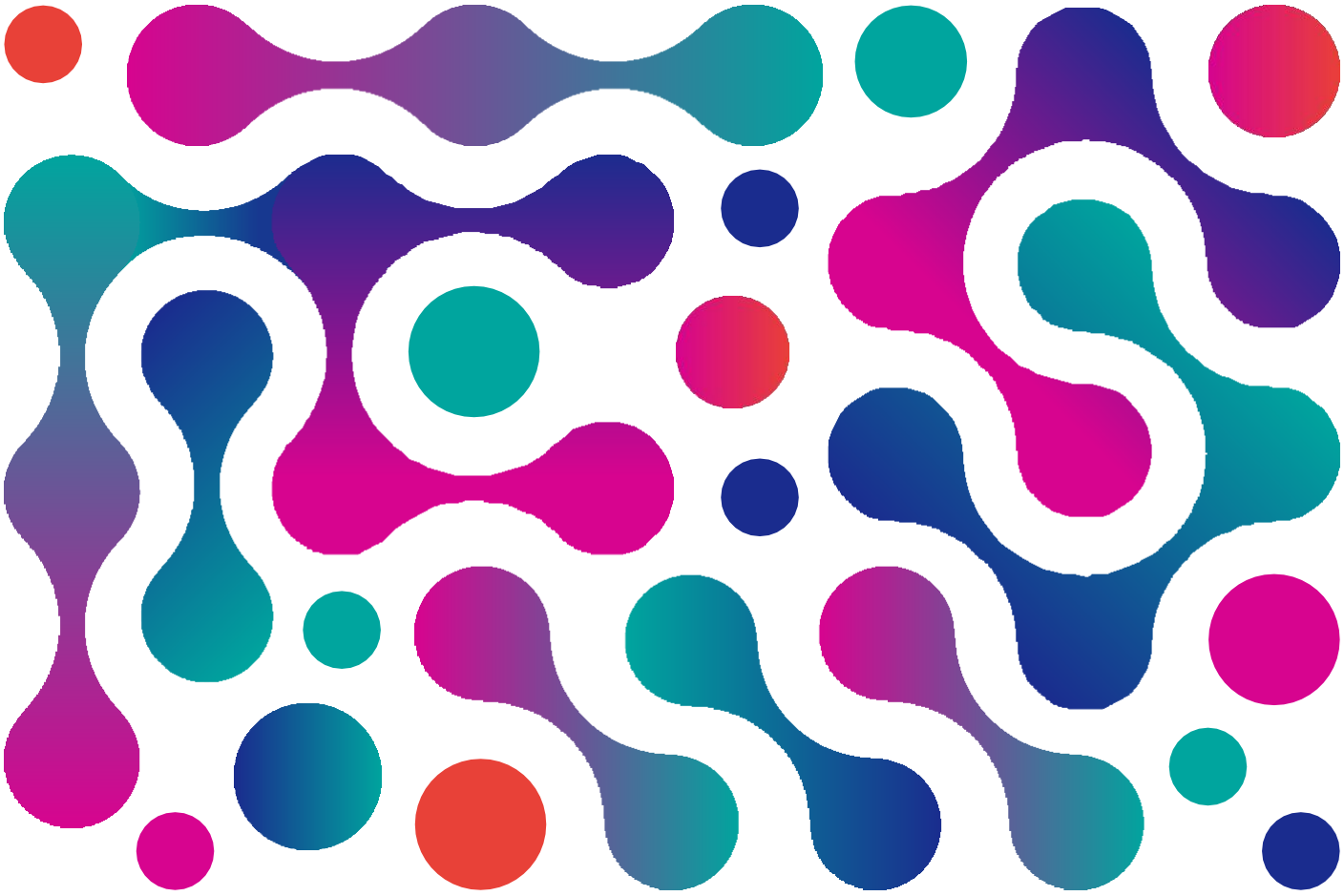
International Evidence-based Guideline for the assessment and management of polycystic ovary syndrome 2023



MONASH University

CREWHiRL Centre for Research Excellence in Women's Health in Reproductive Life

CREPCOS Centre for Research Excellence in Polycystic Ovary Syndrome

asrm American Society for Reproductive Medicine

ENDOCRINE SOCIETY Hormone Science to Health

eshre SCIENCE MOVING PEOPLE MOVING SCIENCE

European Society of Endocrinology

Disclaimer

The Centre for Research Excellence in Women's Health in Reproductive Life (CRE WHiRL), worked in partnership with the American Society of Reproductive Medicine (ASRM), the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology (ESHRE) and in collaboration with professional societies and consumer advocacy groups internationally. These evidence-based guidelines were developed to provide evidence-based recommendations to improve the quality of care, 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 or consumer preferences. In the absence of scientific evidence in PCOS, evidence from the general population was considered and a formal transparent process was followed to obtain consensus between the engaged multidisciplinary stakeholders.

The aim of this 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 characteristics and preferences. All recommendations and practice points need to be considered in the context of regional healthcare settings, resources and 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 individualised consumer preference in diagnosis and treatment. Ultimately, healthcare professionals must make their own clinical decisions on a case-by-case basis, using their clinical judgment, knowledge, and expertise, considering the condition, circumstances, and perspectives of the individual affected, applying shared decision making in consultation with that patient and/or the parent/s or guardian/s.

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Publication approval

Australian Government
National Health and Medical Research Council

The guideline recommendations on pages 21 to 49 of this document were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 27 July 2023 under section 14A of the *National Health and Medical Research Council Act 1992*. In approving the guideline recommendations, NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting.

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

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   - Asia Pacific Paediatric Endocrine Society (APPES)
   - Australia and New Zealand Society for Paediatric Endocrinology and Diabetes (ANZSPED)
   - Australian Diabetes Society (ADS)
   - Brazilian Society of Endocrinology and Metabolism (SBEM)
   - British Fertility Society (BFS)
   - Canadian Society of Endocrinology and Metabolism (CSEM)
   - Dietitians Australia (DA)
   - Endocrine Society Australia (ESA)
   - European Society for Paediatric Endocrinology (ESPE)
   - Exercise and Sports Science Australia (ESSA)
   - Fertility Society Australia and New Zealand (FSANZ)
   - International Federation of Fertility Societies (IFFS)
   - International Federation of Gynaecology and Obstetrics (FIGO)
   - International Society of Endocrinology (ISE)
   - Italian Society of Gynaecology and Obstetrics (SIGO)
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   - Latin American Society for Paediatric Endocrinology (SLEP)
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   - South African Society of Gynaecology and Obstetrics (SASOG)
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Other relevant organisations are welcome to partner in guideline translation once approved.

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Preface

This International Evidence-based Guideline for the assessment and management of Polycystic Ovary Syndrome (PCOS) 2023, is designed to provide clear information to assist clinical decision making, support optimal patient care and improve health outcomes. It is the culmination of the work of over 1000 healthcare professionals, early careers researchers and academics experts, multidisciplinary clinicians and patients/consumers internationally. The vast majority gave of their time and expertise voluntarily. We fully appreciate the considerable contributions of the evidence synthesis team and the management committee (Appendix I), international advisory panel (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; the evidence synthesis team comprised of Dr Chau (Jillian) Tay, Dr Aya Mousa, Mr Loyal Pattuwage and the international early career network; Project Deputy Lead, Dr Anju Joham and Translation Lead, Dr Rhonda Garad. We acknowledge the enthusiasm and engagement of the healthcare professionals and women affected by PCOS, our partners the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology, the American Society for Reproductive Medicine, our collaborating and engaged professional societies, 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 guidelines for diagnosis, assessment and treatment, to improve the lives of those with polycystic ovary syndrome (PCOS) worldwide.

Participants: Extensive health professional and consumer or patient engagement informed the guideline priority areas. International society-nominated panels included consumers, and experts in paediatrics, endocrinology, gynaecology, primary care, reproductive endocrinology, psychology, dietetics, exercise physiology, sleep, bariatric/metabolic surgery, public health, other co-opted experts, project management, evidence synthesis and translation.

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 panel, management committee and five guideline development groups with 52 members, consumer and translation committees. The Centre for Research Excellence in Women's Health in Reproductive Life, funded by the Australian National Health and Medical Research Council (NHMRC), and led by Monash University, partnered with the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology. Thirty-six organisations collaborated with international meetings over nine months. Fifty-five prioritised clinical questions involved 52 systematic and three narrative reviews, generating evidence-based and consensus recommendations with accompanying practice points. Committee members nominated by collaborating organisations provided international peer review, and evidence expert-reviewed methods and outputs were submitted to NHMRC for independent review.

Recommendations: PCOS should be diagnosed using the revised consensus Rotterdam criteria, which are now updated to evidence-based criteria. In adults this requires the presence of two of i) clinical/biochemical hyperandrogenism, ii) ovulatory dysfunction and iii) polycystic ovaries on ultrasound or elevated anti-mullerian hormone (AMH) levels, after other causes of these features are excluded. Where irregular menstrual cycles and hyperandrogenism are present, ultrasound or AMH are not required for diagnosis. In adolescents, both hyperandrogenism and ovulatory dysfunction are required, with ultrasound and AMH not recommended, due to poor specificity. Once diagnosed, assessment and management should address reproductive, metabolic, cardiovascular, dermatologic, sleep and psychological features. A lifelong reproductive health plan is recommended including a focus on preconception risk factors, healthy lifestyle and prevention of weight gain and optimisation of fertility. Metabolic risk factors, diabetes, cardiovascular disease and sleep disorders are all increased in PCOS and screening and management is recommended. PCOS should be considered a high-risk condition in pregnancy with women identified and monitored. An increased premenopausal risk of endometrial cancer should be recognised, whilst absolute risks remain low.

Depressive and anxiety symptoms are significantly increased and should be screened for in all women with PCOS, with psychological assessment and therapy as indicated. Greater awareness of psychological features including eating disorders and impacts on body image and quality of life is needed. Dissatisfaction with PCOS diagnosis and care is high and raised awareness and education is strongly recommended for women and healthcare professionals including high quality, evidence-based resources. Shared decision making and a self-empowerment are fundamental and integrated models of care should be developed, funded and evaluated.

Supported healthy lifestyle remains vital throughout the lifespan in PCOS, with a strong focus on overall health, prevention of weight gain and if required, on weight management. Recognising the benefits if many specific diet and physical activity regimens, there is no one regimen that has benefits over others in PCOS. Weight bias and stigma should be minimised and healthcare professionals should seek permission to weigh women, with explanation of weight-related risks. Combined oral contraceptive pills are first-line pharmacological treatment for menstrual irregularity and hyperandrogenism, with no specific recommended preparation, and a preference for lower dose preparations and those with less side-effects. Metformin is recommended primarily for metabolic features and has greater efficacy than inositol, which offers limited clinical benefits in PCOS. Metformin is not routinely recommended for use in pregnant women with PCOS. Laser therapy is effective for hair reduction in some subgroups, whilst antiandrogens have a limited role, to be used where other therapies are ineffective or are contraindicated. Anti-obesity agents and bariatric/metabolic surgery may be considered based on general population guidelines, balancing potential for benefits and side-effects.

Letrozole is first-line pharmacological infertility therapy, with clomiphene alone or in combination with metformin, gonadotrophins or ovarian surgery having a role as second-line therapy. In the absence of an absolute indication for in vitro fertilisation (IVF), women with PCOS and anovulatory infertility could be offered IVF potentially with in vitro maturation, as third-line therapy where other ovulation induction therapies have failed.

Overall, evidence in PCOS is low to moderate quality. Based on high prevalence and significant health impact, greater priority, funding and research is recommended. Guideline translation will be extensive including multilingual education outputs and evidence-based resources for consumers (the AskPCOS app), healthcare professionals and policy makers.

Plain Language Statement

This guideline is about making new recommendations for doctors, healthcare professionals and those affected by the common health condition called polycystic ovary syndrome (PCOS). To develop these guidelines, many experts and patients from different areas around the world and across many cultures and countries got together, decided on the most important questions, looked at all the best evidence and worked together to agree on what the best advice should be for those with PCOS and the healthcare professionals supporting them.

The new guidelines used best practice to bring together evidence, expert perspectives and the preferences of women with PCOS. They note that PCOS can be diagnosed using specific signs, symptoms, and blood tests. The recommendations also simplify the tests needed for diagnosis. Once diagnosed, their doctors and healthcare professionals should identify and take care of the many different aspects of health and increased health risks affected by PCOS. This includes recognising increased risks in reproductive health such as reduced fertility, metabolism such as diabetes, heart health, skin health, sleep, and mental health such as depression. Doctors need to be aware of increased risks and check and intervene to prevent and limit these.

The guidelines also say that those with PCOS need to be checked for depression and anxiety, and other mental health challenges that are more common in PCOS. It also notes that their doctors should be trained to help detect, prevent and manage these if present. The guidelines suggest that health professionals should work together with those with PCOS to make decisions about their care, and that they should be careful to consider cultural factors and ethnicity and not discriminate, especially based on higher weight, which is very common in PCOS. They recognise the need for greater education and better information for health professionals and those with PCOS, and they highlight the need for shared decision making together, alongside better care and services.

The guidelines suggest that healthy lifestyle is very important, but that no one specific diet or exercise plan is better than any other and patient preferences are most important here. They note that doctors should be aware of PCOS and all its features, including during pregnancy, to allow detection of increased risks and to assist with prevention and treatment. The guidelines also recommend effective medicines and treatments that can be helpful that those with PCOS including the combined contraceptive pill, medications to balance the hormones in PCOS and to reduce symptoms. This includes those who have trouble getting pregnant and it outlines the most effectives treatments that should be offered including fertility treatments which can vary significantly improve the chances of having a family.

The evidence for these guidelines is not always very strong, and the experts say that much more research is needed in the future. The guidelines will be translated into many different languages and tools such as the AskPCOS app, already used in 186 countries by almost 40,000 women. A range of other online tools will also be developed with those with PCOS and their health professionals, and will be freely available in many languages all over the world to improve the health of those with PCOS.

Ask PCOS

POWERED BY MONASH

Executive Summary

These international guideline and translation programs seek to address health professional and consumer priorities. The guideline integrates the best available evidence with international, multidisciplinary clinical expertise and consumer preferences to provide healthcare professionals, consumers, educators, funders and policy makers with guidance. The guideline and translation programs promote accurate and timely diagnosis and best practice, evidence-based, consistent assessment and treatment of polycystic ovary syndrome (PCOS). Education, empowerment and shared decision making is key, with a focus on 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 endocrine, reproductive, cardiometabolic, dermatologic and psychological features. PCOS is one of the most common conditions affecting around 10% of reproductive aged women,[1-5] with many remaining undiagnosed.[4] Women with PCOS have diverse features including psychological (anxiety, depression, sleep and eating disorders),[6-8] dermatologic (hirsutism, acanthosis nigricans and acne), reproductive (irregular menstrual cycles, infertility, endometrial cancer and pregnancy complications)[9] and metabolic features (insulin resistance, metabolic syndrome, type 2 diabetes (T2D), cardiovascular risk factors and increased cardiovascular disease (CVD).[10-12]

Diagnosis and treatment of PCOS remain challenging including accurately defining individual diagnostic criteria, marked clinical heterogeneity, the influence of excess weight, ethnic differences and variation across the life course. These factors contribute to variation in diagnosis, presentation and care.[13] This culminates in delayed diagnosis, poor diagnosis experience and dissatisfaction with care, as reported by women internationally.[14] These challenges are exacerbated by the misleading name of the condition, which focuses only on reproductive features, the lack of recognition of diverse features of PCOS, the very inadequate research funding and limited availability of integrated care.[15] In this context, there is a compelling need for ongoing development and translation of consistent international evidence-based guideline for assessment and management of PCOS, addressing psychological, cardiometabolic, dermatologic and reproductive features of PCOS, promoting consistent evidence-based care, building collaboration, promoting awareness and guiding research.

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, translation and information preferences and needs for healthcare professionals and consumers. This stakeholder engagement directly informed the guideline and translation program and involved over 3000 healthcare professionals and consumers with PCOS in 2018 and over 750 in the 2023 guideline. Our partners and collaborators nominated 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 Australian National Health and Medical Research Council (NHMRC) is the single approving body for the guideline.

Governance included international representation across the international advisory panel, management committee, consumer committee, translation committee and five multidisciplinary guideline development groups comprising partner and collaborator nominated experts, practicing clinicians, academic experts and consumers (Figure 1, Figure 2 and Appendix I-III). Guideline development groups and special interest groups/experts were nominated by the Centre for Research Excellence in Women's Health in Reproductive Life (CRE WHiRL), led by Monash University Australia, and by partner and collaborator organisations, focused on diverse expertise including consumers and geographical representation. Many experts were retained from the 2018 guideline, with expanded representation from low and middle income countries, across seven continents. The CRE WHiRL, funded by the Australian NHMRC, led and primarily funded guideline development and translation. In this endeavour, we partnered with the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology, who provided additional funding and collaborated closely.

