciences, 2016. **21**(1): p. 1-7.

441. Amiri, M., et al., *Effect of metformin and flutamide on anthropometric indices and laboratory tests in obese/ overweight PCOS women under hypocaloric diet*. Journal of Reproduction and Infertility, 2014. **15**(4): p. 205-13.

442. Gambineri, A., et al., *Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study*. Journal of Clinical Endocrinology & Metabolism, 2006. **91**(10): p. 3970-80.

443. Ganie, M.A., et al., *Comparison of efficacy of spironolactone with metformin in the management of polycystic ovary syndrome: an open-labeled study*. The Journal of clinical endocrinology and metabolism, 2004. **89**(6): p. 2756-62.

444. Ganie, M.A., et al., *Improved efficacy of low-dose spironolactone and metformin combination than either drug alone in the management of women with polycystic ovary syndrome (PCOS): a six-month, open-label randomized study*. Journal of Clinical Endocrinology & Metabolism, 2013. **98**(9): p. 3599-607.

445. Mazza, A., et al., *In PCOS patients the addition of low-dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone*. Nutrition Metabolism & Cardiovascular Diseases, 2014. **24**(2): p. 132-9.

446. Viollet, B., et al., *Cellular and molecular mechanisms of metformin: an overview.* Clinical Science (London, England : 1979), 2012. **122**(6): p. 253-270.

447. Naderpoor, N., et al., *Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis*. Human Reproduction Update, 2015. **21**(5): p. 560-74.

448. Liu, Q., et al., *Vitamin B12 status in metformin treated patients: systematic review*. PLoS One, 2014. **9**(6): p. e100379.

449. Bonnet, F. and A. Scheen, *Understanding and overcoming metformin gastrointestinal intolerance.* Diabetes Obes Metab, 2017. **19**(4): p. 473-481.

450. Apovian, C.M., et al., *Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline*. The Journal of Clinical Endocrinology & Metabolism, 2015. **100**(2): p. 342-362.

451. Lindholm, A., et al., *Effect of sibutramine on weight reduction in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial*. Fertility & Sterility, 2008. **89**(5): p. 1221-8.

452. Koiou, E., et al., *Disparate effects of pharmacotherapy on plasma plasminogen activator inhibitor-1 levels in women with the polycystic ovary syndrome*. Hormones, 2013. **12**(4): p. 559-66.

453. Mead, E., et al., *Drug interventions for the treatment of obesity in children and adolescents*. Cochrane Database of Systematic Reviews, 2016(11).

454. Ollendorf, D.A., C.G. Cameron, and S.D. Pearson, *Effectiveness and Value of Treatment Options for Obesity--A Report for the California Technology Assessment Forum*. JAMA Intern Med, 2016. **176**(2): p. 247-8.

455. Tartagni, M.V., et al., *Intermittent low-dose finasteride administration is effective for treatment of hirsutism in adolescent girls: a pilot study.* Journal of Pediatric & Adolescent Gynecology, 2014. **27**(3): p. 161-5.

456. Falsetti, L., et al., *Comparison of finasteride versus flutamide in the treatment of hirsutism*. European Journal of Endocrinology, 1999. **141**(4): p. 361-7.

457. Tartagni, M., et al., *Intermittent low-dose finasteride is as effective as daily administration for the treatment of hirsute women*. Fertility & Sterility, 2004. **82**(3): p. 752-5.

458. Martin, K.A., et al., *Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline*. The Journal of Clinical Endocrinology & Metabolism, 2008. **93**(4): p. 1105-1120.

459. van Zuuren, E.J. and Z. Fedorowicz, *Interventions for hirsutism excluding laser and photoepilation therapy alone: abridged Cochrane systematic review including GRADE assessments*. Br J Dermatol, 2016. **175**(1): p. 45-61.

460. Pundir, J., et al., *Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials*. Bjog, 2018. **125**(3): p. 299-308.

461. Tang, T., et al., *Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility*. Cochrane Database of Systematic Reviews, 2012(5): p. CD003053.

462. Unfer, V., et al., *Effects of Inositol(s) in Women with PCOS: A Systematic Review of Randomized Controlled Trials*. Int J Endocrinol, 2016. **2016**: p. 1849162.

463. Crawford, T.J., et al., *Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes*. Cochrane Database Syst Rev, 2015(12): p. Cd011507.

464. Balen, A.H., et al., *The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance*. Hum Reprod Update, 2016. **22**(6): p. 687-708.

465. World Health Organization, *Pre-conception care: maximizing the gains for maternal and child health, in Policy brief*, W.H. Organization, Editor. 2013, World Health Organization: Geneva.

466. Lang, A.Y., et al., *Optimizing preconception health in women of reproductive age*. Minerva Ginecol, 2018. **70**(1): p. 99-119.

467. Ravn, P., A.G. Haugen, and D. Glintborg, *Overweight in polycystic ovary syndrome. An update on evidence based advice on diet, exercise and metformin use for weight loss*. Minerva Endocrinol, 2013. **38**(1): p. 59-76.

468. Hughes, R.C., et al., *Response to comment on Hughes et al. An early pregnancy HbA1c >/=5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes*. Diabetes Care 2014;37:2953-2959. Diabetes Care, 2015. **38**(6): p. e93.

469. Al Subhi, T., et al., *Prevalence of tubal obstruction in the hysterosalpingogram of women with primary and secondary infertility*. J Reprod Infertil, 2013. **14**(4): p. 214-6.

470. Broeze, K.A., et al., *Are patient characteristics associated with the accuracy of hysterosalpingography in diagnosing tubal pathology? An individual patient data meta-analysis*. Hum Reprod Update, 2011. **17**(3): p. 293-300.

471. Schankath, A.C., et al., *Hysterosalpingography in the workup of female infertility: indications, technique and diagnostic findings*. Insights Imaging, 2012. **3**(5): p. 475-83.

472. Luttjeboer, F., et al., *The value of medical history taking as risk indicator for tuboperitoneal pathology: a systematic review*. BJOG: An International Journal of Obstetrics & Gynaecology, 2009. **116**(5): p. 612-625.

473. Mitwally, M. and R. Casper, *Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate*. Fertility & Sterility, 2001. **75**: p. 305–309.

474. Elizur, S. and T. Tuland, *Drugs in infertility and fetal safety*. Fertility & Sterility, 2008. **89**: p. 1595–1602.

475. Adashi, E., *Clomiphene citrate: mechanism(s) and site(s) of action—a hypothesis revisited*. Fertility & Sterility 1984. **42**: p. 331–344.

476. Kamath, M., et al., *Aromatase inhibitors in women with clomiphene citrate resistance: a randomized, double-blind, placebo-controlled trial*. Fertility & Sterility, 2010.

477. Franik, S., et al., *Aromatase inhibitors for subfertile women with polycystic ovary syndrome*. Cochrane Database of Systematic Reviews, 2014. **2**: p. CD010287.

478. Misso, M.L., et al., *Aromatase inhibitors for PCOS: a systematic review and meta-analysis*. Human Reproduction Update, 2012. **18**(3): p. 301-12.

479. Atay, V., et al., *Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation*. Journal of International Medical Research, 2006. **34**(1): p. 73-6.

480. Banerjee Ray, P., A. Ray, and P.S. Chakraborti, *Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome*. Archives of Gynecology & Obstetrics, 2012. **285**(3): p. 873-7.

481. Kar, S., *Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: A prospective randomized trial*. Journal of Human Reproductive Sciences, 2012. **5**(3): p. 262-265.

482. Nazik, H. and Y. Kumtepe, *Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction for women with polycystic ovarian syndrome*. HealthMED, 2012. **6**(3): p. 879-883.

483. Selim, M.F. and T.F. Borg, *Letrozole and Clomiphene Citrate Effect on Endometrial and Subendometrial Vascularity in Treating Infertility in Women with Polycystic Ovary Syndrome*. Journal of Gynecologic Surgery, 2012. **28**(6): p. 405-410.

484. Sheikh-El-Arab Elsedeek, M. and H.A.H. Elmaghraby, *Predictors and characteristics of letrozole induced ovulation in comparison with clomiphene induced ovulation in anovulatory PCOS women*. Middle East Fertility Society Journal, 2011. **16**(2): p. 125-130.

485. Zeinalzadeh, M., Z. Basirat, and M. Esmailpour, *Efficacy of letrozole in ovulation induction compared to that of clomiphene citrate in patients with polycystic ovarian syndrome*. J Reprod Med, 2010. **55**(1-2): p. 36-40.

486. Dehbashi, S., et al., *Comparison of the effects of letrozole and clomiphene citrate on ovulation and pregnancy rate in patients with polycystic ovary syndrome*. Iranian Journal of Medical Sciences, 2009. **34**(1): p. 23-28.

487. Begum, M.R., et al., *Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome*. Fertility & Sterility, 2009. **92**(3): p. 853-7.

488. Bayar, U., et al., *Use of an aromatase inhibitor in patients with polycystic ovary syndrome: a prospective randomized trial*. Fertility and Sterility, 2006. **86**(5): p. 1447-51.

489. Badawy, A., et al., *Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial*. Fertility and Sterility, 2009. **92**(3): p. 849-52.

490. Legro, R.S., et al., *Letrozole versus clomiphene for infertility in the polycystic ovary syndrome*.[Erratum appears in N Engl J Med. 2014 Oct 9;317(15):1465]. New England Journal of Medicine, 2014. **371**(2): p. 119-29.

491. Roy, K., et al., *A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome*. Journal of Human Reproductive Sciences, 2012. **5**(1): p. 20-25.

492. Abu Hashim, H., T. Shokeir, and A. Badawy, *Letrozole versus combined metformin and clomiphene citrate for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial*. Fertility & Sterility, 2010. **94**(4): p. 1405-9.