Guideline development engagement and processes were extensive and followed best practice. management committee and guideline development groups met online and face to face across Europe, USA and Australia over nine months and enabled priority setting, training, guideline development and informed translation. Fifty-five prioritised clinical questions were addressed with 52 systematic and three narrative reviews, generating recommendations supported by practice points.

Building on the 2018 international evidence-based guideline for the assessment and management of Polycystic Ovary Syndrome, we applied international best practice methods for evidence review and guideline development, aligned with the NHMRC requirements. A highly experienced team led 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 (Appendix IV). A process of research integrity assessment was introduced for guideline development group (GDG) five in infertility management (Appendix V, Figure 3) as a pilot process. It was initiated in GDG 5, given the concerns around evidence integrity and the retractions that have occurred in infertility research. Feasibility and timelines prevented extension to the full guideline, however this will occur in the next update. Recommendations were formulated using the considered judgment process in the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework[16] across the quality of available evidence, integrating clinical expertise and consumer preference, and considering the applicability, feasibility, equity, cost effectiveness, implementation and value for consumers and healthcare 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, aims and expected outcomes

The purpose of this international evidence-based guideline is to integrate best available evidence with multidisciplinary expertise and consumer preferences to provide healthcare professionals, consumers and policy makers with transparent evidence-based guidance on timely diagnosis, accurate assessment and optimal treatment of PCOS. We also aim 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 health outcomes
- identifying knowledge gaps and promoting research and translation into practice and policy
- co-developing resources to upskill healthcare professionals and empower consumers, including a mobile app and online resources
- delivering an international translation program with in-depth evaluation
- guiding research priorities
- ultimately improving the care and health outcomes for those with PCOS.

Key principles

Principles that underpinned the development and interpretation of all evidence-based guidelines include:

- codesign, coproduction, patient agency and priorities, partnership in care and being patient centered
- the need for consumers and healthcare professionals to recognise the implications of PCOS across the life course
- understanding individual differences, preferences and modulating or exacerbating factors
- recognising the metabolic, dermatologic, reproductive and psychological features
- education, information and optimal lifestyle and emotional wellbeing are important in PCOS; and
- consideration of underserved populations including an Australian adaptation focused on the needs of Australian Indigenous and Torres Strait Islander peoples as high-risk populations.

Whilst diverse features of PCOS are dealt with individually here, implementation should focus on:

- consistency across recommendations, and diverse PCOS features
- cross-talk between symptoms and outcomes that matter to those with PCOS.

Population

This guideline is relevant to the assessment and management of adolescents (defined as any person between ages 10 and 19 as per the World Health Organisation), those of reproductive age and postmenopausal women and people who have PCOS, encompassing those with all relevant complications and comorbidities including reduced fertility. This guideline does not apply to those with hypogonadotrophic or hypergonadotrophic ovulatory dysfunction. Recommendations include women from lean to higher weight, unless BMI is specified in the recommendation.

Setting and audience

The guideline is designed to apply in a broad range of healthcare settings and to a broad audience including:

- Those with PCOS (patients/consumers)
- General practitioners/primary care physicians
- Obstetricians and gynaecologists
- Endocrinologists, paediatricians, other physicians, as relevant
- Dermatologists
- Allied healthcare professionals - psychologists, dietitians, exercise physiologists, physiotherapists
- Community care practitioners
- Indigenous health care workers
- Nurses
- Policy makers
- Community support groups
- General public
- Students.

When translating the guideline into practice, issues such as cost, accessibility, resources and ethnicity are considered. An Aboriginal and Torres Strait Islander advisor has been engaged throughout and will be actively involved with other broader indigenous stakeholders in the national implementation and dissemination plan. Our diverse international partnerships include culturally and linguistically diverse representatives across world regions engaged in all phases of guideline development and will lead dissemination including language translation with their communities globally.

Inclusiveness and stigma

In this guideline, we recognise the need to consider the impact of language and the potential for lack of inclusion and the need to be inclusive, considering the needs and preferences of the diverse world-wide population of guideline end-users. Hence, we have sought considerable multidisciplinary expert and consumer input into this guideline across ethnicities, (including input from Indigenous Australians), geographic world regions, different cultures and non-binary and different genders. We have also considered stigma associated with language around PCOS features, especially weight related stigma. Cultural, ethnic, gender and stigma related issues were considered at all stages during the development of the guidelines, including in developing the clinical questions, evidence search strategies, data extraction, analysis, interpretation, when making recommendations using the GRADE framework and in the language used in the guideline (see Chapter 6). We have also avoided the use of the terms overweight, obese or obesity and used more inclusive or medical accurate terms reflecting biological parameters such as body mass index or weight.

Regarding gender inclusive language, we acknowledge the rich discourse and evolution occurring in this area, as well as the variation across cultures and ethnicities. From a position of ally ship, we have considered language and aimed to improve gender inclusiveness in this guideline update, whilst also using medically accurate, concise language that is sensitive to the needs of those with lived experience of PCOS. We acknowledge that binary language may not be appropriate for all, expanding our language to broaden inclusion and relevance for all with PCOS. We also acknowledge a lack of consensus on optimal language and we continue to respect that many want to avoid the erasure of gender terms including 'woman/women'.

To this end, we have applied the following approaches throughout this guideline update:

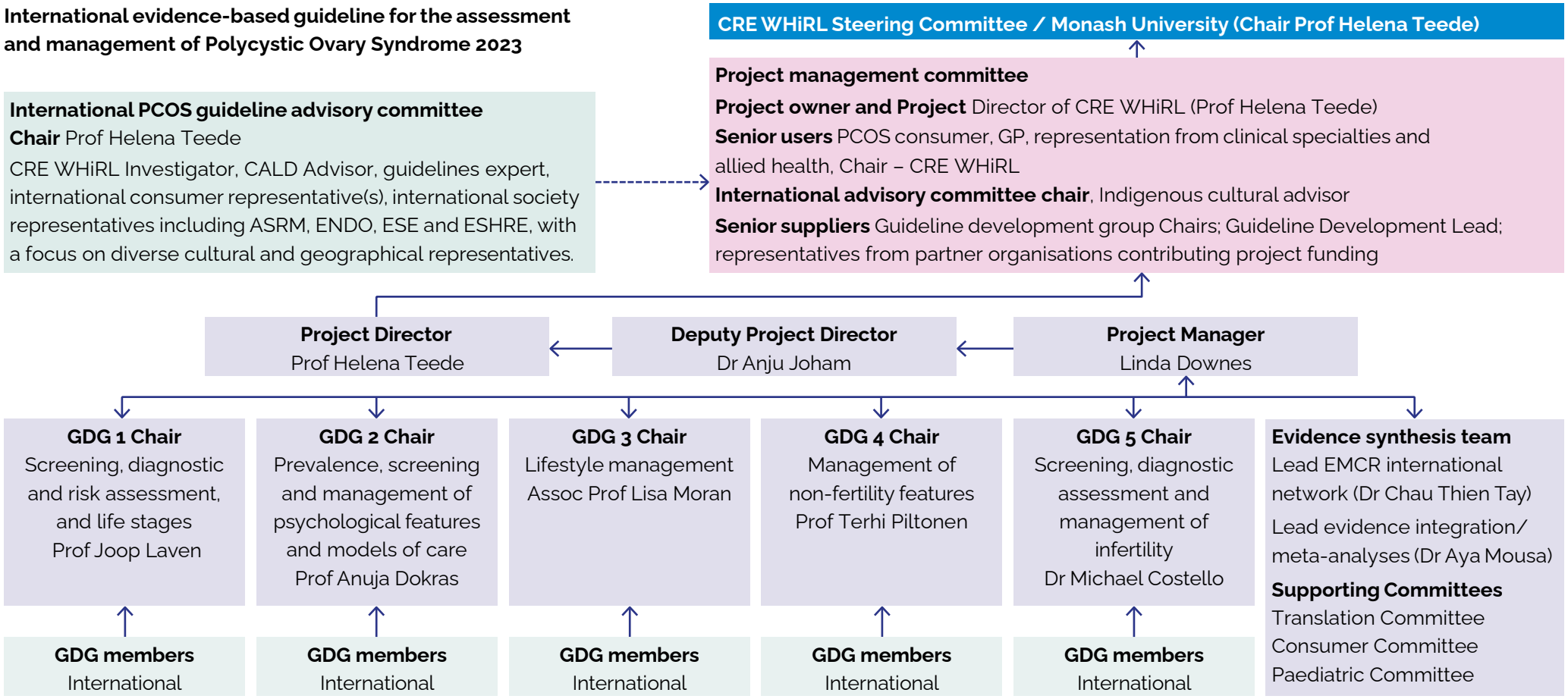
1. Increasing the use of gender-neutral terminology (e.g. adolescents, adults, individuals and those with PCOS), when gender is not central to the subject matter.
2. Using accessible language that is inclusive of persons with lower levels of health and/or PCOS literacy.
3. Increasing use of the term female, where biological sex is most relevant.
4. Retaining use of the term 'woman/women' which where used, intends to encompass all genders affected by PCOS irrespective of how they choose to identify.

Governance

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

Figure 1: Governance

International evidence-based guideline for the assessment and management of Polycystic Ovary Syndrome 2023



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(s): Represents end users of the delivered service. Chairs, Project user group if there is one.

Senior supplier(s): Senior representative(s) of project's suppliers. There may be more than one.

Project manager: Project owner's eyes and ears on the job. Undertakes day to day management and decisions on behalf of the project owner.

International advisory committee: Represents key stakeholders with valid interest, but not sufficiently central to project success to warrant a seat on the management committee. Concerns and issues in this group have a direct conduit to the management committee.

Management committee: Oversees the project to ensure the integrity of the guideline, manages stakeholder engagement and provides strategic guidance for implementation/translation activities

Guideline development groups

Guideline development groups (GDGs) were formed in 2018 and expanded in 2023 to extend geographical representation. These were based on skills (clinical and academic), expertise, geographical spread and were nominated by the CRE and 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, evidence synthesis team and Early Career Network and the translation and consumer committees. Whilst this does not encompass all leaders internationally with expertise in PCOS, these were engaged in the initial 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 were engaged, however given primary funding was from the Australian Government, diverse Australian organisational engagement was sought.

Prioritised clinical questions

Prioritisation of guideline clinical questions was informed initially by the 2018 international Delphi exercise. For this 2023 guideline, an international survey of 750 consumers with PCOS, representatives of the partner organisations and the multidisciplinary GDG members, contributed, with final questions addressed across:

GDG 1	Screening, diagnostic assessment, risk assessment and life stage
GDG 2	Prevalence, screening and management of psychological features and models of care
GDG 3	Lifestyle management
GDG 4	Management of non-fertility features
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 individual'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, healthcare settings and resources. This 2023 guideline includes a systematic review of cost effectiveness, however very limited studies precluded evidence-based assessments of economic feasibility and impact. The potential impact of cost on recommendations was however considered in the GRADE process.

Community and consumer engagement

Extensive engagement and formative research on unmet needs of women with PCOS was a key driver for this work. We adopted the International Association for Public Participation (IPA), Public Participation Spectrum framework, in which the 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 approach, ensuring that the lived experiences of women with PCOS were prioritised. Far-reaching engagement included extensive formative research, focus groups and international surveys in the 2018 guideline, extensive engagement in the process to develop a core outcome set for PCOS in 2020[1,17] and further surveys and focus groups with over 750 individuals with PCOS in 2022.

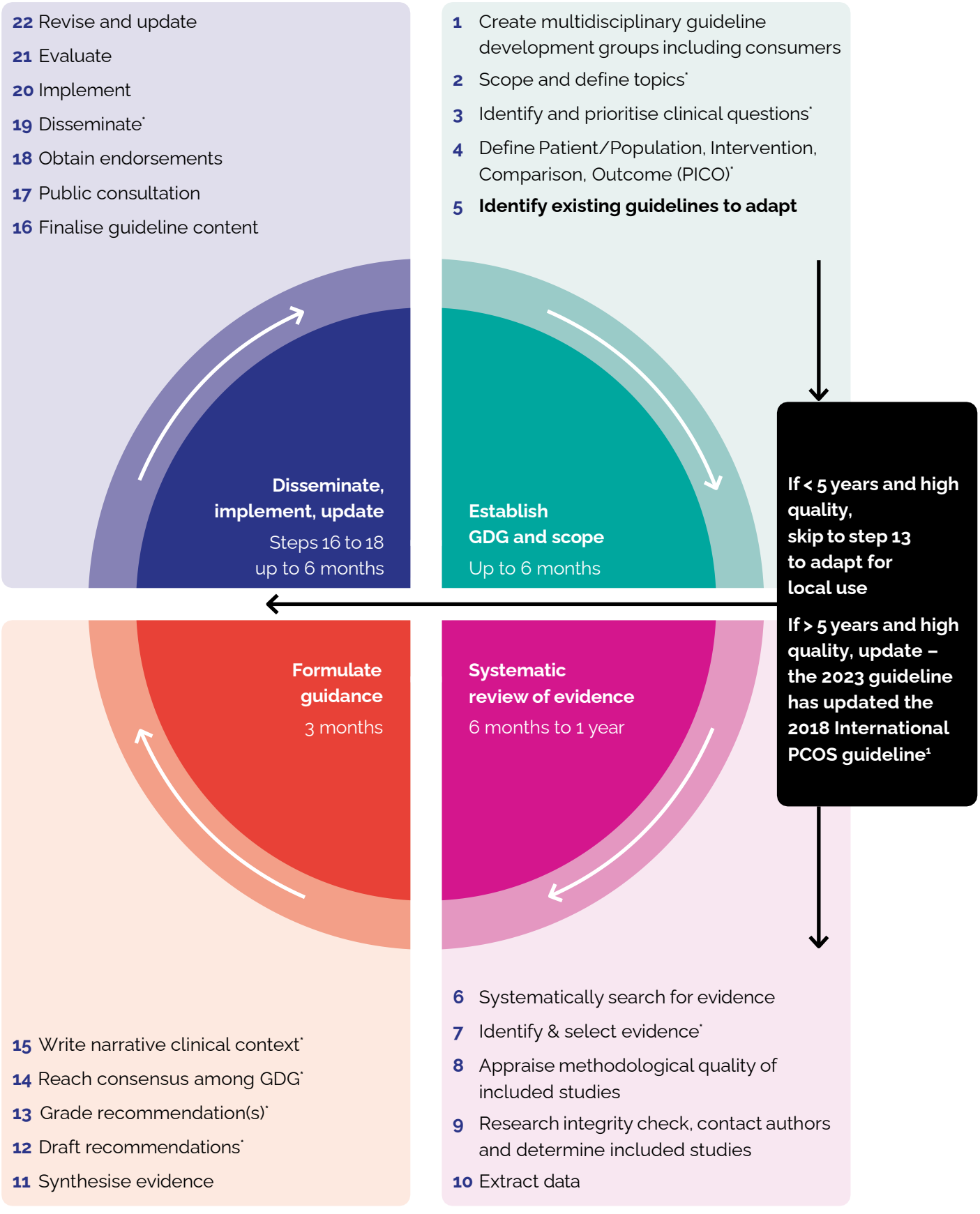
Consumer representatives were informed about the process of participation, were trained, had role descriptions, were remunerated for time spent in preparation and at meetings including all Guideline development group meetings, to embed consumer perspectives within the GRADE decision making process. Consumers were empowered to ensure that all decisions optimised consumer perspectives. Consumer groups participated in the surveys to define the questions and outcomes, in the GDGs (1 consumer per group and overarching meetings throughout with consumers across all groups), engagement throughout with the executive teams of each consumer collaborating group, feedback and public consultation processes across the public and all PCOS partner community groups and a dedicated consumer translation team for codesign of the multilingual implementation, translation and dissemination program. Further detail is provided in Chapter 6.

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 NHMRC and ESHRE processes and 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)



* *Time points and tasks where prioritisation of engagement from GDG occurred.*

Funding

The Australian NHMRC funded guideline development through the Centre for Research Excellence in Women's Health in Reproductive Life (CRE WHiRL) (APP1171592) and the Centre for Research Excellence in Polycystic Ovary Syndrome (CRE PCOS) (APP1078444) led by Monash University, Australia and partners including The American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology.

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 approve the guideline process. Partners nominated experts in PCOS who participated in the management committee and GDGs and formed special interest groups to provide feedback on the guideline during public consultation. Here they were acting as independent experts and not working for their nominating partner organisation. All feedback was reviewed by the management committee 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, considered when making recommendations and are publicly available (see Disclosures statement).

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:

- educate and build capability of healthcare professionals to deliver high-quality, evidence-based assessment and management of PCOS that meets the needs of those with PCOS
- augment the health literacy of PCOS health consumers, optimising diagnosis and improving health outcomes
- promote best practice evidence-based PCOS care.

The guiding principles of the comprehensive international translation and dissemination program include that:

- 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
- dissemination strategies are multi-faceted, multi-modal, multilingual and targeted communication channels of end-users.

Central to the translation and dissemination program is active engagement of 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 (outlined under Dissemination and implementation).

Context statement on diagnosis: Prelude to the guideline

Here, we build on the 2018 International Evidence-based Guideline for the Assessment, Diagnosis and Management of PCOS, and on the initial consensus-based Rotterdam PCOS diagnostic criteria.[18] Here, we progress evidence-based diagnostic criteria and in adults recommend that this requires two of i) clinical/biochemical hyperandrogenism, ii) ovulatory dysfunction or iii) polycystic ovaries on ultrasound and here add elevated anti-mullerian hormone (AMH) levels. We have included the role of AMH in diagnosis in adults but do not recommend AMH or ultrasound 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 suspected androgen producing tumors, noting that overt virilisation is not consistent with PCOS. Clinicians should refer to other relevant guidelines for these diagnoses.

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 and anti-mullerian (AMH) levels are 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, focused on specificity, to improve diagnostic accuracy.

Resource use in diagnosis will also be reduced with a focus on clinical features in diagnosis, limited indications for ultrasound and AMH as an alternative and with a focus on clinical overt biochemical hyperandrogenism.

We also endorse the recommendation of the National Institutes of Health (NIH) evidence-based methodology workshop of PCOS 2012 that the name of the condition is a distraction and should be changed. We are building on the evidence and guideline efforts with consumer partnership and processes towards a change in the name.

The value and optimal timing of assessment and diagnosis of PCOS should be discussed with the individual patient, considering psychosocial and cultural factors and 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 in all stages from conceptualisation, prioritisation, development, review and translation. Variability in resources, health systems and access to healthcare professionals, investigations and therapies was considered across international settings and consistent with best practice, adaptation may be required in translation. Assistance with adaptation can be obtained by contacting helena.teede@monash.edu.

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 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 relevant populations was considered and if appropriate and there was consensus, the GDG made consensus recommendations. Practice points highlight important clinical and implementation issues arising from GDG consideration of evidence-based or consensus recommendations.

Table 1: Categories of the PCOS guideline recommendations

EBR	Evidence-based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group.
CR	Consensus recommendations: In the absence of adequate evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population.
PP	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 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. Conditional recommendations are reflected using the terms 'could' or 'should/could consider' which are 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, transparent consideration of the GRADE framework[16] 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 included 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
- 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[16] and was largely determined by the expert evidence synthesis team.

Table 2: Quality (certainty) of evidence categories (adapted from GRADE)[16]

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 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.[16]

The recommendations summary in Table 3 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.

Aligned to Cochrane methods, certainty of evidence varies significantly across outcomes for each clinical question. In this guideline, the recorded evidence certainty reflects the lowest certainty for the top three critical outcomes for each question. Here, evidence was often stronger for the most critical outcome and often high quality randomised controlled trials (RCTs) had addressed an individual question, but consideration of multiple outcomes and inclusion of additional low-quality studies may have resulted in low certainty evidence overall. These nuances in the evidence were considered by the GDG for every clinical question and are outlined in the technical report and GRADE tables. Hence, an apparent discrepancy may be observed between the strength of the recommendation and the certainty of the evidence. Where this occurs, a justification is added to the guideline under the relevant clinical question.

This is a living guideline as outlined in Chapter 6. For the most rapidly progressing areas of the guideline where new evidence is anticipated in the shorter term, an annual scoping review will be completed to search for additional evidence and the process followed as per Chapter 6. In the recommendations table and summary, these are denoted by #.

Recommendations summary

Table 3: Recommendations

The recommendation and technical report numbers correspond. Consensus recommendations (CR) and practice points (PP) do not have 'GRADE' ratings, however the evidence summaries outline how they were informed by PCOS and general population evidence. # denoted priority for living guideline updates.

No. Living#	Type	Recommendation	Grade/ Quality
1		**Screening, diagnostic and risk assessment and life stages**	
		General principles	
	PP	All diagnostic assessments are recommended for use in accordance with the diagnostic algorithm one.	
1.1		**Irregular cycles and ovulatory dysfunction**	
1.1.1	**CR**	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 these PCOS Guidelines.	❖❖❖❖
1.1.2	**PP**	The mean age of menarche may differ across populations.	
1.1.3	**PP**	In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors.	
1.1.4	**PP**	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.	
1.1.5	**PP**	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	

No. Living#	Type	Recommendation	Grade/ Quality
1.2		**Biochemical hyperandrogenism**	
1.2.1	**EBR**	Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index.	❖❖❖❖ ⊕◯◯◯
1.2.2	**EBR**	If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and greater age associated decrease in DHEAS.	❖❖❖ ⊕◯◯◯
1.2.3	**EBR**	Laboratories should use validated, highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone and if needed, for androstenedione and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis or ammonium sulfate precipitation.	❖❖❖❖ ⊕◯◯◯
1.2.4	**EBR**	Laboratories should use LC-MS/MS assays over direct immunoassays (e.g. radiometric, enzyme-linked, etc.) for assessing total or free testosterone, which have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS.	❖❖❖❖ ⊕⊕◯◯
1.2.5	**PP**	For the detection of hyperandrogenism in PCOS, the assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism (i.e. hirsutism).	
1.2.6	**PP**	It is very difficult to reliably assess for biochemical hyperandrogenism in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP, yet assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception should be managed otherwise during this time.	
1.2.7	**PP**	Repeated androgen measures for the ongoing assessment of PCOS in adults have a limited role.	
1.2.8	**PP**	In most adolescents, androgen levels reach adult ranges at 12-15 years of age.	
1.2.9	**PP**	If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.	

No. Living#	Type	Recommendation	Grade/ Quality
1.2.10	PP	Reference ranges for different methods and laboratories vary widely, and are often based on an arbitrary percentile or variances of the mean from a population that has not been fully characterised and is highly likely to include women with PCOS. Normal values should be determined either by the range of values in a well characterised healthy control population or by cluster analysis of general population values.	
1.2.11	PP	Laboratories involved in androgen measurements in females should consider: • determining laboratory normal values by either the range of values in a well characterised healthy control population or by cluster analysis of the values of a large general population • applying the most accurate methods where available • using extraction/chromatography immunoassays as an alternative to mass spectrometry only where adequate expertise is available • future improvements may arise from measurement of 11-oxygenated androgens, and from establishing cut-off levels or thresholds based on large-scale validation in populations of different ages and ethnicities.	
1.3		**Clinical hyperandrogenism**	
1.3.1	EBR	The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism and PCOS in adults.	❖❖❖ ⊕○○○
1.3.2	EBR	Healthcare professionals could recognise that female pattern hair loss and acne in isolation (without hirsutism) are relatively weak predictors of biochemical hyperandrogenism.	❖❖❖❖ ⊕○○○
1.3.3	CR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents.	❖❖❖❖
1.3.4	CR	Healthcare professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and should consider the reporting of unwanted excess hair growth and/or female pattern hair loss as being important, regardless of apparent clinical severity.	❖❖❖

No. Living#	Type	Recommendation	Grade/ Quality
1.3.5	CR	A modified Ferriman Gallwey score (mFG) of 4–6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment.	❖❖❖❖
1.3.6	CR	Healthcare professionals should consider that the severity of hirsutism may vary by ethnicity but the prevalence of hirsutism appears similar across ethnicities.	❖❖❖
1.3.7	PP	Healthcare professionals should: • be aware that standardised visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas • consider the Ludwig or Olsen visual scales for assessing female pattern hair loss • note that there are no universally accepted visual instruments for assessing the presence of acne • recognise that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity • appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination • be aware that only terminal hairs need to be considered in defining hirsutism, and these can reach > 5 mm if untreated, vary in shape and texture and are generally pigmented • note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis • monitor clinical signs of hyperandrogenism, including hirsutism, acne and female pattern hair loss, for improvement or treatment adjustment during therapy.	
1.4		**Ultrasound and polycystic ovarian morphology**	
1.4.1	EBR	Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOM) in adults.	❖❖❖❖ ⊕⊕○○
1.4.2	EBR	Follicle number per ovary (FNPO), follicle number per cross-section (FNPS) and ovarian volume (OV) should be considered accurate ultrasound markers for PCOM in adults.	❖❖❖❖ ⊕⊕○○
1.4.3	CR	PCOM criteria should be based on follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).	❖❖❖❖
1.4.4	CR	Follicle number per ovary (FNPO) ≥ 20 in at least one ovary should be considered the threshold for PCOM in adults.	❖❖❖❖
1.4.5	CR	Ovarian volume (OV) ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in at least one ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary.	❖❖❖❖

No. Living#	Type	Recommendation	Grade/ Quality
1.4.6	**PP**	There are no definitive criteria to define polycystic ovary morphology (PCOM) on ultrasound in adolescents, hence it is not recommended in adolescents.	
1.4.7	**PP**	When an ultrasound is indicated, if acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM.	
1.4.8	**PP**	Transabdominal ultrasound should primarily report ovarian volume (OV) with a threshold of ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in either ovary in adults given the difficulty of assessing follicle counts throughout the entire ovary with this approach.	
1.4.9	**PP**	In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis.	
1.4.10	**PP**	Thresholds for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut-off values for PCOM should be defined.	
1.4.11	**PP**	There is a need for training in careful and meticulous follicle counting per ovary and clear standardised protocols are recommended for PCOM reporting on ultrasound including at a minimum: • last menstrual period (or stage of cycle) • transducer bandwidth frequency • approach/route assessed • total number of 2–9 mm follicles per ovary • measurements in three dimensions (in cm) or volume of each ovary • other ovarian features and/or pathology including ovarian cysts, corpus lutea, dominant follicles (≥ 10 mm) (which should not be included in ovarian volume calculations) • reliance on the contralateral ovary FNPO for diagnosis of PCOM, where a dominant follicle is noted • uterine features and/or pathology including endometrial thickness and pattern.	
1.5#		**Anti-mullerian hormone in the diagnosis of PCOS**	
1.5.1	**EBR**	Serum anti-mullerian hormone (AMH) could be used for defining PCOM in adults.	❖❖❖ ⊕⊕⊕◯
1.5.2	**EBR**	Serum AMH should only be used in accordance with the diagnostic algorithm, noting that in patients with irregular menstrual cycles and hyperandrogenism, an AMH level is not necessary for PCOS diagnosis.	❖❖❖❖ ⊕⊕⊕◯
1.5.3	**EBR**	We recommend that serum AMH should not be used as a single test for the diagnosis of PCOS.	❖❖❖❖ ⊕⊕⊕◯

No. Living#	Type	Recommendation	Grade/ Quality
1.5.4	EBR	Serum AMH should not yet be used in adolescents.	❖❖❖❖ ⊕⊕⊕◯
1.5.5	PP	Either serum AMH or ultrasound may be used to define PCOM; however, both tests should not be performed to limit overdiagnosis.	
1.5.6	PP	Laboratories and healthcare professionals need to be aware of factors that influence AMH in the general population including: • age: Serum AMH generally peaks between the ages of 20-25 years in the general population • body mass index (BMI): Serum AMH is lower in those with higher BMI in the general population • hormonal contraception and ovarian surgery: Serum AMH may be suppressed by current or recent COCP use • menstrual cycle day: Serum AMH may vary across the menstrual cycle.	
1.5.7	PP	Laboratories involved in AMH measurements in females should use population and assay specific cut-offs.	
1.6#		**Ethnic variation**	
1.6.1	EBR	Healthcare professionals should be aware of the high prevalence of PCOS in all ethnicities and across world regions, ranging from 10-13% globally using the Rotterdam criteria.	❖❖❖❖ ⊕⊕◯◯
1.6.2	EBR	Healthcare professionals should be aware that PCOS prevalence is similar across world regions and ethnicities, but may be higher in South East Asian and Eastern Mediterranean regions.	❖❖❖❖ ⊕⊕◯◯
1.6.3	PP	Healthcare professionals should be aware that the presentation of PCOS may vary across ethnic groups.	
1.7		**Menopause life stage**	
1.7.1	CR	A diagnosis of PCOS could be considered as enduring/lifelong.	❖❖❖
1.7.2	CR	Healthcare professionals could consider that both clinical and biochemical hyperandrogenism persist in the postmenopause for women with PCOS.	❖❖❖
1.7.3	CR	PCOS diagnosis could be considered postmenopause, if there is a past diagnosis, or a long-term history of oligo-amenorrhoea with hyperandrogenism and/or PCOM, during the earlier reproductive years (age 20-40).	❖❖❖
1.7.4	CR	Further investigations should be considered to rule out androgen-secreting tumours and ovarian hyperthecosis in postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism.	❖❖❖

No. Living#	Type	Recommendation	Grade/ Quality
1.8#		**Cardiovascular disease risk**	
1.8.1	**EBR**	Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in premenopausal women is low.	❖❖❖ ⊕○○○
1.8.2	**EBR**	All women with PCOS should be assessed for cardiovascular disease risk factors.	❖❖❖❖ ⊕○○○
1.8.3	**CR**	All women with PCOS, regardless of age and BMI, should have a 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 hyperlipidaemia and additional risk factors or global cardiovascular risk.	❖❖❖❖
1.8.4	**CR**	All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.	❖❖❖❖
1.8.5	**CR**	Funding bodies should recognise that PCOS is highly prevalent with multisystem effects including cardiometabolic disease, and should diversify and increase research support accordingly.	❖❖❖❖
1.8.6	**CR**	Cardiovascular general population guidelines could consider the inclusion of PCOS as a cardiovascular risk factor.	❖❖❖
1.8.7	**CR**	Healthcare professionals, women with PCOS and other stakeholders should all prioritise preventative strategies to reduce cardiovascular risk.	❖❖❖❖
1.8.8	**PP**	Consideration should be given to the differences in cardiovascular risk factors, and cardiovascular disease, across ethnicities (see 1.6.1) and age, when determining frequency of risk assessment.	
1.9		**Impaired glucose tolerance and type 2 diabetes risk**	
1.9.1	**EBR**	Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes.	❖❖❖❖ ⊕⊕○○
1.9.2	**EBR**	Glycaemic status should be assessed at diagnosis in all adults and adolescents with PCOS.	❖❖❖❖ ⊕⊕○○
1.9.3	**CR**	Glycaemic status should be reassessed every one to three years, based on additional individual risk factors for diabetes.	❖❖❖❖
1.9.4	**CR**	Healthcare professionals, women with PCOS and other stakeholders should prioritise preventative strategies to reduce type 2 diabetes risk.	❖❖❖❖

No. Living#	Type	Recommendation	Grade/ Quality
1.9.5	CR	Funding bodies should recognise that PCOS is highly prevalent, has significantly higher risk for diabetes and should be funded accordingly.	❖❖❖❖
1.9.6	CR	Diabetes general population guidelines should consider the inclusion of PCOS as an independent risk factor for diabetes.	❖❖❖❖
1.9.7	PP	Healthcare professionals, adults and adolescents with PCOS and their first-degree relatives, should be aware of the increased risk of diabetes and the need for regular glycaemic assessment.	
1.9.8	PP	Women with type 1 and type 2 diabetes have an increased risk of PCOS and screening should be considered in individuals with diabetes.	
		Glycaemic testing	
1.9.9	EBR	Healthcare professionals and women with PCOS should recommend the 75g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS, regardless of BMI.	❖❖❖❖ ⊕◯◯◯
1.9.10	EBR	If an OGTT cannot be performed, fasting plasma glucose and/or glycated haemoglobin (HbA1c) could be considered, noting significantly reduced accuracy.	❖❖❖ ⊕◯◯◯
1.9.11	EBR	An OGTT should be considered in all women with PCOS and without pre-existing diabetes, 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 could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation.	❖❖❖ ⊕◯◯◯
1.9.12	PP	Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and are not recommended in routine care (refer to 3.1.10).	
1.10		**Obstructive sleep apnea**	
1.10.1	EBR	Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea (OSA) compared to women without PCOS, independent of BMI.	❖❖❖❖ ⊕⊕⊕◯
1.10.2	EBR	Women with PCOS should be assessed for symptoms (i.e. snoring in combination with waking unrefreshed from sleep, daytime sleepiness or fatigue) and if present, screen with validated tools or refer for assessment.	❖❖❖❖ ⊕⊕⊕◯
1.10.3	PP	Simple obstructive sleep apnea screening questionnaires (such as the Berlin questionnaire, validated in the general population) can assist in identifying obstructive sleep apnea in women with PCOS, noting that diagnosis requires a formal sleep study.	
1.10.4	PP	Goals of treatment should target obstructive sleep apnea related symptom burden.	