493. Abdellah, M.S., *Reproductive outcome after letrozole versus laparoscopic ovarian drilling for clomiphene-resistant polycystic ovary syndrome*. International Journal of Gynaecology & Obstetrics, 2011. **113**(3): p. 218-21.

494. Abu Hashim, H., A.M. Mashaly, and A. Badawy, *Letrozole versus laparoscopic ovarian diathermy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial*. Archives of Gynecology & Obstetrics, 2010. **282**(5): p. 567-71.

495. Ibrahim, M.H., et al., *Letrozole versus laparoscopic ovarian drilling in infertile women with PCOS resistant to clomiphene citrate*. Middle East Fertility Society Journal, 2017. **22**(4): p. 251-254.

496. Farquhar, C., J. Brown, and J. Marjoribanks, *Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome*. Cochrane Database of Systematic Reviews, 2012. **6**: p. CD001122.

497. Healey, S., et al., *Effects of letrozole on superovulation with gonadotrophinsin women undergoing intrauterine insemination*. Fertility & Sterility, 2003. **80**: p. 1325–9.

498. Casper, R., *Letrozole: Ovulation or superovulation?* Fertility & Sterility, 2003. **80**(6): p. 1335–7.

CONTENTS

499. Legro, R.S., et al., *Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome*. N Engl J Med, 2007. **356**(6): p. 551-66.

500. Imani, B., et al., *Predictors of chances to conceive in ovulatory patients during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility*. J Clin Endocrinol Metab, 1999. **84**(5): p. 1617-22.

501. Imani, B., et al., *Prediction of the individual follicle-stimulating hormone threshold for gonadotropin induction of ovulation in normogonadotropic anovulatory infertility: an approach to increase safety and efficiency*. Fertility & Sterility, 2002 January. **77**(1): p. 83-90.

502. Holzer, H., R. Casper, and T. Tulandi, *A new era in ovulation induction*. Fertility & Sterility, 2006. **85**: p. 277–284.

503. Legro, R.S., et al., *Letrozole versus clomiphene for infertility in the polycystic ovary syndrome*. N Engl J Med, 2014. **371**(2): p. 119-29.

504. Biljan, M., R. Hemmings, and N. Brassard, *The outcome of 150 babies following the treatment with letrozole or letrozole and gonadotropins*. Fertility & Sterility, 2005. **84**(supp.1): p. O-231, Abstract 1033.

505. Forman, R., et al., *Fetal safety of letrozole and clomiphene citrate for ovulation induction*. Journal of Obstetrics and Gynaecology Canada, 2007. **29**: p. 668-671.

506. Tulandi, T., et al., *Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate*. Fertility & Sterility, 2006. **85**: p. 1761–5.

507. Tatsumi, T., et al., *No increased risk of major congenital anomalies or adverse pregnancy or neonatal outcomes following letrozole use in assisted reproductive technology*. Hum Reprod, 2016.

508. Sharma, S., et al., *Congenital malformations among babies born following letrozole or clomiphene for infertility treatment*. PLoS One, 2014. **9**(10): p. e108219.

509. Diamond, M.P., et al., *Letrozole, Gonadotropin, or Clomiphene for Unexplained Infertility*. N Engl J Med, 2015. **373**(13): p. 1230-40.

510. Wang, R., et al., *Treatment strategies for women with WHO group II anovulation: systematic review and network meta-analysis*. BMJ, 2017. **356**.

511. Davies, M.J., et al., *Reproductive technologies and the risk of birth defects*. N Engl J Med, 2012. **366**(19): p. 1803-13.

512. Shelly, W., et al., *Selective estrogen receptor modulators: An update on recent clinical findings*. Obstetrical & Gynecological Survey 2008. **63**: p. 163-181.

513. Pritts, E., *Letrozole for ovulation induction and controlled ovarian hyperstimulation*. Current Opinion in Obstetrics & Gynecology, 2010. **22**: p. 289–294.

514. Palomba, S., A. Falbo, and F. Zullo, *Management strategies for ovulation induction in women with polycystic ovary syndrome and known clomifene citrate resistance*. Current Opinion in Obstetrics & Gynecology, 2009. **21**: p. 465–473.

515. Kafy, S. and T. Tulandi, *New advances in ovulation induction*. Current Opinion in Obstetrics & Gynecology, 2007. **19**: p. 248–252.

516. Rossing, M., J. Daling, and N. Weiss, *Ovarian tumours in a cohort of infertile women*. New England Journal of Medicine, 1994. **331**: p. 771–776.

517. Dunaif, A., et al., *Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome*. Diabetes, 1989. **38**(9): p. 1165-74.

518. DeUgarte, C., C. Bartolucci, and R. Azziz, *Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment*. Fertility & Sterility, 2005. **83**(5): p. 1454 - 1460.

519. Costello, M. and J. Eden, *A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome*. Fertility & Sterility 2003. **79**: p. 1-13.

CONTENTS

520. Palomba, S., et al., *Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review*. Endocrine Reviews, 2009. **30**(1): p. 1-50.

521. Morley, L.C., et al., *Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility*. Cochrane Database Syst Rev, 2017. **11**: p. Cd003053.

522. Kjotrod, S.B., et al., *Use of metformin before and during assisted reproductive technology in non-obese young infertile women with polycystic ovary syndrome: a prospective, randomized, double-blind, multi-centre study*. Hum Reprod, 2011. **26**(8): p. 2045-53.

523. Palomba, S., et al., *Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis*. Clinical Endocrinology, 2009. 70(2): p. 311-21.

524. Johnson, N., et al., *PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene*. Human Reproduction, 2010. 25(7): p. 1675-83.

525. Karimzadeh, M. and M. Javedani, *An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome*. Fertility & Sterility, 2010. **94**(1): p. 216-20.

526. Maged, A.M., et al., *The adjuvant effect of metformin and N-acetylcysteine to clomiphene citrate in induction of ovulation in patients with Polycystic Ovary Syndrome*. Gynecol Endocrinol, 2015. **31**(8): p. 635-8.

527. Lopez, E., et al., *Ovulation induction in women with polycystic ovary syndrome: randomized trial of clomiphene citrate versus low-dose recombinant FSH as first line therapy*. Reproductive Biomedicine Online, 2004. **9**(4): p. 382-90.

528. Homburg, R., et al., *Clomifene citrate or low-dose FSH for the first-line treatment of infertile women with anovulation associated with polycystic ovary syndrome: a prospective randomized multinational study*. Hum Reprod, 2012. **27**(2): p. 468-73.

529. Brown, J. and C. Farquhar, *Clomiphene and other antioestrogens for ovulation induction in polycystic ovarian syndrome*. Cochrane Database Syst Rev, 2016. **12**: p. Cd002249.

530. Abu Hashim, H., M. Bazeed, and I. Abd Elaal, *Minimal stimulation or clomiphene citrate as first-line therapy in women with polycystic ovary syndrome: a randomized controlled trial*. Gynecol Endocrinol, 2012. **28**(2): p. 87-90.

531. Mukherjee, S., S. Sharma, and B.N. Chakravarty, *Comparative evaluation of pregnancy outcome in gonadotrophin-clomiphene combination vs clomiphene alone in polycystic ovarian syndrome and unexplained infertility-A prospective clinical trial*. J Hum Reprod Sci, 2010. **3**(2): p. 80-4.

532. Lunenfeld, B. and V. Insler, *Classification of amenorrhoeic states and their treatment by ovulation induction*. Clin Endocrinol (Oxf), 1974. **3**(2): p. 223-37.

533. Hamilton-Fairley, D., et al., *Low-dose gonadotrophin therapy for induction of ovulation in 100 women with polycystic ovary syndrome*. Hum Reprod, 1991. **6**(8): p. 1095-9.

534. White, D.M., et al., *Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women*. J Clin Endocrinol Metab, 1996. **81**(11): p. 3821-4.

535. van Santbrink, E.J., et al., *Gonadotrophin induction of ovulation using a step-down dose regimen: single-centre clinical experience in 82 patients*. Hum Reprod, 1995. **10**(5): p. 1048-53.

536. Nugent, D., et al., *Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome*. Cochrane Database Syst Rev, 2000(4): p. CD000410.

537. Abu Hashim, H., A. Wafa, and M. El Rakhawy, *Combined metformin and clomiphene citrate versus highly purified FSH for ovulation induction in clomiphene-resistant PCOS women: a randomised controlled trial*. Gynecol Endocrinol, 2011. **27**(3): p. 190-6.

538. Begum, M.R., et al., *Pretreatment and co-administration of oral anti-diabetic agent with clomiphene citrate or rFSH for ovulation induction in clomiphene-citrate-resistant polycystic ovary syndrome*. J Obstet Gynaecol Res, 2013. **39**(5): p. 966-73.

539. Abu Hashim, H., O. Foda, and E. Ghayaty, *Combined metformin-clomiphene in clomiphene-resistant polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials*. Acta Obstet Gynecol Scand, 2015. **94**(9): p. 921-30.

540. Ghanem, M.E., et al., *Clomiphene citrate co-treatment with low dose urinary FSH versus urinary FSH for clomiphene resistant PCOS: randomized controlled trial*. J Assist Reprod Genet, 2013. **30**(11): p. 1477-85.

541. Domecq, J.P., et al., *Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis*. J Clin Endocrinol Metab, 2013. **98**(12): p. 4655-63.

542. Legro, R.S., et al., *Randomized Controlled Trial of Preconception Interventions in Infertile Women With Polycystic Ovary Syndrome*. J Clin Endocrinol Metab, 2015. **100**(11): p. 4048-58.

543. Stein, I., *Duration of infertility following ovarian wedge resection*. West Journal of Surgery, 1964. **72**: p. 237.