No. Living#	Type	Recommendation	Grade/ Quality
1.11		**Endometrial hyperplasia and cancer**	
1.11.1	**EBR**	Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer.	❖❖❖❖ ⊕◯◯◯
1.11.2	**PP**	Women with PCOS should be informed about the increased risk of endometrial hyperplasia and endometrial cancer, acknowledging that the overall chance of developing endometrial cancer is low, therefore routine screening is not recommended.	
1.11.3	**PP**	Long-standing untreated amenorrhea, higher weight, type 2 diabetes and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer.	
1.11.4	**PP**	Women with PCOS should be informed of preventative strategies including weight management, cycle regulation and regular progestogen therapy.	
1.11.5	**PP**	When excessive endometrial thickness is detected, consideration of a biopsy with histological analysis and withdrawal bleed is indicated.	
1.12 #		**Risks in relatives**	
1.12.1	**EBR**	Healthcare professionals could consider that fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension.	❖❖❖ ⊕◯◯◯
1.12.2	**PP**	The cardiometabolic risk in female first-degree relatives of women with PCOS remains inconclusive.	
2		**Prevalence, screening and management of psychological features and models of care**	
		General principles	
	PP	Psychological features are common and important component of PCOS that all health professionals should be aware of.	
	PP	Funding bodies should recognise that PCOS is highly prevalent, has significantly higher psychological disorders which should be prioritised and funded accordingly.	
2.1		**Quality of life**	
2.1.1	**EBR**	Healthcare professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults.	❖❖❖❖ ⊕⊕◯◯
2.1.2	**PP**	Women with PCOS should be asked about their perception of PCOS related symptoms, impact on quality of life, key concerns and priorities for management.	

No. Living#	Type	Recommendation	Grade/ Quality
2.2		**Depression and anxiety**	
2.2.1	**EBR**	Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adults and adolescents with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.2.2	**EBR**	Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.2.3	**CR**	If moderate or severe depressive or anxiety symptoms are detected, practitioners should further assess, refer appropriately or offer treatment.	❖❖❖❖
2.2.4	**PP**	Severity of symptoms and clinical diagnosis of depression or anxiety should guide management. The optimal interval for anxiety and depression screening is not known. A pragmatic approach could include screening at diagnosis with repeat screening based on clinical judgement, risk factors, comorbidities and life events, including the perinatal period. Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of self-harm and suicidal intent.	
2.3		**Psychosexual function**	
2.3.1	**CR**	Healthcare professionals could consider the multiple factors that can influence psychosexual function in PCOS including higher weight, hirsutism, mood disorders, infertility and PCOS medications.	❖❖❖
2.3.2	**CR**	Permission to discuss psychosexual function should be sought noting that the diagnosis of psychosexual dysfunction requires both low psychosexual function, combined with related distress.	❖❖❖❖
2.4		**Body Image**	
2.4.1	**EBR**	Healthcare professionals should be aware that features of PCOS can have a negative impact on body image.	❖❖❖❖ ⊕⊕○○
2.5		**Eating disorders and disordered eating**	
2.5.1	**EBR**	Eating disorders and disordered eating should be considered in PCOS, regardless of weight, especially in the context of weight management and lifestyle interventions (see sections 2.4 and 3.6).	❖❖❖ ⊕⊕○○
2.5.2	**PP**	If disordered eating or eating disorders are suspected, appropriately qualified practitioners should further assess via a full diagnostic interview. If an eating disorder or disordered eating is detected, appropriate management and support should be offered.	

No. Living#	Type	Recommendation	Grade/ Quality
2.6		**Information resources, models of care, cultural and linguistic considerations**	
2.6.1		**Information needs**	
2.6.1.1	**EBR**	Tailored information, education and resources that are high-quality, culturally appropriate and inclusive should be provided to all with PCOS.	❖❖❖❖ ⊕⊕⊕◯
2.6.1.2	**EBR**	Information, education and resources are a high priority for patients with PCOS and should be provided in a respectful and empathic manner.	❖❖❖❖ ⊕⊕⊕◯
2.6.1.3	**CR**	Entities responsible for health professional education should ensure that information and education on PCOS is systemically embedded at all levels of health professional training to address knowledge gaps.	❖❖❖❖
2.6.1.4	**PP**	The diversity of the population should be considered when adapting practice paradigms. Healthcare professional opportunities should be optimised at all stages of graduate and postgraduate training, continuing professional development and in practice support resources.	
2.6.1.5	**PP**	Women should be counselled on the risk of misinformation and guided to evidence-based resources.	
2.6.2 #		**Models of care**	
2.6.2.1	**CR**	Models of care should prioritise equitable access to evidence-based primary care with pathways for escalation to integrated specialist and multidisciplinary services as required.	❖❖❖❖
2.6.2.2	**PP**	Strategies to deliver optimal models of care could include health professional education, care pathways, virtual care, broader health professional engagement (e.g. nurse practitioners) and coordination tools.	
2.6.3		**Support to manage PCOS**	
2.6.3.1	**CR**	Public health actors should consider increasing societal awareness and education on PCOS to reduce stigma and marginalisation.	❖❖❖
2.6.3.2	**PP**	Culturally appropriate resources and education on PCOS across the life span for families of those with the condition, should be considered.	

No. Living#	Type	Recommendation	Grade/ Quality
2.6.4		**Patient care**	
2.6.4.1	**EBR**	Healthcare professionals should employ shared decision making and support patient agency or ability to take independent actions to manage their health and care.	❖❖❖❖ ⊕⊕⊕◯
2.6.4.2	**EBR**	The importance of being knowledgeable about PCOS, of applying evidence-based practices when sharing news on diagnosis, treatment and health implications, and of ascertaining and focusing on patient priorities, should be recognised.	❖❖❖❖ ⊕⊕⊕◯
2.6.4.3	**CR**	Healthcare system leaders should enable system wide changes to support health professional training, knowledge and practice in sharing news optimally, shared decision making and patient agency, including ensuring adequate consultation time and accessible resources.	❖❖❖❖
2.6.4.4	**PP**	Evidence-based strategies for shared decision making and for sharing news (such as the SPIKES framework) are readily available and should be used to inform PCOS care. All healthcare professionals partnering with women with PCOS should be knowledgeable in sharing news, in shared decision making and in supporting patient self-management. Evidence-based strategies and resources can be used to support patient activation, which refers to modifiable knowledge, skills, ability, confidence and willingness to self-manage one's own health and care.	
2.7		**Psychological therapy**	
2.7.1	**CR**	Women with PCOS diagnosed with depression, anxiety, and/or eating disorders should be offered psychological therapy guided by regional general population guidelines and the preference of the woman with PCOS.	❖❖❖❖
2.7.2	**CR**	Women with PCOS with disordered eating, body image distress, low self-esteem, problems with feminine identity, or psychosexual dysfunction should be offered evidence-based treatments (e.g. cognitive behaviour therapy) where appropriate.	❖❖❖❖
2.8		**Antidepressant and anxiolytic treatment**	
2.8.1	**CR**	Psychological therapy could be considered first-line management, and antidepressant medications considered in adults where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, based on general population guidelines.	❖❖❖
2.8.2	**PP**	Lifestyle intervention and other therapies (e.g. COCP, metformin, laser hair removal) that target PCOS features should be considered, given their potential to improve psychological symptoms. Where pharmacological treatment for anxiety and depression is offered in PCOS, healthcare professionals should apply caution: • to avoid inappropriate treatment with antidepressants or anxiolytics • to limit use of agents that exacerbate PCOS symptoms, including weight gain. Healthcare professionals should be aware that not managing anxiety and depression may impact adherence to PCOS treatment/management.	

No. Living#	Type	Recommendation	Grade/ Quality
3		**Lifestyle management**	
3.1		**Effectiveness of lifestyle interventions**	
3.1.1	**EBR**	Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioural strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile.	❖❖❖❖ ⊕◯◯◯
3.1.2	**CR**	Healthy lifestyle behaviours encompassing healthy eating and/or physical activity should be recommended in all women with PCOS to optimise general health, quality of life, body composition and weight management (maintaining weight, preventing weight gain and/or modest weight loss).	❖❖❖❖
3.1.3	**PP**	Healthcare professionals should be aware that lifestyle management is a core focus in PCOS management.	
3.1.4	**PP**	Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS, and value women's individualised preferences.	
3.1.5	**PP**	There are benefits to a healthy lifestyle even in the absence of weight loss.	
3.1.6	**PP**	In those with higher weight, weight management can be associated with significant clinical improvements and the following key points need to be considered including: • a lifelong focus on prevention of further weight gain • if the goal is to achieve weight loss, a tailored energy deficit could be prescribed for women, considering individual energy requirements, body weight and physical activity levels • the value of improvement in central adiposity (e.g. waist circumference, waist-hip ratio) or metabolic health • the need for ongoing assessment and support.	
3.1.7	**PP**	Healthcare professionals should be aware of weight stigma when discussing lifestyle management with women with PCOS [see 3.6].	
3.1.8	**PP**	Healthy lifestyle and optimal weight management, in the context of structured, intensive and ongoing clinical support, appears equally effective in PCOS as in the general population.	
3.1.9	**PP**	In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain.	
3.1.10	**PP**	Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care (refer to 1.9.12).	

No. Living#	Type	Recommendation	Grade/ Quality
3.2		**Behavioural strategies**	
3.2.1	**CR**	Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, problem solving, assertiveness training, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS.	❖❖❖
3.2.2	**PP**	Behavioural support could include: goal-setting, problem solving, self-monitoring and reviewing, or SMART goals (Specific, Measurable, Achievable, Realistic and Timely).	
3.2.3	**PP**	Comprehensive healthy 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 interventions**	
3.3.1	**EBR**	Healthcare professionals and women should consider that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	❖❖❖ ⊕○○○
3.3.2	**CR**	Any diet composition consistent with population guidelines for healthy eating will have health benefits, and within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals.	❖❖❖❖
3.3.3	**PP**	Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population guidelines.	
3.3.4	**PP**	Barriers and facilitators to optimise engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, as well as personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimising their diet.	
3.4		**Exercise interventions**	
3.4.1	**EBR**	Healthcare professionals and women could consider that there is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	❖❖❖ ⊕○○○
3.4.2	**CR**	Any physical activity consistent with population guidelines will have health benefits and within this, healthcare professionals should advise sustainable physical activity based on individual preferences and goals.	❖❖❖❖

No. Living#	Type	Recommendation	Grade/ Quality
3.4.3	CR	Healthcare professionals should encourage and advise the following in concordance with general population physical activity guidelines: • All adults should undertake physical activity as doing some physical activity is better than none. • Adults should limit the amount of time spent being sedentary (e.g. sitting, screen time) as replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits. For the prevention of weight gain and maintenance of health, adults (18-64 years) should aim for a minimum of 150 to 300 minutes of moderate-intensity activities or 75 to 150 minutes of vigorous-intensity aerobic activity per week or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week. For promotion of greater health benefits including modest weight loss and prevention of weight regain, adults (18-64 years) should aim for a minimum of 250 min/week of moderate-intensity activities or 150 min/week of vigorous intensities or an equivalent combination of both, plus muscle strengthening activities (e.g. resistance/flexibility) ideally on two non-consecutive days per week. Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day including activities that strengthen muscle and bone, at least three times per week.	❖❖❖❖
3.4.4	PP	Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. It includes leisure time physical activity, transportation (e.g. walking or cycling), occupational (i.e. work), household chores, playing games, sports or planned exercise, or activities in the context of daily, family and community activities.	
3.4.5	PP	Aerobic activity is best performed in bouts of at least 10 minutes duration, aiming to achieve at least 30 minutes daily on most days.	
3.4.6	PP	Barriers and facilitators to optimise engagement and adherence to physical activity should be discussed, including psychological factors (e.g. body image concerns, fear of injury, fear of failure, mental health), personal safety concerns, environmental factors, physical limitations, socioeconomic factors, sociocultural factors, and personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered for optimising physical activity in women with PCOS.	
3.4.7	PP	Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be considered as an adjunct to support and promote active lifestyles and minimise sedentary behaviours.	

No. Living#	Type	Recommendation	Grade/ Quality
3.5		**Factors affecting weight gain in PCOS**	
3.5.1	**EBR**	Healthcare professionals and women with PCOS could consider that there is a lack of consistent evidence of physiological or behavioural lifestyle differences, related to weight, in women with PCOS compared to women without PCOS.	❖❖❖ ⊕○○○
3.5.2	**PP**	Whilst the specific mechanisms are unclear, it is recognised that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI which may: • underpin greater challenges with weight management • highlight the importance of lifelong healthy lifestyle strategies and prevention of excess weight gain • assist women with PCOS and healthcare professionals in forming realistic, tailored lifestyle goals.	
3.6 #		**Weight stigma**	
3.6.1	**EBR**	Many women with PCOS experience weight stigma in healthcare and other settings and the negative biopsychosocial impacts of this should be recognised.	❖❖❖❖ ⊕⊕○○
3.6.2	**CR**	Healthcare professionals should be aware of their weight biases and the impact this has on their professional practice and on women with PCOS.	❖❖❖❖
3.6.3	**CR**	Health policy makers, managers and educators should promote awareness of weight stigma and invest in weight stigma education and minimisation strategies.	❖❖❖❖
3.6.4	**PP**	Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes. In PCOS this includes: • acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only one indicator of health and broader factors should be assessed • asking permission to discuss and measure weight and using strategies to minimise discomfort (e.g. blind weighing) • recognising that the terms 'overweight' and 'obese/obesity' can be stigmatising with suggested alternatives including 'higher weight' • if weighing, explaining how weight information will be used to inform risks prevention and treatment and how not knowing may impact on recommendations • ensuring appropriate equipment is available for women of all sizes • offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without focusing on intentional weight loss) tailored to individual goals and preferences • offering all women best practice assessment, treatment and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone.	
3.6.5	**PP**	Increasing awareness of weight stigma among family members of women and adolescents with PCOS should be considered.	

No. Living#	Type	Recommendation	Grade/ Quality
4		**Management of non-fertility features**	
4.1		**Pharmacology treatment principles in PCOS**	
	PP	Shared decision making between the patient (and parent/s or guardian/s, if the patient is a child) and the healthcare professional is required.	
	PP	An individual's characteristics, preferences and values must be elicited and considered when recommending any intervention alone or in combination.	
	PP	Understanding how individual adults and adolescents value treatment outcomes is essential when prescribing medications.	
	PP	Medical therapy is generally not approved for use specifically in PCOS and recommended use is therefore evidence-based, but off-label. Healthcare professionals need to inform adults, adolescents and their parents/s or guardian/s and discuss the evidence, possible concerns and side-effects. Regulatory agencies should consider approval of evidence-based medications for use in PCOS.	
4.2		**Combined oral contraceptive pills**	
4.2.1	**EBR**	The combined oral contraceptive pill (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕◯◯◯
4.2.2	**EBR**	The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕◯◯◯
4.2.3	**EBR**	Health professionals could consider that there is no clinical advantage of using high dose ethinylestradiol (≥ 30 µg) versus low dose ethinylestradiol (< 30 µg) when treating hirsutism in adults with PCOS.	❖❖❖ ⊕◯◯◯
4.2.4	**EBR**	General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestins, estrogens or combinations of COCP cannot currently be recommended.	❖❖❖ ⊕◯◯◯
4.2.5	**EBR**	The 35 µg ethinyl estradiol plus cyproterone acetate preparations should be considered as second-line therapy over other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks.	❖❖❖ ⊕◯◯◯

No. Living#	Type	Recommendation	Grade/ Quality
4.2.6	EBR	Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited.	❖❖❖ ⊕○○○
4.2.7	PP	When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS: • It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies. • Shared decision making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence. • Natural estrogen preparations and the lowest effective estrogen doses (such as 20-30 micrograms of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side-effects, cost and availability. • The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines • The relative and absolute contraindications and side-effects of COCPs need to be considered and be the subject of individualised discussion. • PCOS specific features such as higher weight and cardiovascular risk factors, need to be considered.	
4.3		**Metformin**	
4.3.1	EBR	Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m² for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles.	❖❖❖ ⊕○○○
4.3.2	EBR	Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.	❖❖❖ ⊕○○○
4.3.3	CR	Metformin alone may be considered in adults with PCOS and BMI < 25 kg/m², acknowledging limited evidence.	❖❖❖
4.3.4	PP	Where metformin is prescribed the following need to be considered: • Shared decision making needs to consider feasibility and effectiveness of active lifestyle intervention. Women should be informed that metformin and active lifestyle intervention have similar efficacy. • Mild adverse effects, including gastrointestinal side-effects are generally dose dependent and self-limiting. • Starting at a low dose, with 500 mg increments 1-2 weekly and extended-release preparations may minimise side-effects and improve adherence. • Suggested maximum daily dose is 2.5 g in adults and 2 g in adolescents. • Use appears safe long-term, based on use in other populations, however indications for ongoing requirement needs to be considered. • Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (e.g. diabetes, post bariatric/metabolic surgery, pernicious anaemia, vegan diet etc.), where monitoring should be considered.	

No. Living#	Type	Recommendation	Grade/ Quality
4.4		**Metformin and combined oral contraceptive pills**	
4.4.1	**EBR**	COCP could be used over metformin for management of hirsutism in irregular menstrual cycles in PCOS.	❖❖❖ ⊕◯◯◯
4.4.2	**EBR**	Metformin could be used over COCP for metabolic indications in PCOS.	❖❖❖ ⊕◯◯◯
4.4.3	**EBR**	The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with PCOS with a BMI ≤30 kg/m².	❖❖❖ ⊕◯◯◯
4.4.4.	**PP**	In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m², diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.	
4.4.5	**PP**	Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed.	
4.5#		**Anti-obesity pharmacological agents**	
4.5.1	**CR**	Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.	❖❖❖
4.5.2	**PP**	Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible, for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.	
4.5.3	**PP**	Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects.	
4.5.4	**PP**	Shared decision making, when discussing GLP-1 receptor agonist use with women with PCOS, needs to consider side-effects, and the potential need for long-term use in weight management, given the high risk for weight regain after discontinuation, and the lack of long-term safety data.	
4.6		**Anti-androgen pharmacological agents**	
4.6.1	**EBR**	In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.	❖❖❖ ⊕◯◯◯

No. Living#	Type	Recommendation	Grade/ Quality
4.6.2	CR	Given the negative psychological impact of female pattern hair loss, anti-androgens in combination with COCP could be trialed, acknowledging the lack of evidence in the PCOS population.	❖❖❖
4.6.3	PP	Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/s or guardian/s, regarding the risks of incomplete development of external genital structures of male fetuses (undervirilisation) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counseled to use effective contraception (e.g. intrauterine device or COCPs).	
4.6.4	PP	Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated.	
4.6.5	PP	When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that: • spironolactone at 25-100 mg/day appears to have lower risks of adverse effects • cyproterone acetate at doses ≥ 10 mg is not advised due to an increased risk including for meningioma • finesteride has an increased risk of liver toxicity • flutamide and bicalutamide have an increased risk of severe liver toxicity. The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants.	
4.7#		**Inositol**	
4.7.1	EBR	Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, yet with limited clinical benefits including in ovulation, hirsutism or weight.	❖❖❖ ⊕◯◯◯
4.7.2	EBR	Metformin should be considered over inositol for hirsutism and central adiposity, noting that metformin has more gastrointestinal side-effects than inositol.	❖❖❖ ⊕◯◯◯
4.7.3	PP	Women taking inositol and other complementary therapies are encouraged to advise their health professional.	
4.7.4	PP	Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence.	
4.7.5	PP	Shared decision making should include discussion that regulatory status and quality control of inositol in any form (like other nutrient supplements) can differ from those for pharmacological products and doses and qualities may vary.	
4.7.6	PP	Policy makers and healthcare professionals have a responsibility to ensure women have access to unconflicted, evidence-based information to inform shared-decision making, whilst also acknowledging and respecting individual values and preferences, including for complementary therapies.	

No. Living#	Type	Recommendation	Grade/ Quality
4.8		**Mechanical laser and light therapies for hair reduction**	
4.8.1	**EBR**	Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety and quality of life in women with PCOS.	❖❖❖ ⊕○○○
4.8.2	**EBR**	A greater number of laser treatment sessions may be required in women with PCOS, compared to women with idiopathic hirsutism, to achieve hair reduction.	❖❖❖ ⊕○○○
4.8.3	**CR**	Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers.	❖❖❖❖
4.8.4	**PP**	Where laser hair removal is prescribed, the following need to be considered: • Wavelength and delivery of laser treatment varies by skin and hair colour. • Laser is relatively ineffective in women with blond, grey or white hair. • The addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone. Low and high fluence laser appear to have similar efficacy in reducing facial hair, while low fluence laser has reduced associated pain.	
4.8.5	**PP**	Mechanical hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence to support the efficacy of home-based IPL kits.	
4.8.6	**PP**	Policy makers should consider funding this evidence-based effective therapy for women with PCOS to alleviate distressing symptoms of hirsutism, and related negative impact on quality of life, body image and psychological health.	
4.9 #		**Bariatric/metabolic surgery**	
4.9.1	**CR**	Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation and pregnancy rates in women with PCOS.	❖❖❖
4.9.2	**CR**	Bariatric/metabolic surgery in women with PCOS should be informed by general population guidelines.	❖❖❖❖
4.9.3	**CR**	PCOS is a metabolic condition and could be considered an indication at a lower BMI threshold for bariatric/metabolic surgery similarly to other metabolic conditions including diabetes.	❖❖❖
4.9.4	**CR**	Women should be strongly counseled on the likelihood of rapid return of fertility and the need to commit to effective contraception, ideally prior to surgery. Even when pregnancy is desired, contraception should be continued until a stable weight is achieved, usually after one year, to avoid significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy complications and prolonged hospitalisation of the infant.	❖❖❖❖

No. Living#	Type	Recommendation	Grade/ Quality
4.10		**Pregnancy outcomes**	
4.10.1	**EBR**	Women with PCOS have higher risk pregnancies, and healthcare professionals should ensure that PCOS status is identified during antenatal care, and appropriate monitoring and support is provided.	❖❖❖❖ ⊕○○○
4.10.2	**EBR**	Healthcare professionals should recognise that pregnant women with PCOS have an increased risk of: • higher gestational weight gain • miscarriage • gestational diabetes • hypertension in pregnancy and preeclampsia • intrauterine growth restriction, small for gestational age babies and low birth weight • preterm delivery • caesarean section.	❖❖❖❖ ⊕○○○
4.10.3	**EBR**	Assisted reproductive technology in women with PCOS should be considered as not conferring additional risk of miscarriage, preterm birth, impaired fetal growth and caesarean section, over that observed in women without PCOS.	❖❖❖ ⊕○○○
4.10.4	**EBR**	Women with PCOS should be considered as not having an increased risk of large for gestational age babies, macrosomia and instrumental delivery.	❖❖❖ ⊕○○○
4.10.5	**PP**	Early lifestyle intervention should be offered to pregnant women with PCOS, given the risk of higher baseline weight, excess gestational weight gain and pregnancy complications.	
4.10.6	**PP**	Blood pressure measurement should be performed when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities in women with PCOS.	
4.10.7	**PP**	An OGTT should be offered to all women with PCOS when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed in the preconception phase, an OGTT should be offered at the first antenatal visit and repeated at 24-28 weeks gestation.	

No. Living#	Type	Recommendation	Grade/ Quality
4.11		**Metformin in pregnancy**	
4.11.1	**EBR**	Healthcare professionals should be aware that metformin in pregnant women with PCOS has not been shown to prevent: • gestational diabetes • late miscarriage (12 weeks +1 day to 21 weeks +6 days gestational age) • hypertension in pregnancy • pre-eclampsia • macrosomia or birthweight ≥ 4000 g.	❖❖❖❖ ⊕⊕◯◯
4.11.2	**EBR**	Metformin could be considered in some circumstances (e.g. risk for preterm birth), to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS.	❖❖❖ ⊕⊕⊕◯
4.11.3	**PP**	Women should be counselled that the consequences of metformin exposure on long-term offspring health remain unclear and there is a suggestion of increased childhood weight, although causality is not certain.	
4.11.4	**PP**	Side-effects of metformin are mostly mild, transient gastrointestinal symptoms and are not worse in pregnancy.	
5		**Assessment and treatment of infertility**	
		General principles	
	PP	All fertility treatment in PCOS should be guided by the fertility management algorithm.	
	PP	Those with PCOS should be reassured that pregnancy can often be successfully achieved either naturally or with assistance.	
	PP	Prenatal vitamins supplementation should be commenced with ovulation induction therapy aligned to routine preconception care.	
	PP	Pregnancy should be excluded prior to ovulation induction therapy.	
	PP	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, healthcare professionals need to inform women and discuss the evidence, possible concerns and side-effects.	
	PP	There should be ongoing monitoring of patients for adverse effects and infants for congenital anomalies in all studies conducted with ovulation induction agents and these should be reported in any published papers.	

No. Living#	Type	Recommendation	Grade/ Quality
5.1#		**Preconception risk factors**	
5.1.1	**EBR**	Women with PCOS should be counseled on the adverse impact of excess weight on clinical pregnancy, miscarriage and live birth rates, following infertility treatment.	❖❖❖❖ ⊕◯◯◯
5.1.2	**CR**	Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, diet and nutritional status, folate supplementation (higher dose in those with BMI > 30), exercise, sleep and mental, emotional and sexual health should be considered and optimised to improve reproductive and pregnancy outcomes and overall health.	❖❖❖❖
5.1.3	**PP**	A reproductive life plan and age appropriate education on optimising reproductive health, is recommended in adolescents and women with PCOS, including healthy lifestyle, prevention of excess weight gain, and optimising preconception risk factors.	
5.1.4	**PP**	Healthcare professionals are encouraged to seek permission and if given, to assess weight and body mass index and initiate a dialogue on the importance of weight and lifestyle on women's health before pregnancy. This requires caution to avoid weight stigma and needs to consider the cultural, social and environmental determinants of health (see 3.6).	
5.1.5	**PP**	Chronic conditions such as diabetes, high blood pressure, anxiety, depression and other mental health conditions, should be optimally managed and women should be counseled regarding the risk of adverse pregnancy outcomes.	
5.2		**Tubal patency testing**	
5.2.1	**CR**	In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing and techniques of tubal patency testing in relation to the cost and complexity of the treatment, should be considered on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination.	❖❖❖
5.3		**Letrozole**	
5.3.1	**EBR**	Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.	❖❖❖❖ ⊕⊕⊕⊕
5.3.2	**PP**	The use of letrozole is still off-label in many countries. Where it is not allowed, clinicians could use other ovulation induction agents.	
5.3.3	**PP**	Letrozole should not be given where there is any possibility of a pre-existing pregnancy, though there is no evidence for increased teratogenicity compared to other ovulation induction agents.	

No. Living#	Type	Recommendation	Grade/ Quality
5.4		**Clomiphene citrate and metformin**	
5.4.1		**Metformin versus placebo**	
5.4.1.1	**EBR**	Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women that there are more effective ovulation agents.	❖❖❖ ⊕⊕◯◯
5.4.1.2	**PP**	Women should be counseled as to potential mild gastrointestinal side-effects with metformin.	
5.4.1.3	**PP**	Healthcare and resource burden including monitoring, travel and costs are lower with metformin.	
5.4.1.4	**PP**	Consideration of age and screening for other fertility factors needs to be discussed before prescribing metformin.	
5.4.2		**Clomiphene citrate versus metformin**	
5.4.2.1	**EBR**	Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy and live birth rates.	❖❖❖ ⊕⊕◯◯
5.4.2.2	**PP**	The risk of multiple pregnancy is increased with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene cycles may require ultrasound monitoring.	
5.4.3		**Clomiphene citrate and metformin versus clomiphene citrate alone**	
5.4.3.1	**EBR**	Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.	❖❖❖ ⊕⊕◯◯
5.4.4		**Clomiphene citrate and metformin versus metformin alone**	
5.4.4.1	**EBR**	Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates.	❖❖❖ ⊕⊕◯◯
5.4.4.2	**PP**	Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone.	
5.4.5		**Clomiphene citrate versus Letrozole**	
5.4.5.1	**EBR**	Letrozole should be used rather than clomiphene citrate in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates.	❖❖❖❖ ⊕◯◯◯
5.4.5.2	**PP**	Current evidence demonstrates no difference in fetal abnormality rates between letrozole or clomiphene citrate ovulation induction or natural conception.	

No. Living#	Type	Recommendation	Grade/ Quality
5.5		**Gonadotrophins**	
5.5.1	**EBR**	Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates (refer to PP 5.5.6).	❖❖❖ ⊕⊕◯◯
5.5.2	**EBR**	Gonadotrophins alone could be used over gonadotrophins combined with clomiphene citrate in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure, and no other infertility factors.	❖❖❖ ⊕⊕◯◯
5.5.3	**EBR**	Gonadotrophins could be considered rather than the combination of clomiphene citrate and metformin in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance and no other infertility factors.	❖❖❖ ⊕◯◯◯
5.5.4	**EBR**	Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance and no other infertility factors, following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophins.	❖❖ ⊕⊕◯◯
5.5.5	**EBR**	Gonadotrophins could be second-line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first-line oral ovulation induction.	❖❖❖ ⊕⊕◯◯
5.5.6	**PP**	Where gonadotrophins are to be prescribed, the following should be considered: • Cost of the intervention for ovulation induction. • Expertise required for the use of the intervention for ovulation induction. • The degree of intensive ultrasound monitoring that is required. • A low dose step-up gonadotrophin protocol should be used to optimise the chance of monofollicular development. • Implications of potential multiple pregnancy.	
5.5.7	**PP**	There appears to be no difference in the clinical efficacy of the available gonadotrophin preparations.	
5.5.8	**PP**	When using gonadotrophins, best clinical practice is to avoid multiple pregnancy. Considerations here include cancelling cycles when there is more than a total of two follicles greater than 14 mm in diameter and advising avoidance of unprotected intercourse.	
5.5.9	**PP**	Live birth rate, clinical pregnancy rate per patient and ovulation rate per cycle are higher with gonadotrophins than with clomiphene citrate.	
5.5.10	**PP**	A low dose gonadotrophin protocol should be used to optimise the chance of monofollicular growth and minimise multiple pregnancy.	
5.5.11	**PP**	Cycle monitoring and drug costs coupled with multiple injection will influence choice in gonadotrophin use.	

No. Living#	Type	Recommendation	Grade/ Quality
5.6		**Laparoscopic ovarian surgery**	
5.6.1	**EBR**	Laparoscopic ovarian surgery could be second-line therapy for women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors.	❖❖❖ ⊕⊕○○
5.6.2	**PP**	When using laparoscopic ovarian surgery, the following should be considered: • Comparative cost of the intervention for ovulation induction. • Expertise required for the safe use of the intervention for ovulation induction. • Both intraoperative and postoperative risks, which are higher in women who are above healthy weight.	
5.7		**In vitro fertilisation and in vitro maturation**	
5.7.0.1	**CR**	In the absence of an absolute indication for in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI), IVF could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies have failed.	❖❖❖
5.7.0.2	**PP**	In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimised.	
5.7.0.3	**PP**	Women with PCOS undergoing IVF/ICSI treatment should be counselled prior to starting treatment about the increased risk of ovarian hyperstimulation syndrome and options to reduce the risk should be offered.	
5.7.1		**Gonadotrophin releasing hormone protocol**	
5.7.1.1	**PP**	Gonadotrophin releasing hormone protocol (GnRH) antagonist protocol cannot be recommended over GnRH agonist long protocol for women with PCOS undergoing IVF/ICSI to improve clinical pregnancy or live birth rate.	
5.7.1.2	**PP**	The use of a GnRH antagonist protocol for women with PCOS undergoing IVF/ICSI is recommended as it enables the use of an agonist trigger, with the freezing of all embryos generated if required, without compromising the cumulative live birth rate, to reduce the risk of significant ovarian hyperstimulation syndrome.	
5.7.2		**Trigger type**	
5.7.2.1	**CR**	Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos is recommended, in an IVF/ICSI cycle with a GnRH antagonist protocol, where a fresh embryo transfer is not intended or where there is an increased risk of ovarian hyperstimulation syndrome.	❖❖❖❖
5.7.3		**Choice of follicle stimulating hormone**	
5.7.3.1	**CR**	Either urinary or recombinant follicle stimulating hormone (FSH) could be used in women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, with insufficient evidence to recommend a particular type of FSH preparation.	❖❖

No. Living#	Type	Recommendation	Grade/ Quality
5.7.4		**Exogenous luteinising hormone**	
5.7.4.1	**CR**	Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF/ICSI.	❖
5.7.5		**Adjunct metformin**	
5.7.5.1	**EBR**	Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage.	❖❖❖ ⊕⊕◯◯
5.7.5.2	**PP**	Good practice in PCOS and IVF is the use of a GnRH antagonist protocol as it gives the flexibility of using a GnRH agonist trigger, freeze all strategy to reduce the risk of ovarian hyperstimulation syndrome. However, if using a GnRH agonist long protocol then metformin could be considered. If using metformin, the following could be considered: • Commence metformin at the start of GnRH agonist treatment. • Gradually titrate metformin up to a dose of between 1000 mg to 2500 mg daily in order to minimise side-effects. • Stopping metformin therapy at the time of the pregnancy test or period, unless the metformin therapy is otherwise indicated.	
5.7.6		**In vitro maturation**	
5.7.6.1	**EBR**	The use of in vitro maturation (IVM) and ICSI could be considered in women with PCOS, as an alternative to a stimulated IVF/ICSI cycle, where an embryo is frozen and replaced in a subsequent embryo transfer cycle, acknowledging there is no risk of ovarian hyperstimulation syndrome, but a lower cumulative live birth rate.	❖❖❖ ⊕⊕◯◯
5.7.6.2	**CR**	The use of IVM and ICSI could be considered prior to stimulated IVF/ICSI cycles acknowledging both benefits and limitations.	❖❖
5.7.6.3	**PP**	IVM should only be considered in services with sufficient expertise, and advocacy is needed for regional or national centres of expertise.	
5.7.6.4	**PP**	IVM could be offered as an option in women with prior severe ovarian hyperstimulation syndrome and where the risk of severe ovarian hyperstimulation syndrome is deemed unacceptably high, provided that expertise in IVM techniques exists.	
5.7.6.5	**PP**	Evidence suggests that IVM/ICSI is less effective than standard IVF/ICSI in terms of clinical pregnancy per patient and live birth rate per patient.	