544. Gjønnæss, H., *Polycystic ovarian syndrome treated by ovarian electrocautery through the laparoscope*. Fertility & Sterility, 1984. **41**: p. 20–25.

545. Hamed, H., et al., *Metformin versus laparoscopic ovarian drilling in clomiphene- and insulin-resistant women with polycystic ovary syndrome*. International Journal of Gynecology & Obstetrics, 2010. **108**: p. 143–147.

546. Palomba, S., et al., *Metformin administration versus laparoscopic ovarian diathermy in clomiphene citrate-resistant women with polycystic ovary syndrome: a prospective parallel randomized double-blind placebo-controlled trial*. Journal of Clinical Endocrinology & Metabolism, 2004. **89**(10): p. 4801-9.

547. Palomba, S., et al., *Plasminogen activator inhibitor 1 and miscarriage after metformin treatment and laparoscopic ovarian drilling in patients with polycystic ovary syndrome*. Fertility & Sterility, 2005. **84**(3): p. 761-5.

548. Abu Hashim, H., et al., *Laparoscopic ovarian diathermy after clomiphene failure in polycystic ovary syndrome: is it worthwhile? A randomized controlled trial*. Arch Gynecol Obstet, 2011. **284**(5): p. 1303-9.

549. Amer, S., et al., *Randomized controlled trial comparing laparoscopic ovarian diathermy with clomiphene citrate as a first-line method of ovulation induction in women with polycystic ovary syndrome*. Human Reproduction, 2009. **24**(1): p. 219-225.

550. Abd Elgafor, I., *Efficacy of combined metformin-letrozole in comparison with bilateral ovarian drilling in clomiphene-resistant infertile women with polycystic ovarian syndrome*. Arch Gynecol Obstet, 2013. **288**(1): p. 119-23.

551. Lunde, O., O. Djoseland, and P. Grottum, *Polycystic ovarian syndrome: a follow-up study on fertility and menstrual pattern in 149 patients 15-25 years after ovarian wedge resection*. Human Reproduction, 2001. **16**(7): p. 1479-85.

552. Sturm, R. and A. Hattori, *Morbid obesity rates continue to rise rapidly in the United States*. Int J Obes (Lond), 2013. **37**(6): p. 889-91.

553. Scottish Intercollegiate Guidelines Network, *Management of obesity: A national clinical guideline.* 2010: Edinburgh, Scotland.

554. National Institute for Health and Clinical Excellence, *NICE clinical guideline 43: Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children.* 2006: London, UK.

555. Jensen, M.D., et al., *2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society*. Circulation, 2013.

556. Lager, C.J., et al., *Roux-En-Y Gastric Bypass Vs. Sleeve Gastrectomy: Balancing the Risks of Surgery with the Benefits of Weight Loss*. Obes Surg, 2017. **27**(1): p. 154-161.

557. Mingrone, G., et al., *Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes*. N Engl J Med, 2012.

558. Schauer, P.R., D.L. Bhatt, and S.R. Kashyap, *Bariatric Surgery or Intensive Medical Therapy for Diabetes after 5 Years*. N Engl J Med, 2017. **376**(20): p. 1997.

559. Shah, D. and E. Ginsburg, *Bariatric surgery and fertility*. Current Opinion in Obstetrics & Gynecology, 2010. **22**(3): p. 248-54.

560. Mutsaerts, M.A., et al., *Randomized Trial of a Lifestyle Program in Obese Infertile Women*. N Engl J Med, 2016. **374**(20): p. 1942-53.

561. Nilsen, R., et al., *Patterns and predictors of folic acid supplement use among pregnant women: the Norwegian Mother and Child Cohort Study*. The American Journal of Clinical Nutrition, 2006. **84**(5): p. 1134-1141.

562. Johansson, K., et al., *Outcomes of pregnancy after bariatric surgery.* N Engl J Med, 2015. **372**(9): p. 814-24.

563. Gonzalez, I., et al., *Maternal and perinatal outcomes after bariatric surgery: a Spanish multicenter study*. Obes Surg, 2015. **25**(3): p. 436-42.

564. Walls, M.L., et al., *In vitro maturation as an alternative to standard in vitro fertilization for patients diagnosed with polycystic ovaries: a comparative analysis of fresh, frozen and cumulative cycle outcomes*. Hum Reprod, 2015. **30**(1): p. 88-96.

565. Al-Inany, H.G., A.M. Abou-Setta, and M. Aboulghar, *Gonadotrophin-releasing hormone antagonists for assisted conception: a Cochrane review*. Reprod Biomed Online, 2007. **14**(5): p. 640-9.

566. Mancini, F., et al., *Gonadotrophin-releasing hormone-antagonists vs long agonist in in-vitro fertilization patients with polycystic ovary syndrome: a meta-analysis.* Gynecological Endocrinology, 2011. **27**(3): p. 150-5.

567. Lin, H., et al., *Is a GnRH antagonist protocol better in PCOS patients? A meta-analysis of RCTs*. PLoS One, 2014. **9**(3): p. e91796.

568. *Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline*. Fertil Steril, 2016. **106**(7): p. 1634-1647.

569. Hwang, J.L., et al., *Ovarian stimulation by concomitant administration of cetrorelix acetate and HMG following Diane-35 pre-treatment for patients with polycystic ovary syndrome: a prospective randomized study*. Hum Reprod, 2004. **19**(9): p. 1993-2000.

570. Kurzawa, R., et al., *Comparison of embryological and clinical outcome in GnRH antagonist vs. GnRH agonist protocols for in vitro fertilization in PCOS non-obese patients. A prospective randomized study*. J Assist Reprod Genet, 2008. **25**(8): p. 365-74.

571. Tehraninejad, E.S., et al., *Comparison of GnRH antagonist with long GnRH agonist protocol after OCP pretreatment in PCOs patients*. Arch Gynecol Obstet, 2010. **282**(3): p. 319-25.

572. Bahceci, M., et al., *Use of a GnRH antagonist in controlled ovarian hyperstimulation for assisted conception in women with polycystic ovary disease: a randomized, prospective, pilot study.* J Reprod Med, 2005. **50**(2): p. 84-90.

573. Lainas, T.G., et al., *Initiation of GnRH antagonist on Day 1 of stimulation as compared to the long agonist protocol in PCOS patients. A randomized controlled trial: effect on hormonal levels and follicular development*. Hum Reprod, 2007. **22**(6): p. 1540-6.

574. Lainas, T.G., et al., *Flexible GnRH antagonist protocol versus GnRH agonist long protocol in patients with polycystic ovary syndrome treated for IVF: a prospective randomised controlled trial (RCT)*. Hum Reprod, 2010. **25**(3): p. 683-9.

575. Mokhtar, S., et al., *ART Outcomes in GnRH Antagonist Protocol (Flexible) and Long GnRH Agonist Protocol during Early Follicular Phase in Patients with Polycystic Ovary Syndrome: A Randomized Clinical Trial*. J Reprod Infertil, 2015. **16**(3): p. 148-54.

576. Haydardedeoglu, B., et al., *IVF/ICSI outcomes of the OCP plus GnRH agonist protocol versus the OCP plus GnRH antagonist fixed protocol in women with PCOS: a randomized trial*. Arch Gynecol Obstet, 2012. **286**(3): p. 763-9.

577. Youssef, M.A., et al., *Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology*. Cochrane Database Syst Rev, 2014(10): p. Cd008046.

578. Figen Turkcapar, A., et al., *Human Menopausal Gonadotropin versus Recombinant FSH in Polycystic Ovary Syndrome Patients Undergoing In Vitro Fertilization*. Int J Fertil Steril, 2013. **6**(4): p. 238-43.

579. van Wely, M., et al., *Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles*. Cochrane Database Syst Rev, 2011(2): p. CD005354.

580. Jacobs, H.S. and R.R. Homburg, *The endocrinology of conception*. Baillieres Clin Endocrinol Metab, 1990. **4**(2): p. 195-205.

581. Willis, D.S., et al., *Premature response to luteinizing hormone of granulosa cells from anovulatory women with polycystic ovary syndrome: relevance to mechanism of anovulation*. J Clin Endocrinol Metab, 1998. **83**(11): p. 3984-91.

582. Tarlatzis, B.C., et al., *The prognostic value of basal luteinizing hormone:follicle-stimulating hormone ratio in the treatment of patients with polycystic ovarian syndrome by assisted reproduction techniques*. Hum Reprod, 1995. **10**(10): p. 2545-9.

583. Schwarze, J.E., J.A. Crosby, and F. Zegers-Hochschild, *Addition of neither recombinant nor urinary luteinizing hormone was associated with an improvement in the outcome of autologous in vitro fertilization/ intracytoplasmatic sperm injection cycles under regular clinical settings: a multicenter observational analysis*. Fertil Steril, 2016. **106**(7): p. 1714-1717 e1.

584. Konig, T.E., et al., *Recombinant LH supplementation to a standard GnRH antagonist protocol in women of 35 years or older undergoing IVF/ICSI: a randomized controlled multicentre study*. Hum Reprod, 2013. **28**(10): p. 2804-12.

585. Baskind, N.E. and A.H. Balen, *Hypothalamic-pituitary, ovarian and adrenal contributions to polycystic ovary syndrome*. Best Pract Res Clin Obstet Gynaecol, 2016. **37**: p. 80-97.

586. Costello, M.F., M. Chapman, and U. Conway, *A systematic review and meta-analysis of randomized controlled trials on metformin co-administration during gonadotrophin ovulation induction or IVF in women with polycystic ovary syndrome*. Human Reproduction, 2006. **21**(6): p. 1387-1399.

587. Huang, X., et al., *A systematic review and meta-analysis of metformin among patients with polycystic ovary syndrome undergoing assisted reproductive technology procedures*. Int J Gynaecol Obstet, 2015. **131**(2): p. 111-6.