No. Living#	Type	Recommendation	Grade/ Quality
5.8 #		**Inositol**	
5.8.1	**EBR**	Inositol in any form alone, or in combination with other therapies, should be considered experimental therapy in women with PCOS with infertility, with benefits and risks currently too uncertain to recommend the use of these agents as fertility therapies.	❖❖❖ ⊕◯◯◯
5.8.2	**PP**	There is limited evidence with uncertain results, on the effect of inositol on ovulation, clinical pregnancy and live birth rates.	
5.8.3	**PP**	Side-effects and safety are not known for inositol.	
5.8.4	**PP**	Women need to be aware that these agents can have limited regulation with variable dose, quality, consistency and combination with other agents.	
5.8.5	**PP**	Women's personal goals and preferences should be considered when discussing complimentary therapies.	
5.9 #		**Anti-obesity pharmacological agents**	
5.9.1	**CR**	We recommend using anti-obesity agents in PCOS for reproductive outcomes only in research settings to establish the efficacy and safety.	❖

Summary of key guideline changes from 2018- 2023:

In updating these International guidelines, recommendations most likely to change practice including significantly changed or new recommendations are highlighted under each clinical question and in the technical report. However, in summary, overall evidence is strengthened and evidence-based recommendations are increased in 2023. Specifically, in diagnosis recommendations now include anti-mullerian hormone (AMH) levels as an alternative to ultrasound in adults. Key features of PCOS now include cardiovascular disease and evidence is strengthened in sleep apnea and endometrial cancer. Increased prevalence and severity of depression and anxiety now firmly identify these as core features of PCOS. Extensive new recommendations focus on improving patient experience, information needs, models of care, support, health professional patient interactions, shared decision making, patient empowerment and recognising and addressing stigma. Lifestyle recommendations now align more closely to advancing understanding of environmental and systems drivers of higher weight and the limitation of reliance on individual lifestyle interventions for effective, sustainable reduction in weight. They also highlight broader benefits of healthy lifestyle over weight-centric approaches and acknowledge and seek to address weight stigma. Evidence on non-fertility therapies include new recommendations for mechanical laser and light therapy as an effective treatment for hair reduction. Recommendations on medical therapies are generally strengthened and the limitations of current evidence on inositol, anti-obesity agents and bariatric surgery are noted, with a priority for further research. New recommendations now define PCOS as a high-risk condition in pregnancy, recommending those affected are identified and monitored and the limited role for metformin in pregnancy is highlighted. Key preconception risks for adverse fertility and infertility treatment outcomes including higher weight are recognised and a robust integrity check process was applied to infertility therapy with few changes in recommendations, giving greater confidence for health professionals managing PCOS. Recommendations targeting education, research funding and policy makers were also included as key to advancing research, evidence and healthcare to support those with PCOS and improve health outcomes.

Chapter One
Screening, diagnostic and risk assessment and life stages

Diagnosis and treatment of polycystic ovary syndrome (PCOS) has been controversial, with challenges defining individual components within the diagnostic criteria and significant clinical heterogeneity, which is further influenced 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.

	General principles
PP	All diagnostic assessments are recommended for use in accordance with the diagnostic algorithm one.

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 original 2003 Rotterdam criteria and in the 2018 International PCOS Guideline[1]. 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 a normal component of the pubertal and menopausal transitions and defining abnormality at these life stages remains challenging. Indeed, the greatest controversy in PCOS 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. Young women may also be commenced on the combined oral contraceptive pill prior to assessment and diagnosis, potentially delaying diagnosis. Given the lack of definitive evidence identified in 2018, and the importance of diagnostic criteria in PCOS, this clinical question was prioritised.

Summary of systematic and narrative review evidence

We did not identify any evidence in our patient population to answer the question and therefore a consensus recommendation has been made informed by the natural history of menstrual cycles and ovulation in adolescents (aged < 18 years), building on the recommendations generated in 2018 and peer reviewed internationally.

Given the lack of evidence identified on systematic review, a narrative review was completed for the 2023 guideline. 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.[19] The average adult menstrual cycle is 28 days, ranging from 24 – 35 days,[20] The majority of irregular cycles may be ovulatory two years post-menarche,[20-23] with 80% of cycles being within 21 - 45 days.[21,23-25] By the third post-menarcheal year, 95% of cycles fall into this range, however cycles can remain irregular until the fifth year.[26,27]

A significant remaining controversy here related to the application identifying 95th centiles of cycle duration as abnormal in generally poorly screened populations which include those with PCOS. Using this percentile to define a diagnostic feature (e.g. menstrual cycles), unrelated to clinical associations and implications, is a crude and simplistic approach. This challenge was considered here and the body of literature on normal menstrual cycles reviewed to identify the 85th to 90th percentile, pending appropriate cluster analysis and longitudinal clinical follow-up data. This approach was approved by the Paediatric committee (Appendix III).

Regular ovulatory cycle onset is also related to age at menarche.[28] 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.[28] At age 15, more than 50% of girls who are oligo-amenorrhoeic remain so at age 18 [29]. 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 up to perimenopause.

Recommendations

1.1		Irregular cycles and ovulatory dysfunction	
1.1.1	**CR**	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 these PCOS Guidelines.	❖❖❖❖
1.1.2	**PP**	The mean age of menarche may differ across populations.	
1.1.3	**PP**	In adolescents with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient and their parent/s or guardian/s, considering diagnostic challenges at this life stage and psychosocial and cultural factors.	
1.1.4	**PP**	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.	
1.1.5	**PP**	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	

Justification

Whilst no evidence was found to specifically address this question in PCOS, recommendations are informed by the best available evidence on normal adolescent menstrual patterns and ovulatory function and by previously available guidelines, multidisciplinary expertise and consumer perspectives. The GDG and the paediatric endocrine and gynecology expert panel, carefully considered the available literature, the international feedback from 2018 peer review, the validation of the 2018 recommendations in a longitudinal cohort study, 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 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. These recommendations align to the 2018 guideline and have been validated in a long-term study from birth until the age of 30, showing application of these refined criteria avoided overdiagnosis in adolescents and identified those most at risk of long-term weight gain warranting diagnosis and prevention.[30]

1.2 Biochemical hyperandrogenism

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

Clinical need for the question

Hyperandrogenism is a key diagnostic feature of PCOS affecting between 60-100% with the condition with both clinical (hirsutism, female pattern hair loss and acne) and biochemical hyperandrogenism. Hyperandrogenism is challenging to assess with variation by methods, ethnicity and confounding factors including excess weight and life stage. Assessment of biochemical hyperandrogenism has been controversial in terms of optimal type of androgens and assays, definition of normal ranges, overlaps between 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 are commonly used,[31] as is free androgen index [FAI = 100 x (total testosterone/sex hormone binding globulin (SHBG)]. Direct testosterone assays have significant deficiencies in accuracy, which limit use. As per the last guideline, standardised testosterone measurements that are accurate, reliable and comparable over time are essential.[32,33] 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

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.2.

Serum total testosterone: Fifteen studies were identified with two using radioimmunoassay, eight immunoassay and five mass spectrometry. Five were moderate and others were high risk of bias. Eleven were included in meta-analysis.

Serum androstenedione: Nine studies were identified with two studies using radioimmunoassay, four using immunoassay and three studies using mass spectrometry with two of moderate risk of bias, and the rest of high risk of bias. Five studies were included in the meta-analysis

Serum dehydroepiandrosterone sulfate (DHEAS): Six studies were identified and all used immunoassay except one used mass spectrometry. Two studies were moderate risk of bias, while the rest were high risk of bias. Five were included in the meta-analysis.

FAI: Eleven studies were identified and two studies used radioimmunoassay, six used immunoassay and the other three used mass-spectrometry. Three were moderate risk of bias and the rest were all high risk. Nine were included in the meta-analysis.

Serum free testosterone: Six studies were identified and all were included in the meta-analysis. These studies used immunoassay and mass spectrometry and three studies were of high risk of bias, whilst the rest were moderate risk.

Serum Dihydrotestosterone (DHT): Only one study examined DHT for diagnosing hyperandrogenism using immunoassay, which was high risk of bias.

Serum SHBG: Four studies using radioimmunoassay, one with a high risk of bias and three moderate risk.

Salivary testosterone: One study examined this option.

Meta-analyses results showed that calculated free testosterone and calculated FAI had the best sensitivity and specificity to diagnose biochemical hyperandrogenism compared with all other tests. For both tests, sensitivity was greater than 80%. Specificity was higher for calculated free testosterone (93.3%, 0.799-0.980) than calculated FAI (64.0%, 0.767-0.924). Serum total testosterone, androstenedione and DHEAS had similar sensitivity around 70% and specificity around 75-85%. Salivary testosterone and DHT only had one study each included with no meta-analysis. All outcomes had very low certainty.

Recommendations

1.2		Biochemical hyperandrogenism	
1.2.1	EBR	Healthcare professionals should use total and free testosterone to assess biochemical hyperandrogenism in the diagnosis of PCOS; free testosterone can be estimated by the calculated free androgen index.	❖❖❖❖ ⊕◯◯◯
1.2.2	EBR	If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and greater age associated decrease in DHEAS.	❖❖❖ ⊕◯◯◯
1.2.3	EBR	Laboratories should use validated, highly accurate tandem mass spectrometry (LC-MS/MS) assays for measuring total testosterone and if needed, for androstenedione and DHEAS. Free testosterone should be assessed by calculation, equilibrium dialysis or ammonium sulfate precipitation.	❖❖❖❖ ⊕◯◯◯
1.2.4	EBR	Laboratories should use LC-MS/MS assays over direct immunoassays (e.g. radiometric, enzyme-linked, etc.) for assessing total or free testosterone, which have limited accuracy and demonstrate poor sensitivity and precision for diagnosing hyperandrogenism in PCOS.	❖❖❖❖ ⊕⊕◯◯
1.2.5	PP	For the detection of hyperandrogenism in PCOS, the assessment of biochemical hyperandrogenism is of greatest value in patients with minimal or no clinical signs of hyperandrogenism (i.e. hirsutism).	
1.2.6	PP	It is very difficult to reliably assess for biochemical hyperandrogenism in women on the combined oral contraceptive pill (COCP) as the pill increases sex hormone-binding globulin and reduces gonadotrophin-dependent androgen production. If already on the COCP, yet assessment of biochemical androgens is imperative, the pill should be withdrawn for a minimum of three months and contraception should be managed otherwise during this time.	
1.2.7	PP	Repeated androgen measures for the ongoing assessment of PCOS in adults have a limited role.	
1.2.8	PP	In most adolescents, androgen levels reach adult ranges at 12-15 years of age.	
1.2.9	PP	If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing's syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.	

1.2.10	**PP**	Reference ranges for different methods and laboratories vary widely, and are often based on an arbitrary percentile or variances of the mean from a population that has not been fully characterised and is highly likely to include women with PCOS. Normal values should be determined either by the range of values in a well characterised healthy control population or by cluster analysis of general population values.
1.2.11	**PP**	Laboratories involved in androgen measurements in females should consider: • determining laboratory normal values by either the range of values in a well characterised healthy control population or by cluster analysis of the values of a large general population • applying the most accurate methods where available • using extraction/chromatography immunoassays as an alternative to mass spectrometry only where adequate expertise is available • future improvements may arise from measurement of 11-oxygenated androgens, and from establishing cut-off levels or thresholds based on large-scale validation in populations of different ages and ethnicities.

Justification

Total testosterone alone can identify 20-30% of women with PCOS as having biochemical hyperandrogenism, while measures of laboratory calculated unbound or free testosterone will identify 50-60%. High quality assays provide a more accurate diagnosis and the additional associated cost was deemed important and justified after considering all elements of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. Access issues were acknowledged. Additional evidence available for this guideline update, showed differential sensitivity and specificity in PCOS diagnosis across the relevant androgens and resulted in clarification of recommended biochemical androgen assessment. 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). Previous recommendations are strengthened here. A strong recommendation for the option is provided for 1.2.1, even though the certainty of the evidence was very low, due to the nature of the appropriate study design being observational, which unduly impacted on evidence certainty ratings. Clarity around simplified and standardised assessment for biochemical hyperandrogenism provided by the guideline is likely to be valued.

1.3 Clinical hyperandrogenism

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

Clinical need for the question

Signs and symptoms of severe androgen excess can result in virilisation (e.g. male pattern balding, severe hirsutism, and clitoromegaly) and masculinisation, which are rare in PCOS. Clinical evidence of mild to moderate androgen excess is more common including hirsutism, acne, and female pattern hair loss. The interrelationships of these clinical features remain unclear, with variation 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 therapy can be significant. Given the fundamental role of hyperandrogenism in diagnosis,[34,35] and the adverse impact on quality of life,[36] this question was prioritised.

Summary of systematic review evidence

Seven studies of moderate risk of bias reported on markers of clinical hyperandrogenism to detect PCOS.[37-43] Three studies reported sensitivity and specificity of Ferriman Gallwey score (mFG) ≥ 8 against total testosterone and free testosterone;[37,40,42] however, meta-analysis was not possible due to heterogeneity. Two studies reported sensitivity and specificity of mFG ≥ 8 against DHEAS;[37,42] however, meta-analysis wan't possible. Of the seven studies, six reported hirsutism, three acne and one female pattern hair loss. Two studies showed that hirsutism in those with PCOS was associated with a higher level of biochemical hyperandrogenism than in those with PCOS without hirsutism.[37,42] Evidence for all outcomes was very low certainty. Further details on this evidence can be found in the technical report in Section 1.3.

Recommendations

1.3		Clinical hyperandrogenism	
1.3.1	EBR	The presence of hirsutism alone should be considered predictive of biochemical hyperandrogenism and PCOS in adults.	❖❖❖ ⊕○○○
1.3.2	EBR	Healthcare professionals could recognise that female pattern hair loss and acne in isolation (without hirsutism) are relatively weak predictors of biochemical hyperandrogenism.	❖❖❖❖ ⊕○○○
1.3.3	CR	A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, female pattern hair loss and hirsutism in adults, and severe acne and hirsutism in adolescents.	❖❖❖❖
1.3.4	CR	Healthcare professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism and should consider the reporting of unwanted excess hair growth and/or female pattern hair loss as being important, regardless of apparent clinical severity.	❖❖❖
1.3.5	CR	A modified Ferriman Gallwey score (mFG) of 4–6 should be used to detect hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment.	❖❖❖❖

1.3.6	**CR**	Healthcare professionals should consider that the severity of hirsutism may vary by ethnicity but the prevalence of hirsutism appears similar across ethnicities.	❖❖❖
1.3.7	**PP**	Healthcare professionals should: • be aware that standardised visual scales are preferred when assessing hirsutism, such as the mFG scale in combination with a photographic atlas • consider the Ludwig or Olsen visual scales for assessing female pattern hair loss • note that there are no universally accepted visual instruments for assessing the presence of acne • recognise that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity • appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination • be aware that only terminal hairs need to be considered in defining hirsutism, and these can reach > 5 mm if untreated, vary in shape and texture and are generally pigmented • note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis • monitor clinical signs of hyperandrogenism, including hirsutism, acne and female pattern hair loss, for improvement or treatment adjustment during therapy.	

Justification

While some studies compare clinical markers of hyperandrogenism (hirsutism, acne, and female pattern hair loss) to biochemical hyperandrogenemia, the variability in androgens assessed, methodologies used, normative values for hyperandrogenemia, and in cut-offs values for hirsutism, as well as the paucity of universally accepted scales for acne, add limitations to the recommendations that can be made. 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 overestimated 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 is of most relevance to those affected by PCOS and understanding the significant personal impact, using a standardised assessment enabling treatment for clinical hyperandrogenism, is likely to be valued. Previous recommendations are strengthened here.

1.4 Ultrasound and polycystic ovarian morphology

What are the most effective ultrasound criteria to diagnose PCOS?

Clinical need for the question

Polycystic ovarian morphology (PCOM) was incorporated into the diagnosis of PCOS in 2003 in the Rotterdam criteria, based on associations with clinical and endocrine features of the condition.[44] This introduced greater heterogeneity into PCOS with limited data on natural history, prompting calls for better characterisation and more research.[45] The definition of PCOM in the Rotterdam criteria was 12 or more follicles measuring 2-9 mm throughout the entire ovary or an ovarian volume ≥ 10 ml.[18] The Rotterdam criteria were consensus based, underpinned by a single report on sensitivity and specificity in PCOS compared to controls. Also, two decades have seen ultrasound technology advance, yet variable operator skills and lack of standard reporting persist, long with, 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.[46] The term 'cystic' is a misnomer referring to arrested follicles (not cysts). Also, identification of PCOM is neither sufficient nor required for the diagnosis of PCOS and identification of PCOM alone can lead to overdiagnosis. Diagnosis of PCOS mandates not only PCOM, but accompanying features of hyperandrogenism and/or ovulatory dysfunction. 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 important in the accurate diagnosis of PCOS.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.4.

Twenty eight studies of moderate to high risk of bias[47-74] and one study of low risk of bias,[75] reported the diagnostic accuracy of different ovarian morphology parameters to diagnose PCOS. Four of the 29 studies were in adolescents. 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. For follicle number per ovary (FNPO) there were 21 studies with 4975 adults, demonstrating a sensitivity of 70-94% and specificity of 70-100% as an ultrasound diagnostic criterion to diagnose PCOS. 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 follicle number per cross-section (FNPS) there were 11 studies with 2516 adult participants demonstrating a sensitivity of 21-94% and specificity of 60-100% as an ultrasound diagnostic criterion to diagnose PCOS. For ovarian volume, there were 29 studies with 6786 participants demonstrating a sensitivity of 21-94% and specificity of 60-100% as an ultrasound criterion to diagnose PCOS. There is insufficient evidence to suggest use of other ultrasound parameters including ovarian area; maximum number follicles in a single sonographic plane; 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.

Recommendations

1.4		Ultrasound and polycystic ovarian morphology	
1.4.1	EBR	Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOM) in adults.	❖❖❖❖ ⊕⊕○○
1.4.2	EBR	Follicle number per ovary (FNPO), follicle number per cross-section (FNPS) and ovarian volume (OV) should be considered accurate ultrasound markers for PCOM in adults.	❖❖❖❖ ⊕⊕○○
1.4.3	CR	PCOM criteria should be based on follicle excess (FNPO, FNPS) and/or ovarian enlargement (OV).	❖❖❖❖
1.4.4	CR	Follicle number per ovary (FNPO) ≥ 20 in at least one ovary should be considered the threshold for PCOM in adults.	❖❖❖❖
1.4.5	CR	Ovarian volume (OV) ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in at least one ovary in adults should be considered the threshold for PCOM if using older technology or image quality is insufficient to allow for an accurate assessment of follicle counts throughout the entire ovary.	❖❖❖❖
1.4.6	PP	There are no definitive criteria to define polycystic ovary morphology (PCOM) on ultrasound in adolescents, hence it is not recommended in adolescents.	
1.4.7	PP	When an ultrasound is indicated, if acceptable to the individual, the transvaginal approach is the most accurate for the diagnosis of PCOM.	
1.4.8	PP	Transabdominal ultrasound should primarily report ovarian volume (OV) with a threshold of ≥ 10 ml or follicle number per section (FNPS) ≥ 10 in either ovary in adults given the difficulty of assessing follicle counts throughout the entire ovary with this approach.	
1.4.9	PP	In patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for PCOS diagnosis.	
1.4.10	PP	Thresholds for PCOM should be revised regularly with advancing ultrasound technology, and age-specific cut-off values for PCOM should be defined.	
1.4.11	PP	There is a need for training in careful and meticulous follicle counting per ovary and clear standardised protocols are recommended for PCOM reporting on ultrasound including at a minimum: • last menstrual period (or stage of cycle) • transducer bandwidth frequency • approach/route assessed • total number of 2–9 mm follicles per ovary • measurements in three dimensions (in cm) or volume of each ovary • other ovarian features and/or pathology including ovarian cysts, corpus lutea, dominant follicles (≥ 10 mm) (which should not be included in ovarian volume calculations) • reliance on the contralateral ovary FNPO for diagnosis of PCOM, where a dominant follicle is noted • uterine features and/or pathology including endometrial thickness and pattern.	

Justification

In adolescents, it was recognised that the data in young women with a gynaecological age of < 8 years (< 8 years after menarche) are inadequate, that peak ovarian maturity has not yet been reached, anti-mullerian levels are still rising 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 overdiagnosis 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. Inconvenience, access and discomfort were all considered. 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, however this recommendation is limited to the role of ultrasound in PCOS diagnosis.

In adults, ultrasound is not required for diagnosis of PCOS in those with features of hyperandrogenism and ovulatory dysfunction, who already meet PCOS diagnostic criteria. For those with only one diagnostic feature of PCOS, the recommendation to use ultrasound and rely on FNPO as the key diagnostic criteria for PCOM 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 and considered by the GDG experts, especially the limited relevance of the 95th centile cut-offs in determining abnormal FNPO. Previous recommendations are strengthened here. These recommendations also recognise the optimal ultrasound approach, technological ultrasound advances, variability in availability of newer technologies and aim to improve training and standardise reporting. These recommendations are likely to improve the reliability of assessing and reporting FNPO and to provide for more accurate reporting of PCOM in the diagnosis of PCOS. Importantly, they may also limit use and costs of ultrasound, considering inconvenience and accessibility issues.

1.5 Anti-mullerian hormone in the diagnosis of PCOS

Is anti-mullerian hormone effective for diagnosis of PCOS?

Is anti-mullerian 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-mullerian hormone (AMH) has been proposed as an alternative marker of PCOM. AMH is a polypeptide of the transforming growth factor beta (TGF-B) 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.[76,77] Strong correlations have been demonstrated between circulating AMH levels and antral follicle count on ultrasound in PCOS. However, current literature reveals significant heterogeneity and the diagnostic value of serum AMH has been unclear and controversial.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.5.

Overall, 53 new studies were included in the systematic review, in addition to the 28 studies included in the previous search for the guideline in 2018. In total, 62 studies were included in meta-analysis in adults and 11 studies for adolescents. Six studies addressing AMH as a substitute for PCOM in adults were included. Two recent meta-analyses were also included in the systematic review.

Included studies determined the diagnostic test accuracy of AMH for PCOS or for PCOM. Hierarchical random effects models combined the estimates of sensitivity and specificity. The bivariate model was used, which focusses on estimation of a summary point. Pooled analysis showed a sensitivity and specificity of 0.66 (0.58-0.73) and 0.78 (0.71-0.83) respectively in adolescents (n=11 studies) for the use of AMH for PCOS diagnosis. In adults, pooled sensitivity was 0.79 (0.76-0.82) and pooled specificity was 0.87 (0.84-0.89) for AMH in PCOS diagnosis. Excluding studies with high risk of bias, did not change the results.

Further, the pooled sensitivity and specificity did not change between studies where PCOM was excluded from the control group and studies where PCOM was not excluded. Pooled sensitivity and specificity were significantly different between automated immunoassays (n=13), Elecsys immunoassays (n=10) and enzyme-linked immunosorbent assays (ELISAs), except the high sensitivity assay (n=34), with pooled sensitivity ranging from 0.74 to 0.82 and pooled specificity ranging from 0.85 to 0.88. Only six studies investigated the diagnostic accuracy of AMH as a substitute for PCOM in adults. A large heterogeneity exists between the studies (I^2=93% for sensitivity and I^2=76% for specificity). The random effects model revealed a pooled sensitivity of 0.80 (0.72-0.86) and pooled specificity of 0.84 (0.79-0.88).

The included studies identified different AMH thresholds from their ROC curves. In adolescents, there were 10 relevant studies showing an area under ROC of AMH for diagnosis of PCOS of 0.58-0.88. The threshold ranges from 25 to 99 pmol/l. In adults, there are 53 relevant studies showing an area under ROC of AMH for diagnosis of PCOS of 0.58-0.99. The threshold ranges from 8.5-59 pmol/l. Factors influencing these thresholds include the use of different AMH assays, differences in age or BMI and whether PCOS or PCOM was excluded in the control population.

Recommendations

1.5 #		Anti-mullerian hormone in the diagnosis of PCOS	
1.5.1	EBR	Serum anti-mullerian hormone (AMH) could be used for defining PCOM in adults.	❖❖❖ ⊕⊕⊕◯
1.5.2	EBR	Serum AMH should only be used in accordance with the diagnostic algorithm, noting that in patients with irregular menstrual cycles and hyperandrogenism, an AMH level is not necessary for PCOS diagnosis.	❖❖❖❖ ⊕⊕⊕◯
1.5.3	EBR	We recommend that serum AMH should not be used as a single test for the diagnosis of PCOS.	❖❖❖❖ ⊕⊕⊕◯
1.5.4	EBR	Serum AMH should not yet be used in adolescents.	❖❖❖❖ ⊕⊕⊕◯
1.5.5	PP	Either serum AMH or ultrasound may be used to define PCOM; however, both tests should not be performed to limit overdiagnosis.	
1.5.6	PP	Laboratories and healthcare professionals need to be aware of factors that influence AMH in the general population including: • age: Serum AMH generally peaks between the ages of 20-25 years in the general population • body mass index (BMI): Serum AMH is lower in those with higher BMI in the general population • hormonal contraception and ovarian surgery: Serum AMH may be suppressed by current or recent COCP use • menstrual cycle day: Serum AMH may vary across the menstrual cycle.	
1.5.7	PP	Laboratories involved in AMH measurements in females should use population and assay specific cut-offs.	

Justification

Although serum AMH levels in adolescent and adults with PCOS, are significantly higher than those without PCOS in all studies, there are overlaps between the two groups, especially in adolescents. The variations among studies may be partially related to the AMH assays used, the population and the characteristics of women with PCOS studied. AMH assays have improved over time, and the assays were found to be effective and hence a new recommendation on the role of AMH assays was made in adults only. In adolescents (10 to 19 years of age), specificity and accuracy are limited, therefore AMH is not recommended. It should be noted that the use of AMH should be in accordance with the diagnostic algorithm, with either serum AMH or ultrasound being used alone to define PCOM as performing both tests together may contribute to overdiagnosis. This will result in a significant change in clinical practice. It was heralded in the last Guideline as an area of rapidly evolving evidence and in the current guideline the evidence is now strong enough to warrant recommendation. This change in practice offers women low cost, more convenient options without evidence of increasing overdiagnosis. A conditional recommendation for the option is provided for 1.5.1 even though certainty of evidence is moderate, due to the current lack of consensus on specific cut-offs for AMH.

1.6 Ethnic variation

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

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. Nonetheless, 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. With 60% of the world's population of broad Asian ethnicity, and high prevalence and impacts noted at lower weight in these populations, this clinical question was prioritised. Aligned to this, given Australian government funding, and to the high metabolic risk in this population, there was a focus on Indigenous Australian populations.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.6.

Cross-sectional and cohort studies explored prevalence of PCOS among adults globally, from different world regions, and different ethnicities. World regions included Western Pacific, Eastern Mediterranean, South East Asians, the Americas and the European regions, aligned to WHO. Ethnicities included Black or African American and American, European South/North East Asian, Australian Indigenous, Polynesian, North African and Middle Eastern Southern and Central Asian, South American, Central American and Hispanic North American. Studies using ICD codes to diagnose PCOS and studies reporting on cumulative incidence or age adjusted prevalence rates were excluded from the meta-analysis.

Pooled prevalence using Rotterdam criteria among all adult females (95% CI) was 11.77% (10.39%, 13.15%) across 81 studies on world region and 38 studies on ethnicities. When studies reported their prevalence according to several criteria, each of their results were included in the analysis. A sensitivity analysis was generated by Rotterdam criteria. If we exclude these results, the prevalence stays the same.

Two included studies with moderate and high risk of bias, examined the prevalence of PCOS among Australian Indigenous adult women. Using NIH criteria, the prevalence was 16% (11-20%), suggesting higher prevalence. The limited evidence available warrants further investigation of the burden of PCOS in Indigenous women.

Recommendations

1.6 #		Ethnic variation	
1.6.1	**EBR**	Healthcare professionals should be aware of the high prevalence of PCOS in all ethnicities and across world regions, ranging from 10-13% globally using the Rotterdam criteria.	❖❖❖❖ ⊕⊕○○
1.6.2	**EBR**	Healthcare professionals should be aware that PCOS prevalence is similar across world regions and ethnicities, but may be higher in South East Asian and Eastern Mediterranean regions.	❖❖❖❖ ⊕⊕○○
1.6.3	**PP**	Healthcare professionals should be aware that the presentation of PCOS may vary across ethnic groups.	

Justification

Studies included used unselected, community representative populations. Multiple diagnostic criteria were considered including the Rotterdam criteria. World regions were reported but there were no eligible studies from Africa. Ethnicity was often poorly reported and authors were contacted to verify ethnicity. Ethnic differences in prevalence appear limited, however meta-analysis involves aggregated data, making it difficult to directly compare differences in prevalence between groups. Individual patient data meta-analysis will be required to achieve this in future. However, the current recommendation here is based on pooled results from world regions to include higher number of studies and larger sample sizes. Previous recommendations were strengthened here.

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 in the general population. 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.[44] However, the criteria for diagnosis change naturally with age impacting on presentation and presenting challenges in diagnosis. Overall, it is acknowledged that there is inadequate evidence of the long-term natural history of PCOS and the manifestations of PCOS after menopause remain unclear pending better longitudinal studies. This question was prioritised given the uncertainty in assessment and diagnosis at this life stage leads to confusion for healthcare 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 however a narrative review was completed. With aging, changes occur in all three diagnostic criteria. Menstrual cycles become more regular in PCOS.[78-80] Ovarian volume and follicle number decrease longitudinally in PCOS and control women. A cross-sectional study of premenopausal women with PCOS (up to age 39) reported that the proportion of women with infrequent menstruation or amenorrhoea increased with age.[81] Ovarian volume has been demonstrated to decrease with age in the general population.[82] Using cross-sectional data, ovarian volume and follicle number decrease in those with and without PCOS, but the decrease in ovarian volume is less pronounced in women with PCOS. Aging women with PCOS and regular cycles have a lower follicle count than those with irregular cycles.[83] 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.[49]

There is inconsistent evidence on whether postmenopausal women with PCOS have higher androgen levels compared to non-PCOS controls. Case-control studies have previously reported that postmenopausal women with PCOS have higher 17-hydroxyprogesterone, androstenedione, DHEAS, total testosterone, FAI and lower SHBG baseline levels than women without PCOS.[84,85] In one study, only DHEAS and androstenedione remained higher in women aged more than 50 with PCOS compared to women without PCOS after adjustment for BMI.[86] However, in a 32-year follow-up study, there was no difference in SHBG, DHEAS, total/free testosterone, androstenedione or FAI between controls and cases at age 80.[87] It should be noted that androgen assays are unreliable in women with poor precision with all assays at low testosterone levels.[88]

Postmenopausal women with PCOS report more hirsutism than controls.[85,87] Little is known about alopecia in this group. 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 in PCOS compared to controls.[89] Women with PCOS have a later menopause compared to women with no history of PCOS (HR 0.44, 95% CI 0.28-0.71).[90] Mean age of natural menopause in PCOS has been reported at 51.4[91] and 53.3 years,[92] compared to 49.7[91] and 49.3 years in controls.[92]

Recommendations

1.7		Menopause life stage	
1.7.1	CR	A diagnosis of PCOS could be considered as enduring/lifelong.	❖❖❖
1.7.2	CR	Healthcare professionals could consider that both clinical and biochemical hyperandrogenism persist in the postmenopause for women with PCOS.	❖❖❖
1.7.3	CR	PCOS diagnosis could be considered postmenopause, if there is a past diagnosis, or a long-term history of oligo-amenorrhoea with hyperandrogenism and/or PCOM, during the earlier reproductive years (age 20-40).	❖❖❖
1.7.4	CR	Further investigations should be considered to rule out androgen-secreting tumours and ovarian hyperthecosis in postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism.	❖❖❖

Justification

Consensus recommendations were 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. An additional recommendation was added here on the acknowledgement that PCOS has features that are enduring including cardiovascular risk. This recommendation was also considered important by those affected with PCOS who often struggle with the perception of the condition as being entirely focused on reproductive age and function. Evidence for differences in biochemical hyperandrogenism between women with and without PCOS in the postmenopause is inconsistent. The importance of excluding other diagnoses in cases of significant hyperandrogenism was recognised. These recommendations align with the 2018 guidelines, with an emphasis on research to provide clarity on postmenopausal PCOS features.

1.8 Cardiovascular disease risk

Are women with PCOS at increased risk for cardiovascular disease?

Clinical need for the question

Cardiovascular disease (CVD) remains one of the leading causes of death in women with any condition further increasing CVD risk, having 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. The primary challenge here is lack of quality longitudinal studies of well-defined cohorts with and without PCOS, given that CVD generally manifests later in life. Existing cohort studies have poorly defined PCOS status and a focus on younger women,[93] short follow-up or on CVD risk factors, rather than clinical CVD events, making determination of CVD risk in PCOS more challenging. It is well established that metabolic syndrome and CVD risk factors[94,95] are clearly increased in PCOS and that cardiovascular health overall needs to be considered, however the risk of CVD events remains uncertain, with this question prioritised by healthcare professionals and those affected by PCOS.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.8.