588. Kjotrod, S.B., V. von During, and S.M. Carlsen, *Metformin treatment before IVF/ICSI in women with polycystic ovary syndrome; a prospective, randomized, double blind study*. Hum Reprod, 2004. **19**(6): p. 1315-22.

589. Lin, K. and C. Coutifaris, *In vitro fertilization in the polycystic ovary syndrome patient: an update*. Clin Obstet Gynecol, 2007. **50**(1): p. 268-76.

590. Legro, R.S., *Ovulation induction in polycystic ovary syndrome: Current options*. Best Pract Res Clin Obstet Gynaecol, 2016. **37**: p. 152-159.

591. Palomba, S., et al., *Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial*. Fertil Steril, 2011. **96**(6): p. 1384-1390.e4.

592. Tang, T., et al., *The use of metformin for women with PCOS undergoing IVF treatment*. Hum Reprod, 2006. **21**(6): p. 1416-25.

593. Fedorcsak, P., et al., *The effect of metformin on ovarian stimulation and in vitro fertilization in insulin-resistant women with polycystic ovary syndrome: an open-label randomized cross-over trial*. Gynecol Endocrinol, 2003. **17**(3): p. 207-14.

594. Onalan, G., et al., *Metformin treatment in patients with polycystic ovary syndrome undergoing in vitro fertilization: a prospective randomized trial*. Fertil Steril, 2005. **84**(3): p. 798-801.

595. Tso, L.O., et al., *Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome*. Cochrane Database Syst Rev, 2014(11): p. Cd006105.

596. De Vos, M., et al., *The definition of IVM is clear-variations need defining*. Hum Reprod, 2016. **31**(11): p. 2411-2415.

597. Reavey, J., et al., *Human chorionic gonadotrophin priming for fertility treatment with in vitro maturation*. Cochrane Database Syst Rev, 2016. **11**: p. CD008720.

598. De Vos, M., et al., *Clinical outcome of non-hCG-primed oocyte in vitro maturation treatment in patients with polycystic ovaries and polycystic ovary syndrome*. Fertil Steril, 2011. **96**(4): p. 860-4.

599. Roesner, S., et al., *Two-year development of children conceived by IVM: a prospective controlled single-blinded study*. Hum Reprod, 2017. **32**(6): p. 1341-1350.

600. Sauerbrun-Cutler, M.T., et al., *In vitro maturation and its role in clinical assisted reproductive technology*. Obstet Gynecol Surv, 2015. **70**(1): p. 45-57.

601. Walls, M.L., et al., *In vitro maturation is associated with increased early embryo arrest without impairing morphokinetic development of useable embryos progressing to blastocysts*. Hum Reprod, 2015. **30**(8): p. 1842-9.

602. Roesner, S., et al., *Time-lapse imaging reveals differences in growth dynamics of embryos after in vitro maturation compared with conventional stimulation*. Fertil Steril, 2017. **107**(3): p. 606-612 e3.

603. National Health and Medical Research Council, *NHMRC standards and procedures for externally developed guidelines*. 2007: Australia.

604. Centre for Clinical Effectiveness, *Critical Appraisal Templates*, Southern Health, Editor. 2010: Melbourne, Australia.

605. Vermeulen N, L.C.N., D'Angelo A, Tilleman K, Veleva Z, Nelen W, *Manual for ESHRE guideline development Version 3.0*, European Society of Human Reproduction and Embryology, Editor. 2017.

606. The Royal Australian College of General Practitioners, *Clinical guideline for the diagnosis and management of early rheumatoid arthritis*. 2009: Australia.

607. National Health and Medical Research Council, *Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals.* 2009, National Health and Medical Research Council,: Melbourne.

608. National Health and Medical Research Council, NHMRC levels of evidence and grades for recommendations for developers of guidelines. 2009: Australia.

Appendix I:

Project board

ROLE	NAME	DISCIPLINE	ORGANISATIONAL AFFILIATION / REGION
Chair Senior Supplier Endocrinology Representative	Professor Helena Teede	Endocrinologist	Centre for Research Excellence in Polycystic Ovary Syndrome, Australia
Senior user	Mrs Veryan McAllister	Consumer lead	Polycystic Ovary Syndrome Association of Australia
Senior user Senior Supplier Allied Health Representative	Associate Professor Lisa Moran	Dietitian	Centre for Research Excellence in Polycystic Ovary Syndrome, Australia
Senior user General Practitioner Representative	Doctor Mala Thondan	General Practitioner	Harp Family Medical Centre, Australia
Senior user Senior supplier Gynaecology Representative European Society of Human Reproduction and Embryology Representative	Professor Joop Laven	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Erasmus MC Rotterdam, Netherlands
Senior supplier Gynaecology Representative	Doctor Michael Costello	Obstetrician-Gynaecologist;	University of NSW, Australia
Senior supplier American Society for Reproductive Medicine Representative	Professor Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania, USA
Senior supplier European Society of Human Reproduction and Embryology Representative	Associate Professor Terhi Piltonen	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Oulu University Hospital, University of Oulu, Finland
Senior supplier Evidence Synthesis Lead and Guidelines Advisor	Doctor Marie Misso	Evidence synthesis and guidelines advisor	Centre for Research Excellence in Polycystic Ovary Syndrome, Australia

Appendix II:

International Advisory Panel

ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Bart Fauser	Obstetrician-Gynaecologist	University Medical Center Utrecht	Netherlands
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	The University of Adelaide	Australia
Member	Professor	Juha Tapanainen	Obstetrician-Gynaecologist	University of Helsinki	Finland
Member	Professor	Zephne van der Spuy	Obstetrician-Gynaecologist Specialist Reproductive Medicine	University of Cape Town	South Africa
Member	Professor	Duru Shah	Obstetrician-Gynaecologist	Gynaecworld	India
Member	Professor	Richard Legro	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Penn State Clinical and Translational Institute	USA
Member	Professor	Frank Broekmans	Gynaecologist Specialist Reproductive Medicine	University Medical Centre Utrecht	Netherlands
Member	Doctor	Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania	USA
Member	Doctor	Marie Misso	Evidence Synthesis and Guidelines Advisor	Monash Centre for Health Research and Implementation	Australia
Member	Professor	Chii-Ruey Tzeng	Obstetrician-Gynaecologist	Taipei Medical University Hospital	Taiwan
Member	Professor	Jie Qiao	Obstetrician-Gynaecologist	Peking University Third Hospital	China
Member	Professor	Poli Mara Spritzer	Reproductive Endocrinologist	Federal University of Rio Grande Do Sul	Brazil

Appendix III:

Guideline development groups

Terms of reference for each committee can be provided upon request (MCHRI-PCOS-Guideline-Group-l@monash.edu).

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

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Joop Laven	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Erasmus MC Rotterdam	Netherlands
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	The University of Adelaide	Australia
Member	Professor	Marianne Andersen	Endocrinologist	Odense University Hospital	Denmark
Member	Professor	Ricardo Azziz	Reproductive Endocrinologist	State University of New York System Administration	USA
Member	Professor	Preeti Dabadghao	Endocrinologist	Sanjay Gandhi Postgraduate Institute of Medical Sciences	India
Member	Professor	Didier Dewailly	Endocrinologist	University of Lille	France
Member	Professor	Stephen Franks	Endocrinologist	Imperial College London	United Kingdom
Member	Professor	Kathleen Hoeger	Reproductive Endocrinologist	University of Rochester	USA
Member	Doctor	Samantha Hutchison	Endocrinologist	Monash Health	Australia
Member	Professor	Ernest Ng	Obstetrician-Gynaecologist	Department of Obstetrics & Gynaecology, The University of Hong Kong	China
Member	Professor	Sharon Oberfield	Paediatric endocrinologist	Columbia University Medical Center	USA

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Member	Professor	Duru Shah	Obstetrician-Gynaecologist	Gynaecworld	India
Co-opted	Doctor	Jane Woolcock	Obstetrician-Gynaecologist	Women's and Children's Hospital Adelaide	Australia
Co-opted	Assistant Professor	Marla Lujan	Nutritional Science	Cornell University	USA
Co-opted	Associate Professor	Darren Mansfield	Respiratory Physician	Monash Health	Australia
Member	Doctor	Femke Hohmann	General Practitioner	Huisartsenpraktijk Hohmann & De Vet, Rotterdam	Netherlands
Member	Ms	Sasha Ottey	Non-profit Executive Director; Consumer	PCOS Challenge: The National Polycystic Ovary Syndrome Association	USA

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

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania	USA
Deputy Chair	Professor	Elisabet Stener-Victorin	Researcher in Reproductive Endocrinology and Metabolism	Karolinska Institutet	Sweden
Member	Associate Professor	Leah Brennan	Psychologist	Australian Catholic University	Australia
Member	Doctor	Rhonda Garad	Registered Nurse	Monash Centre for Health Research and Implementation	Australia
Member	Doctor	Melanie Gibson-Helm	Women's Public Health Researcher	Monash University	Australia
Co-opted	Professor	Jayashri Kulkarni	Psychiatrist	Monash Alfred Psychiatry Research Centre	Australia
Member	Professor	Rong Li	Obstetrician-gynaecologist	Reproductive Medical Center, Peking University Third Hospital	China
Member	Professor	Jane Speight	Health Psychologist	Deakin University	Australia
Member	Associate Professor	Maria Vogiatzi	Pediatric Endocrinologist	Children's Hospital of Philadelphia, University of Pennsylvania	USA
Member	Professor	Bulent Yildiz	Endocrinologist	Hacettepe University	Turkey
Member		Veryan McAllister	Consumer	Polycystic Ovary Syndrome Association Australia	Australia
Member	Doctor	Mala Thondan	General practitioner	Harp Family Medical Centre	Australia

GDG3: Topic area – Lifestyle management and models of care

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Associate Professor	Lisa Moran	Dietitian; Research Fellow	Monash Centre for Health Research and Implementation	Australia
Deputy Chair	Associate Professor	Nigel Stepto	Accredited Exercise Physiologist	Victoria University	Australia
Member	Associate Professor	Jacqueline Boyle	Obstetrician-Gynaecologist	Monash Centre for Health Research and Implementation	Australia
Member	Doctor	Cheryce Harrison	Research Fellow	Monash Centre for Health Research and Implementation	Australia
Member	Professor	Angelica Hirschberg	Obstetrician-Gynaecologist	Karolinska Institutet	Sweden
Member	Doctor	Kate Marsh	Dietitian	Northside Nutrition & Dietetics	Australia
Member	Associate Professor	Leanne Redman	Obesity; Lifestyle Interventions	Pennington Biomedical Research Center	USA
Member	Professor	Chandrika Wijeyaratne	Endocrinology and Reproductive Medicine	Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Colombo	Sri Lanka
Co-opted	Associate Professor	Leah Brennan	Psychologist	Australian Catholic University	Australia
Co-opted	Miss	Eliza Tassone	Consumer	Monash University	Australia
Co-opted	Doctor	Mala Thondan	General practitioner	Harp Family Medical Centre	Australia

GDG4: Topic area - Medical treatment

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Helena Teede	Endocrinologist	Monash Centre for Health Research and Implementation	Australia
Deputy Chair	Associate Professor	Terhi Piltonen	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Oulu University Hospital, University of Oulu	Finland
Member	Doctor	Anju Joham	Endocrinologist	Monash Health	Australia
Member	Professor	Jaideep Malhotra	Obstetrician-Gynaecologist	Rainbow Hospital	India
Member	Professor	Ben Mol	Obstetrician-Gynaecologist	Monash University	Australia
Member	Doctor	Alexia Peña	Paediatric Endocrinologist	The Robinson Research Institute at the University of Adelaide	Australia
Member	Doctor	Daniela Romualdi	Obstetrician-Gynaecologist	Fondazione Policlinico Universitario Agostino Gemelli, Rome	Italy
Member	Professor	Selma Witchel	Paediatric Endocrinologist	Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh	USA
Member	Ms	Veryan McAllister	Consumer	Polycystic Ovary Syndrome Association Australia	Australia
Member	Doctor	Mala Thondan	General practitioner	Harp Family Medical Centre	Australia

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

GDG ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Doctor	Michael Costello	Obstetrician-Gynaecologist	University of NSW	Australia
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	The University of Adelaide	Australia
Member	Professor	Adam Balen	Reproductive Medicine	Leeds Teaching Hospitals	United Kingdom
Member	Professor	Luigi Devoto	Reproductive Endocrinologist	University of Chile. Faculty of Medicine	Chile
Member	Professor	Roger Hart	Obstetrician-Gynaecologist; Reproductive Endocrinologist	The University of Western Australia	Australia
Member		Cailin Jordan	Psychologist	Genea Hollywood Fertility	Australia
Member	Professor	Richard Legro	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Penn State Clinical and Translational Institute	USA
Member	Doctor	Edgar Mocanu	Obstetrician-Gynaecologist	Rotunda Hospital	Ireland
Member	Professor	Jie Qiao	Obstetrician-Gynaecologist	Peking University Third Hospital	China
Member	Professor	Raymond Rodgers	Reproductive Endocrinologist	The Robinson Research Institute at the University of Adelaide	Australia
Member	Professor	Luk Rombauts	Obstetrician-Gynaecologist; Infertility Specialist	Monash Health	Australia
Member	Professor	Shakila Thangaratinam	Obstetrician-Gynaecologist; Clinical Academic	Queen Mary University of London	United Kingdom
Member	Professor	Eszter Vanky	Obstetrician-Gynaecologist	Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology	Norway
Member		Louise Johnson	Consumer focused organisation representative	Victorian Assisted reproductive Treatment Authority	Australia

Guideline development technical team members

- Professor Helena Teede, Project Director, Monash Centre for Health Research and Implementation, Monash Public Health, Monash University
- Doctor Marie Misso, Evidence Synthesis Lead and Guidelines Advisor, Monash Centre for Health Research and Implementation, Monash Public Health, Monash University
- 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, Monash Public Health, Monash University
- 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

Paediatric GDG panel membership

ROLE	TITLE	NAME	DISCIPLINE	ORGANISATION	COUNTRY
Chair	Professor	Helena Teede	Endocrinologist	Monash Centre for Health Research and Implementation	Australia
Member	Professor	Kathleen Hoeger	Reproductive Endocrinologist	University of Rochester	USA
Member	Professor	Sharon Oberfield	Paediatric endocrinologist	Columbia University Medical Center	USA
Member	Professor	Selma Witchel	Paediatric Endocrinologist	Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh	USA
Member	Doctor	Alexia Peña	Paediatric Endocrinologist	The Robinson Research Institute at the University of Adelaide	Australia

Appendix IV:

Berlin Questionnaire ©1997 IONSLEEP

Sleep Evaluation in Primary Care

1   Complete the following:

Height	Weight
Age	Male / Female

Category 1

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

Category 2

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

Category 3

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

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

Appendix VI:

Glossary

Sources for this glossary include: The Cochrane Resources Glossary (http://www.cochrane.org/glossary/5), Jean Hailes for Women's Health (http://www.jeanhailes.org.au), Diabetes Australia (http://www.diabetesaustralia.com.au), Better Health Channel (http://www.betterhealth.vic.gov.au), the 2009 NHMRC Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals [607] and the 2009 NHMRC levels of evidence and grades for recommendations for developers of guidelines [608].

Adverse effect	An adverse event for which the causal relation between the drug/intervention and the event is at least a reasonable possibility.
Aerobic exercise/activity	Any physical activity that produces energy by combining oxygen with blood glucose or body fat.
AGREE II	An international collaboration of researchers and policy makers whose aim is to improve the quality and effectiveness of clinical practice guidelines (http://www.agreetrust.org).
	The AGREE II instrument developed by the collaboration is designed to assess the quality of clinical guidelines.
Algorithm	A flow chart of the clinical decision pathway described in the guideline, where recommendations are presented in boxes, linked with arrows.
Anovulation	A condition in which the ovary does not produce and release an egg each menstrual cycle.
Anxiety	When fears or thoughts that are chronic (constant) and distressing interfere with daily living.
Area under the receiver operating characteristic curve (AUC)	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.
Assess	In this guideline, assess refers to the process of identifying the severity of the condition
Blood pressure	Blood pressure is the pressure of the blood in the arteries as it is pumped around the body by the heart.
Body image	The way a person may feel, think and view their body including their appearance.
Body mass index (BMI)	A calculated number used to discriminate between lean, overweight, obesity and morbid obesity, calculated from an individual's height (kg) and weight (m).
	BMI = (weight/height)2
Cardiometabolic	Metabolic factors that increase the risk of cardiovascular disease.
Cardiovascular disease (CVD)	A condition that affects either the heart or major blood vessels (arteries) supplying the heart, brain and other parts of the body.
Clinical impact	The potential benefit from application of the recommendations in the guideline on the treatment or treatment outcomes of the target population.
Clinical question (guideline development)	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.

Clomiphene citrate resistant (CCR)	When the patient is unable to ovulate with clomiphene citrate treatment.
Clomiphene citrate failure	When the patient is able to ovulate with clomiphene citrate treatment but does not conceive.
Clomiphene citrate sensitive	When the patient is able to ovulate and conceive with clomiphene citrate treatment.
Cochrane review	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.
Co-morbidity	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.)
Compliance	The extent to which a person adheres to the health advice agreed with healthcare professionals. May also be referred to as 'adherence' or 'concordance'.
Confidence interval	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.
Congenital adrenal hyperplasia	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.
Consensus methods	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.
Contraindication	A condition or factor that serves as a reason to withhold a certain medical treatment.
Depression	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.
Diagnostic accuracy	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.
Disordered eating	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.
Dosage	The prescribed amount of a drug to be taken, including the size and timing of the doses.
Eating disorder	Eating disorders include anorexia, bulimia nervosa and other binge eating disorders.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	The observed association between interventions and outcomes or a statistic to summarise the strength of the observed association.

Evidence statement table	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.
Exclusion criteria (for a systematic evidence review)	Explicit criteria used to decide which studies should be excluded from consideration as potential sources of evidence.
Heterogeneity	Describes the variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of 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. |
| Hormonal profile | Cyclical levels of hormones. |
| Hyperandrogenism | Clinical hyperandrogenism is characterised by hirsutism, acne and male pattern alopecia.

Biochemical hyperandrogenism is characterised by excessive production and/or secretion of androgens. |
Impaired fasting glucose	When fasting morning blood glucose levels are higher than normal but not high enough to diagnose diabetes.
Impaired glucose tolerance	When glucose levels are above normal during or after an oral glucose tolerance test but are not high enough to diagnose diabetes.
Incidence	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.
Inclusion criteria (for a systematic evidence review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Infertility (women)	Infertility problems in women include failure to ovulate, blockages in the fallopian tubes, and disorders of the uterus, such as fibroids or endometriosis.
Interdisciplinary care	An interdisciplinary care model is the collaboration between a woman with PCOS and a care team who have shared goals for her total wellbeing.
Intervention	Any action intended to benefit the patient, for example, drug treatment, surgical procedure, psychological therapy.
Insulin resistance (IR)	A rise in glucose occurs because the body can't make enough insulin or the insulin produced is not working properly.
Irregular cycles / oligomenorrhea	When the duration of menstrual cycles is > 35 or < 21 days.
Laparoscopy	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.
Lean	BMI ≤ 25kg/m2

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Lipid profile	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.
Menarche	The onset of the first period of the menstrual cycle, which occurs on average between the ages of 11 and 14 years.
Meta-analysis	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.
Morbidly obese	BMI ≥ 35kg/m2
Non-clomiphene citrate resistant (Non-CCR)	Those who are either clomiphene citrate sensitive or who have unknown clomiphene citrate sensitivity.
Obese	BMI ≥ 30-35kg/m2
Odds ratio (OR)	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.
Oligo-anovulation	Clinically, irregular cycles lasting <21 or more than 35 days or less than 8 periods per year. Metabolically, hormonally and reproductively, the absence of raised serum progesterone greater than 20nmol/l 7 days prior to a period.
Oligomenorrhea / irregular cycles	When the duration of menstrual cycles is >35 or <21 days.
Oral glucose tolerance test (OGTT)	A test to diagnose diabetes where a high-glucose drink is given and blood samples are checked at regular intervals for two hours.
Ovarian hyperstimulation syndrome (OHSS)	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.
Overweight	BMI ≥ 25.1-30kg/m2
Ovulation	Ovulation is the release of an egg from one of the ovaries.
Ovulation induction	Ovulation induction is the use of medication to stimulate the ovary to increase egg production.
Polycystic ovaries	Characterised by clusters of blister-like cysts on the ovary.
Polycystic ovary syndrome (PCOS)	PCOS is a chronic metabolic and hormonal condition, which can impact on physical health and emotional wellbeing.
Placebo	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.
Post-operative	The period after a patient leaves the operating theatre, following surgery.
Prediabetes	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.
Pre-operative	The period before surgery commences.
Psychosexual dysfunction	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.

P value	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'.
Randomisation	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.
Randomised controlled trial (RCT)	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.
Resource implication	The likely impact of the recommendation in terms of cost, workforce or other health system resources.
Risk of bias	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.
Relative risk (RR)	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.
Screen	In this guideline, screen refers to the process of identifying whether the condition exists and is the first step in offering appropriate management
Selection criteria	Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.
Stakeholder	Those with an interest in the topic. Stakeholders include healthcare professionals, patient/consumer and carer groups, manufacturers and sponsors.
Statistical power	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.
Systematic review	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.
Therapy naive	A patient who has not been administered prior treatment for the condition.
Type 2 diabetes mellitus (DM2)	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.

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Appendix VII:

Evidence-based guideline development pathway

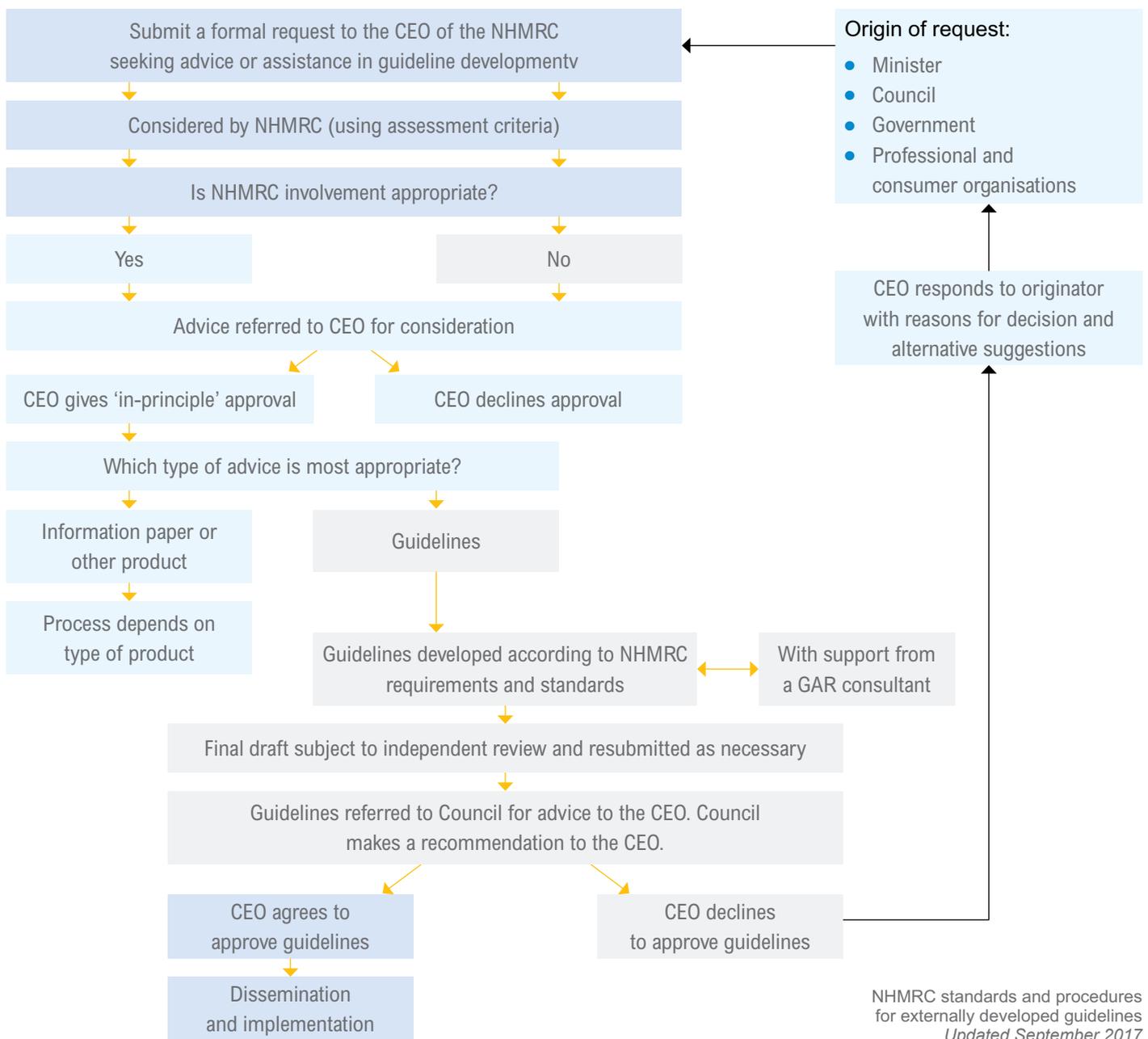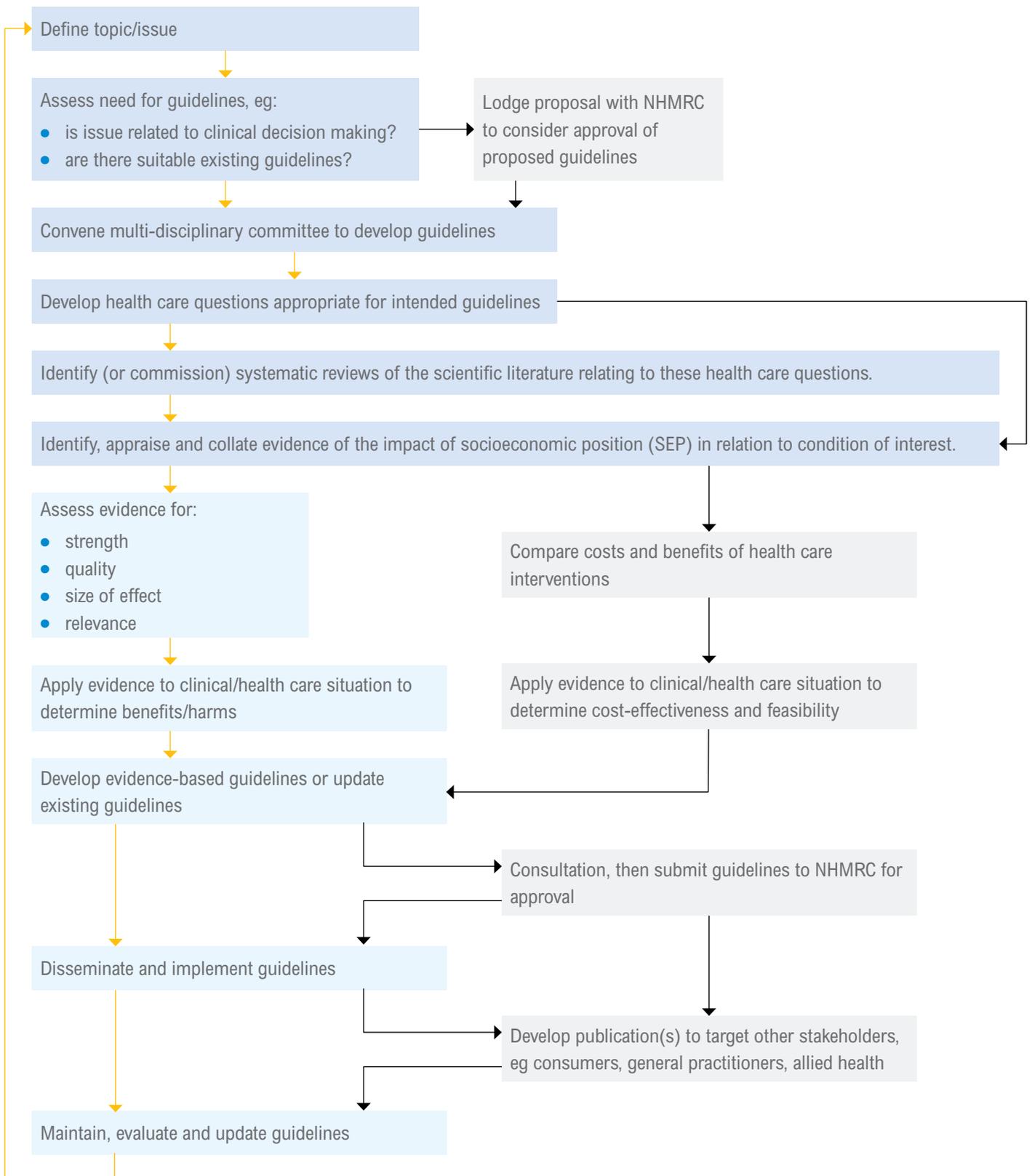## Diagram 1: Key steps in seeking NHMRC approval of externally developed guidelines

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

Considered by NHMRC (using assessment criteria)

Is NHMRC involvement appropriate?

Yes | No

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

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

CEO responds to originator with reasons for decision and alternative suggestions

NHMRC standards and procedures for externally developed guidelines
Updated September 2017

NHMRC standards and procedures for externally developed guidelines
Updated September 2007

Appendix VIII:

Algorithm 1:
Screening, diagnostic assessment, risk assessment and life-stage

Step 1: Irregular cycles + clinical hyperandrogenism
(exclude other causes)* = diagnosis

Step 2: If no clinical hyperandrogenism
Test for biochemical hyperandrogenism (exclude other causes)* = diagnosis

Step 3: If ONLY irregular cycles OR hyperandrogenism
Adolescents ultrasound is not indicated = consider at risk of PCOS and reassess later
Adults - request ultrasound for PCOM, if positive (exclude other causes)* = diagnosis

* Exclusion of other causes requires TSH, Prolactin levels, FSH and if clinical status indicates other causes need to be excluded
(e.g. CAH, Cushings, adrenal tumours etc)

Diagnostic Criteria

Irregular menstrual cycles

- normal in the first year post menarche = pubertal transition.
- > 1 to < 3 years post menarche: < 21 or > 45 days.
- > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year.
- > 1 year post menarche > 90 days for any one cycle.
- Primary amenorrhea by age 15 or > 3 years post thelarche (breast development).

With irregular cycles, PCOS should be considered and assessed according to the guidelines.

Ovulatory dysfunction can still occur with regular cycles. If anovulation suspected test progesterone levels.

Clinical hyperandrogenism

Comprehensive history and physical examination for clinical hyperandrogenism. Adults: acne, alopecia and hirsutism and in adolescents severe acne and hirsutism.

Be aware of potential negative psychosocial impact of clinical hyperandrogenism. Perception of unwanted face and body hair and/or alopecia are important, regardless of apparent clinical severity.

Standardised visual scales are preferred when assessing hirsutism such as the modified Ferriman Gallway score (mFG). A cut-off score of ≥ 4-6 indicates hirsutism, depending on ethnicity. It is acknowledged that self-treatment is common and can limit clinical assessment.

The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.

Hirsutism prevalence is same across ethnicities. mFG cut-offs for hirsutism and severity, vary by ethnicity.

Only terminal hairs relevant in pathological hirsutism (untreated > 5 mm long, variable shape and pigmented).

Biochemical hyperandrogenism

Use calculated free testosterone, free androgen index or calculated bioavailable testosterone in diagnosis.

Androstenedione and dehydroepiandrosterone sulfate (DHEAS) have limited role in PCOS diagnosis.

High quality assays needed for most accurate assessment. Direct free testosterone assays not preferred. Interpretation of androgen levels should be guided by the reference ranges of the laboratory used.

Reliable assessment of biochemical hyperandrogenism not possible on hormonal contraception. Consider withdrawal for ≥ 3 months before testing, advising non-hormonal contraception during this time.

In diagnosis, biochemical hyperandrogenism most useful when clinical hyperandrogenism is unclear.

Where levels are well above laboratory reference ranges, other causes 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.

Ultrasound and polycystic ovarian morphology (PCOM)

Ultrasound should not be used for the diagnosis of PCOS in those with a gynaecological age of < 8 years (< 8 years after menarche), due to the high incidence of multi-follicular ovaries in this life stage.

The transvaginal ultrasound approach is preferred in the diagnosis of PCOS, if sexually active and if acceptable to the individual being assessed.

Using endovaginal ultrasound transducers with a frequency bandwidth that includes 8MHz, the threshold for PCOM should be a follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10ml on either ovary, ensuring no corpora lutea, cysts or dominant follicles are present.

If using older technology, the threshold for PCOM could be an ovarian volume ≥ 10ml on either ovary.

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.

Transabdominal ultrasound should primarily report ovarian volume with a threshold of ≥ 10ml, given the difficulty of reliably assessing follicle number with this approach.

Ethnic variation

Consider ethnic variation in PCOS including:
- relatively mild phenotypes in Caucasians.
- higher BMI in Caucasians, especially North America and Australia.
- more severe hirsutism in Middle Eastern, Hispanic and Mediterranean women.
- increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians.
- lower BMI and milder hirsutism in East Asians.
- higher BMI and metabolic features in Africans.

Anti-müllerian hormone (AMH)

Serum AMH levels should not yet be used as an alternative for the detection of PCOM or to diagnose PCOS.

Cardiovascular disease risk and weight management

All with PCOS should be offered regular monitoring for weight change and excess weight, in consultation with and where acceptable to the individual. Monitoring could be at each visit or at a minimum 6-12 monthly, with frequency planned and agreed between the health professional and the individual.

Weight, height and ideally waist circumference should be measured and BMI calculated.
- BMI categories and waist circumference should follow World Health Organisation guidelines also noting ethnic and adolescent ranges.
- Consideration for Asian and high risk ethnic groups including monitoring waist circumference.

All with PCOS should be assessed for individual cardiovascular risk factors and global CVD risk.

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.

Overweight and obese women with PCOS, regardless of age, should have a fasting lipid profile (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level at diagnosis). Thereafter, measurement should be guided by the results and the global CVD risk.

All women with PCOS should have blood pressure measured annually.

CVD risk in women with PCOS remains unclear pending high quality studies, however prevalence of CVD risk factors is increased, warranting awareness and consideration of screening.

Gestational diabetes, impaired glucose tolerance and type 2 diabetes

Regardless of age, gestational diabetes, impaired glucose tolerance and type 2 diabetes (5 fold in Asia, 4 fold in the Americas and 3 fold in Europe) are increased in PCOS, with risk independent of, yet exacerbated by obesity.

Glycaemic status should be assessed at baseline in all with PCOS and thereafter, every one to three years, based on presence of other diabetes risk factors.

In high risk women with PCOS (including a BMI > 25kg/m^2 or in Asians > 23kg/m^2, history of abnormal glucose tolerance or family history of diabetes, hypertension or high risk ethnicity) an oral glucose tolerance test (OGTT) is recommended. Otherwise a fasting glucose or HbA1c should be performed.

An OGTT should be offered in all with PCOS when planning pregnancy or seeking fertility treatment, given increased hyperglycaemia and comorbidities in pregnancy.

If not performed preconception, an OGTT should be offered at < 20 weeks gestation, and all women with PCOS should be offered the test at 24-28 weeks gestation

Obstructive sleep apnea (OSA)

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.

A simple screening questionnaire, preferably the Berlin tool, could be applied and if positive, referral.

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.

Endometrial cancer

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 remains relatively low.

Health professionals should have a low threshold for investigation of endometrial cancer in PCOS, with transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. Routine ultrasound screening of endometrial thickness in PCOS is not recommended.

Optimal prevention for endometrial hyperplasia and endometrial cancer is not known. A pragmatic approach could include COCP or progestin therapy in those with cycles longer than 90 days.

Algorithm 2: Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

Psychological domains	Screening protocol / tools	Intervention
Quality of life (QoL)	Lower QoL scores in general and PCOS specific tools such as the modified PCOSQ tool.	Capture and consider women's perceptions of their symptoms, impact on their QoL and priorities. Target treatment to areas of greatest concern to those with PCOS.
Anxiety and depressive symptoms	High prevalence of moderate to severe anxiety and depressive symptoms in adults; and a likely increased prevalence in adolescents. Routine screening for all at diagnosis and subsequently based on clinical judgement, considering risk factors, comorbidities and life events. Suggested screening based on regional guidelines OR 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? * Factors including obesity, infertility, hirsutism need consideration along with use of hormonal medications in PCOS, which may independently exacerbate depressive and anxiety symptoms and other aspects of emotional wellbeing.	**If responses to initial screening questions positive:** Assess 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. • If treatment is warranted, psychological therapy and/or pharmacological treatment should be offered to women with PCOS, informed by regional clinical practice guidelines. **Pharmacological treatment:** Avoid inappropriate treatment with antidepressants or anxiolytics and consider impact on weight. 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.
Psychosexual dysfunction	Decreased scores on sexual function screen. If concerns identified, screen adult women with PCOS. **Note:** Obesity and infertility are common in PCOS and also impact sexual function.	If psychosexual dysfunction is suspected, further assessment, referral or treatment should follow as appropriate.
Body Image	Negative body image has been described in PCOS and can be screened based on regional guidelines or by a stepped approach. 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? • 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?	Consider the impact of PCOS features such as hirsutism, acne, and weight gain in assessing and addressing body image in PCOS.
Eating disorders and disordered eating	High prevalence of eating disorders and disordered eating has been described and can be screened based on regional guidelines or by using the following stepped approach. Initial screening questions can include: • Does your weight affect the way you feel about yourself? • Are you satisfied with your eating patterns? Or the SCOFF tool can be used.	If concerns are identified, 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.

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Algorithm 3: Lifestyle

Lifestyle
Effectiveness of lifestyle interventions
Healthy lifestyle behaviours (healthy eating and regular physical activity) should be recommended in all women with PCOS including those with excess weight, to achieve and/or maintain healthy weight and to optimise health, and quality of life across the life course. Ethnic groups at high cardiometabolic risk require more consideration.
Achievable goals such as 5% to 10% weight loss in those with excess weight yields significant clinical improvements and is considered successful weight reduction within six months. Ongoing monitoring is important in weight loss and maintenance. Consider referral to a professional to assist with healthy lifestyle.
SMART (Specific, Measurable, Achievable, Realistic and Timely) goal setting and self-monitoring can enable achievement of realistic lifestyle goals.
Psychological factors such as anxiety and depressive symptoms, body image concerns and disordered eating need consideration to optimise healthy lifestyle engagement.
All patient interactions should be patient-centred and value women's individualised healthy lifestyle preferences and cultural, socioeconomic and ethnic differences.
Adolescent and ethnic-specific body mass index and waist circumference categories should be considered when optimising lifestyle and weight.
Behavioural strategies
Lifestyle interventions (may also include cognitive behavioural interventions) could include 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.
Dietary intervention
General healthy eating principles should be followed for all women with PCOS across the life course, with no one dietary type recommended in PCOS.
To achieve weight loss in those with excess weight, an energy deficit of 30% or 500 - 750 kcal/day (1,200 - 1,500 kcal/day) could be prescribed for women, also considering individual energy requirements, body weight, food preferences and physical activity levels and an individualised approach.
Exercise intervention
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 minute bouts or around 1000 steps, aiming to achieve at least 30 minutes daily on most days.
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 involving major muscle groups on 2 non-consecutive days/week and minimised sedentary, screen or sitting time.
Physical activity can be incidental or structured. Self-monitoring, including with fitness tracking devices and technologies, could support and promote active lifestyles.
Obesity and weight assessment
Women with PCOS have higher weight gain and obesity which can impact health and emotional wellbeing. In addressing this, consider related stigma, negative body image and/or low self-esteem by use of a respectful and considerate approach, considering personal sensitivities, marginalisation and potential weight-related stigma.
Prevention of weight gain, monitoring of weight and encouraging evidence-based and socio-culturally appropriate healthy lifestyle is important in PCOS from adolescence.

Algorithm 4: Pharmacological treatment for non-fertility indications

Off label prescribing: COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

In those with a clear PCOS diagnosis or in adolescents at risk of PCOS (with symptoms)

Education + lifestyle + first line pharmacological therapy for hyperandrogenism and irregular cycles

COCP First line

Use lowest effective estrogen dose (20-30 micrograms ethinyl oestradiol or equivalent)	Consider natural estrogen preparations balancing efficacy, metabolic risk profile, side effects, cost and availability	Follow WHO COCP general population guidelines for relative and absolute contraindications and risks	35 micrograms ethinyloestradiol plus cyproterone acetate not first line in PCOS due to increased adverse effects	Hirsutism requires COCP and additional cosmetic therapy for at least 6 months	Consider additional PCOS related risk factors such as high BMI, hyperlipidemia and hypertension

Note:
Other contraceptives don't suppress hepatic SHBG production with limited efficacy for hyperandrogenism

Second line pharmacological therapies

COCP + lifestyle + metformin

No COCP preparation is superior in PCOS.

Should be considered in women with PCOS for management of metabolic features, where COCP + lifestyle does not achieve goals.

Could be considered in adolescents with PCOS and BMI $\geq 25kg/m^2$ where COCP and lifestyle changes do not achieve desired goals.

Most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.

COCP + anti-androgens

Evidence in PCOS relatively limited.

Anti-androgens must be used with contraception to prevent male fetal virilisation.

Can be considered after 6/12 cosmetic treatment + COCP if they fail to reach hirsutism goals.

Can be considered with androgenic alopecia.

Metformin + lifestyle

With lifestyle, in adults should be considered for weight, hormonal and metabolic outcomes and could be considered in adolescents.

Most useful with BMI $\geq 25kg/m^2$ and in high risk ethnic groups.

Side-effects, including GI effects, are dose related and self-limiting.
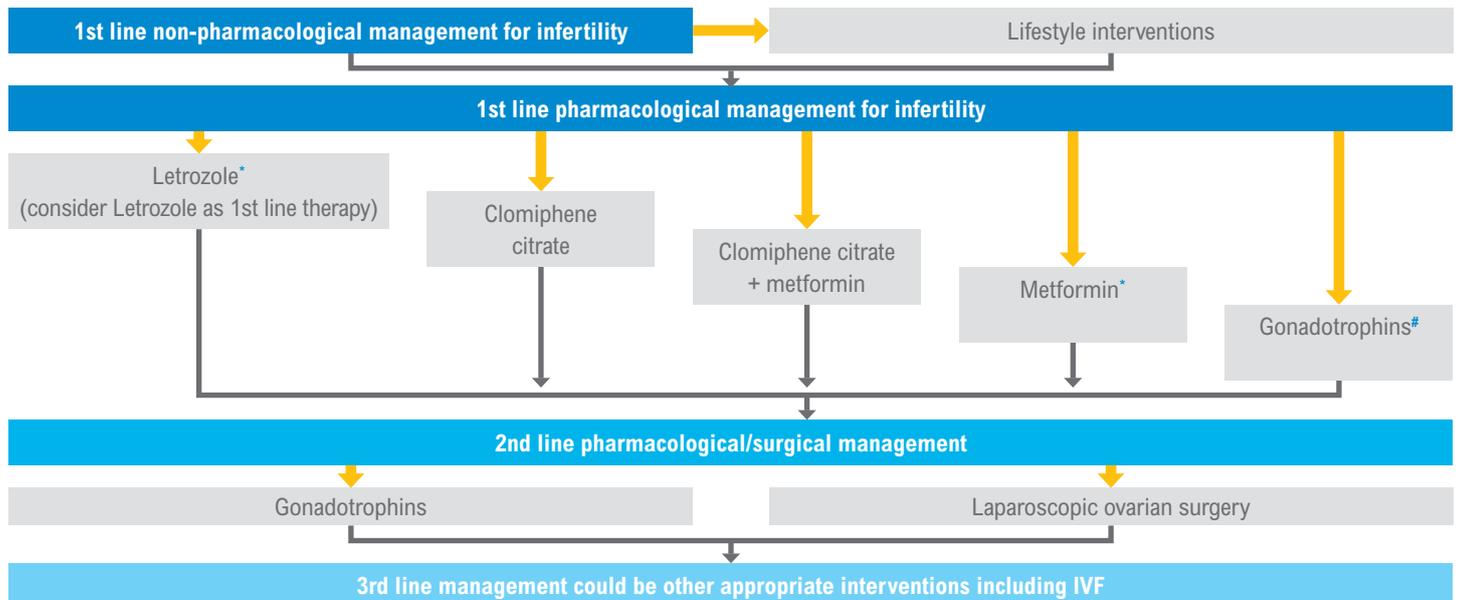
Consider starting low dose, with 500mg increments 1-2 weekly.

Metformin appears safe long-term. Ongoing monitoring required and has been associated with low vitamin B12.

Anti-obesity medications can be considered with lifestyle as per general population guidelines, considering cost, contraindications, side effects, availability and regulatory status and avoiding pregnancy when on therapy.

Inositol (in any form) should currently be considered experimental in PCOS, with emerging evidence of efficacy highlighting the need for further research.

Algorithm 5: Assessment and treatment of infertility

1st line non-pharmacological management for infertility	→	Lifestyle interventions

1st line pharmacological management for infertility

Letrozole* (consider Letrozole as 1st line therapy)	Clomiphene citrate	Clomiphene citrate + metformin	Metformin*	Gonadotrophins#

2nd line pharmacological/surgical management

Gonadotrophins	Laparoscopic ovarian surgery

3rd line management could be other appropriate interventions including IVF

*Off label prescribing: Letrozole, COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

Assessment and treatment of infertility

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

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 the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: www.monash.edu/medicine/sphpm/mchri/pcos

Monitoring during pregnancy is important for women with PCOS, given increased risk of adverse maternal and offspring outcomes.

For 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.

Tubal patency testing should be considered prior to ovulation induction for women with PCOS where there is suspected tubal infertility.

Ovulation induction principles

The use of ovulation induction agents, including letrozole, metformin and clomiphene citrate is off label in many countries*.

Pregnancy should be excluded prior to ovulation induction.

Unsuccessful, prolonged use of ovulation induction agents should be avoided, due to poor success rates.

Letrozole

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.

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

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

Clomiphene citrate and metformin

Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates.

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.

Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese (BMI is ≥ 30 kg/m^2) with anovulatory infertility and no other infertility factors.

If metformin is being used for ovulation induction in women with PCOS who are obese (BMI ≥ 30kg/m^2) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates.

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 and pregnancy rates.

The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered.

Gonadotrophins

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.

#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.

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.

Gonadotrophins with the addition of metformin, could be used rather than gonadotrophins alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.

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.

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 optimise monofollicular development
- risk and implications of potential multiple pregnancy

Gonadotrophin induced ovulation should only be triggered when there are fewer than three mature follicles and should be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.

Anti-obesity agents

Pharmacological anti-obesity agents should be considered an experimental therapy for women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy.

Laparoscopic ovarian surgery

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.

Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.

Risks should be explained to all women with PCOS considering laparoscopic ovarian surgery.

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

Bariatric Surgery

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.

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

CONTENTS

In-vitro fertilisation (IVF)

In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory infertility could be offered IVF third line where other ovulation induction therapies have failed.

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

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 risk of ovarian hyperstimulation

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.

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.

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) .

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.

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.

In IVF ± ICSI cycles in women with PCOS, consideration should be given to an elective freeze of all embryos.

Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing IVF ± ICSI therapy with a gonadotrophin releasing hormone agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS.

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 (refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: www.monash.edu/medicine/sphpm/mchri/pcos)

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 risk of ovarian hyperstimulation syndrome (refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: www.monash.edu/medicine/sphpm/mchri/pcos).

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).

In units with sufficient expertise, IVM could be offered to achieve pregnancy and live birth 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.

International evidence-based guideline
for the assessment and management of
polycystic ovary syndrome 2018