Outcomes studied included composite CVD, composite ischaemic heart disease, myocardial infarction (MI), stroke and cardiovascular mortality captured as odds ratios (OR), incident rate ratios (IRR), and hazard ratios (HR). Evidence certainty was rated as very low to low, as studies were observational, reflecting an inherent limitation of study quality assessment which is designed primarily for RCTs.

Composite CVD: Ten studies reported prevalence or OR of composite CVD in women with and without PCOS and were included in the meta-analysis, all with moderate risk of bias. These studies involved 489071 women, with an OR of 1.68 (1.26–2.23). Nine studies reported longitudinal outcomes of composite CVD, all moderate risk of bias, with eight included in the meta-analysis for incidence rate ratios (analysis A: IRR 1.17, 0.91–1.50; analysis B: IRR 1.43, 1.18–1.73), and five for HR 1.01, 0.66–1.53). All evidence was of low to very low certainty, due to observational study design.

Composite Ischaemic heart disease (IHD): Eleven studies reported prevalence or OR of composite IHD in women with and without PCOS. Three studies were excluded from the meta-analysis, with an OR in eight studies in 175341 women of OR of 1.48 (1.07-2.05) with low to very low certainty of evidence.

Myocardial infarction (MI): Nine studies report prevalence or OR of myocardial infarct in women with and without PCOS and were included in the meta-analysis. One was high risk and the rest were moderate risk of bias. These studies in 464024 women showed an OR of 2.5 (1.43-4.38) with low to very low certainty of evidence. Only three studies reported longitudinal myocardial infarction outcomes in women with and without PCOS (analysis A: IRR 1.29, 1=0.95–1.75; analysis B: IRR 1.31, 1.07–1.62; HR 0.91, 0.52–1.82) and they were of moderate risk of bias.

Stroke: Twelve studies report prevalence or OR of stroke in women with and without PCOS, with 10 included in the meta-analysis in 485365 women with an OR of 1.71 (2.20-2.44) with low to very low certainty of evidence. Five reported longitudinal stroke outcome (analysis A: IRR 1.09, 0.89–1.34; analysis B: 1.27, 0.93–1.75; HR 0.89, 0.45–1.79) and all were judged as moderate risk of bias.

Cardiovascular mortality: Four cohort studies reported cardiovascular mortality outcomes in women with and without PCOS and were moderate risk of bias. The IRR was 1.21 (1.08–1.88) with low certainty of evidence.

Overall women with PCOS had higher OR and/or incidence rate ratio for composite cardiovascular disease, composite ischemic heart disease, myocardial infarction, stroke and cardiovascular mortality. The level of evidence for these outcomes are of very low to low certainty only as they were generated from observational studies, however this is an inherent limitation of study quality assessment which is designed primarily for RCTs, not suitable to address this question.

Recommendations

1.8 #		Cardiovascular disease risk	
1.8.1	EBR	Women with PCOS should be considered at increased risk of cardiovascular disease and potentially of cardiovascular mortality, acknowledging that the overall risk of cardiovascular disease in premenopausal women is low.	❖❖❖ ⊕○○○
1.8.2	EBR	All women with PCOS should be assessed for cardiovascular disease risk factors.	❖❖❖❖ ⊕○○○
1.8.3	CR	All women with PCOS, regardless of age and BMI, should have a 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 hyperlipidaemia and additional risk factors or global cardiovascular risk.	❖❖❖❖
1.8.4	CR	All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities.	❖❖❖❖
1.8.5	CR	Funding bodies should recognise that PCOS is highly prevalent with multisystem effects including cardiometabolic disease, and should diversify and increase research support accordingly.	❖❖❖❖
1.8.6	CR	Cardiovascular general population guidelines could consider the inclusion of PCOS as a cardiovascular risk factor.	❖❖❖
1.8.7	CR	Healthcare professionals, women with PCOS and other stakeholders should all prioritise preventative strategies to reduce cardiovascular risk.	❖❖❖❖
1.8.8	PP	Consideration should be given to the differences in cardiovascular risk factors, and cardiovascular disease, across ethnicities (see 1.6.1) and age, when determining frequency of risk assessment.	

Justification

The high prevalence of cardiometabolic risk factors is well established including higher weight, impaired glucose tolerance, diabetes, dyslipidemia and metabolic syndrome in women with PCOS.[93,96-99] Consistently, the literature shows higher cardiovascular surrogate markers in PCOS. Here, with greater evidence available since the last guideline, we showed in a series of robust meta-analyses, that those with PCOS have higher OR and/or IRR for composite CVD, composite ischemic heart disease, myocardial infarction, stroke and cardiovascular mortality. This is a new recommendation based on best available evidence and will have implications for the broader understanding of this condition beyond reproductive health. This strengthens the recommendation for cardiovascular factor risk screening in this condition. Together, evidence on increased CVD risk factors, surrogate markers and most importantly the clinical CVD data presented here, all informed a strong recommendation from the expert GDG on CVD in PCOS. With cardiometabolic risk prioritised by those with PCOS and by healthcare professionals, and the contribution these recommendations will make to definitively understanding PCOS with broader manifestations than reproductive features, these recommendations will be valued by stakeholders. This also highlights the need for assessment of CVD risk in PCOS which needs to encompass assessment of weight, BMI, waist circumference, lipid profiles, blood pressure, glucose levels and lifestyle. With PCOS now confirmed as a high-risk group for CVD, consideration of PCOS in risk prediction and assessment tools for females, may also be warranted.

1.9 Impaired glucose tolerance and type 2 diabetes

Are women with PCOS at increased risk for impaired glucose tolerance, 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-offs for impaired glucose tolerance (IGT) and type 2 diabetes (T2D) remain controversial and somewhat arbitrary, however these cut-offs are informed by clinical sequelae; in IGT long-term health risks including CVD are increased and in T2D, both micro and macrovascular risks are increased. Increased risks of IGT and T2D[9] and underlying insulin resistance[100] have been demonstrated in PCOS on meta-analyses, independent of BMI. In the general population, screening protocols vary and the most reliable tests for screening and diagnosis [oral glucose tolerance tests (OGTT), fasting glucose or glycated haemoglobin (HbA1c)] remain controversial. These controversies extend to PCOS, with proposed benefits of an OGTT, requiring balance with increased inconvenience, cost and poor implementation, despite past guideline recommendations. 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.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.9.

Hyperglycaemia conditions: Outcomes studied included prevalence and incidence of T2D, impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Fifty-four studies were included in this systematic review of which 19 studies had high risk of bias and remaining had moderate to low risk of bias. Ten studies reported no cases of T2D in both PCOS and control groups and were excluded from the meta-analysis. These mainly included adolescents and younger adults (< 30 years old). Six studies from a recent systematic review and seven from a 2018 systematic review[101] were cohort studies with significantly variable follow-up of 2 to 24 years.

Pooled analysis of 41 studies showed a higher risk of T2D with an OR of 2.87 ([1.37, 6.01) with moderate certainty, 12 studies in IFG showed an OR of 3.18 [2.22, 4.56] with low certainty and 19 studies in IGT had an OR of 3.90 [2.44, 6.22] with moderate certainty among women with PCOS compared with controls. These results remained unchanged after excluding studies with a high risk of bias. Among age-matched studies, combined with those with no significant difference in age between PCOS and control groups, women with PCOS retained a higher risk of T2D, IFG and IGT. Among studies with no significant difference in BMI between PCOS and control groups, women with PCOS had a similar risk of IFG but higher risk of T2D (14 studies, OR 3.04 [2.06, 4.49]) and IGT (9 studies, 2.53 [1.27, 5.04]). In subgroup analysis, the risk of IFG in adolescents with PCOS was similar to controls, yet the risk of IGT was higher (5 studies, OR 4.87 [1.68, 14.06] and there was a likely increased risk of T2D, (6 studies 5.73 [0.93, 35.31]), however the latter was not significantly different. Studies that included both pre and post-menopausal adults, demonstrated a higher risk of T2D in PCOS compared with control groups. There were no studies investigating the risk of IFG, IGT and pre-diabetes focused on the older population.

Screening: Six studies were included in this systematic review, comparing other tests to OGTT as the reference tests. All studies suggested that OGTT was most accurate for the diagnosis of glucose abnormalities including T2D in PCOS, rather than fasting plasma glucose (FPG) and HbA1c. A cross-sectional study in premenopausal women with PCOS recommended that glycaemic disorders including T2D be screened by 2-hour (2-h) OGTT regardless of risk factors like BMI or family history of diabetes.[102] The advantages of OGTT in the diagnosis of T2D were supported by all remaining studies. None supported the other available tests for the screening of T2D in PCOS. Indeed, HbA1c is a relatively poor diagnostic marker of T2D in women with PCOS, whilst fasting plasma glucose is less accurate in predicting IGT and T2D; however combining both tests may reduce missed diagnosis.[103] Overall, results suggest that FPG or HbA1c cannot replace OGTT, which remains the preferred method of evaluating glycaemia in PCOS, with low certainty of evidence.

Recommendations

1.9		Impaired glucose tolerance and type 2 diabetes risk	
1.9.1	EBR	Healthcare professionals and women with PCOS should be aware that, regardless of age and BMI, women with PCOS have an increased risk of impaired fasting glucose, impaired glucose tolerance and type 2 diabetes.	❖❖❖❖ ⊕⊕◯◯
1.9.2	EBR	Glycaemic status should be assessed at diagnosis in all adults and adolescents with PCOS.	❖❖❖❖ ⊕⊕◯◯
1.9.3	CR	Glycaemic status should be reassessed every one to three years, based on additional individual risk factors for diabetes.	❖❖❖❖
1.9.4	CR	Healthcare professionals, women with PCOS and other stakeholders should prioritise preventative strategies to reduce type 2 diabetes risk.	❖❖❖❖
1.9.5	CR	Funding bodies should recognise that PCOS is highly prevalent, has significantly higher risk for diabetes and should be funded accordingly.	❖❖❖❖
1.9.6	CR	Diabetes general population guidelines should consider the inclusion of PCOS as an independent risk factor for diabetes.	❖❖❖❖
1.9.7	PP	Healthcare professionals, adults and adolescents with PCOS and their first-degree relatives, should be aware of the increased risk of diabetes and the need for regular glycaemic assessment.	
1.9.8	PP	Women with type 1 and type 2 diabetes have an increased risk of PCOS and screening should be considered in individuals with diabetes.	

		Glycaemic testing	
1.9.9	**EBR**	Healthcare professionals and women with PCOS should recommend the 75g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS, regardless of BMI.	❖❖❖❖ ⊕○○○
1.9.10	**EBR**	If an OGTT cannot be performed, fasting plasma glucose and/or glycated haemoglobin (HbA1c) could be considered, noting significantly reduced accuracy.	❖❖❖ ⊕○○○
1.9.11	**EBR**	An OGTT should be considered in all women with PCOS and without pre-existing diabetes, 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 could be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation.	❖❖❖ ⊕○○○
1.9.12	**PP**	Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and are not recommended in routine care (refer to 3.1.10).	

Justification

T2D risk factors significantly increase background population risk and prevalence of IGT and T2D. These are more prevalent in PCOS, independent of BMI, age and ethnicity. The evidence consistently shows an increased risk of hyperglycaemia across all measures and independent of BMI with generally moderate certainty. Hence the GDG recommended that screening was warranted in all adults with PCOS and in adolescents with additional risk factors at baseline. Screening tests include fasting glucose, HbA1c or OGTT. 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, based on evidence of comparisons between these tests. Frequency of testing should be a minimum of three yearly, informed by additional risk factors. Whilst the quality of evidence is low, the findings are consistent and support a weak recommendation for OGTT as the preferred tool for diagnosis of T2D in women with PCOS. Given the practical and logistical considerations (time, inconvenience, cost, accessibility) involved in performing OGTT for T2D diagnosis, there is a clear need for further research to compare alternative diagnostic strategies against the OGTT, which may need to incorporate a combination of parameters, such as fasting glucose and HbA1c, to simplify glycaemic evaluation in settings where regular OGTT may not be practical. Previous recommendations are strengthened here with increased evidence. A strong recommendation for the option is provided for 1.9.9, even though the certainty of the evidence was very low, due to the nature of the appropriate study design being observational, the highest level of study design for this type of clinical question, yet a design that is ranked as providing low levels of certainty of evidence.

1.10 Obstructive sleep apnea

Are women with PCOS at increased risk for obstructive sleep apnea?

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 is more common in those with higher weight, a common feature of PCOS. OSA prevalence among general adult populations varies across cohorts and is between 9-38%,[104] with half being minimally symptomatic. Unlike conditions such as hypertension and diabetes, where clinical sequelae are measurable at a particular cut-off point that informs treatment decisions, there is no established cut-off point of apnea hypopnea index, which warrants treatment. Treatment involves a personalised care plan that factors in symptomatology and disruptive impact of associated snoring, fatigue and quality of life (with a lack of evidence for prevention of other long term implications such as CVD), with treatment usually offered routinely to severe cases.[105,106] 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 and acceptability of device-based treatments such as continuous positive airway pressure (CPAP). Given the apparent increase in prevalence and the impact on fatigue and quality of life this question was prioritised.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.10.

Ten studies were included in the systematic review, of which eight were primary research studies conducted using a cross-sectional study design, and two were systematic reviews. The meta-analysis of primary studies included 280 women with PCOS compared to 662 women without PCOS. OSA was defined variably as (i) apnea hypopnea index (AHI) > 5, (ii) AHI > 5 + specific symptoms, or (iii) AHI > 10. Overall 38.9% and 3.3% women with and without PCOS had OSA respectively. Pooled analysis suggested that women with PCOS were nearly at nearly 10 times higher risk of OSA (AHI > 5 or AHI > 5 + specific symptoms or AHI > 10) compared to those without PCOS with an OR of 9.52 (3.90-23.26). The association was more profound when considering the more inclusive definition of OSA, AHI > 5, alongside symptoms) [17.95 (95% CI 6.17-52.22)]. The magnitude of effect estimate was relatively smaller when considering the more limited outcome definition, AHI > 5 only [3.90 (95% CI 1.63-9.34)]. In a subgroup analysis of women with BMI > 25 kg/m², there was a 7.1 times and 4.3 times higher risk of (i) AHI > 5 or AHI > 5 + symptoms or AHI > 10 and (ii) AHI > 5 among women with PCOS compared to women without PCOS respectively [OR: 7.10 (95% CI 2.13-23.65) and 4.29 (95% CI 1.75-10.52) respectively]. Certainty of evidence was moderate.

Recommendations

1.10		Obstructive sleep apnea	
1.10.1	EBR	Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea (OSA) compared to women without PCOS, independent of BMI.	❖❖❖❖ ⊕⊕⊕◯
1.10.2	EBR	Women with PCOS should be assessed for symptoms (i.e. snoring in combination with waking unrefreshed from sleep, daytime sleepiness or fatigue) and if present, screen with validated tools or refer for assessment.	❖❖❖❖ ⊕⊕⊕◯
1.10.3	PP	Simple obstructive sleep apnea screening questionnaires (such as the Berlin questionnaire, validated in the general population) can assist in identifying obstructive sleep apnea in women with PCOS, noting that diagnosis requires a formal sleep study.	
1.10.4	PP	Goals of treatment should target obstructive sleep apnea related symptom burden.	

Justification

Given the multiple studies and consistent evidence, which has advanced since the last guideline, showing a very high prevalence of OSA in PCOS, screening and identification of women with symptomatic OSA who may benefit from treatment is warranted. Recommendations are strengthened from the last guideline. Wide scale screening on the basis of unproven metabolic benefits of OSA treatment is not currently warranted. Resource implications of selective screening in symptomatic women were considered including clinician time and subsequent sleep studies if required. Ambulatory or in laboratory polysomnography in conjunction with clinical follow-up of the results and treatment planning may also not be universally accessible. In making the recommendations the potential challenges with accessibility were balanced with the potential to reduce symptoms of OSA and improve quality of life in PCOS.

1.11 Endometrial hyperplasia and cancer

Are women with PCOS at increased risk of endometrial cancer?

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 higher weight, and with potential influence from PCOS treatments. Pathophysiology is related to unopposed estrogen in the setting of anovulation and prevention is both important and feasible. Overall, given the prevalence and interrelated comorbidities between endometrial cancer and PCOS, this question was prioritised.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.11.

Fifteen studies were captured in the systematic review and meta-analysis for composite outcomes of endometrial cancer and/or endometrial hyperplasia in women with and without PCOS. Three were cohort studies, six were cross-sectional and six were case control studies. Nine were high risk of bias with two studies with low risk of bias, while four were moderate risk.

In all meta-analysis, women with PCOS had significantly increased composite endometrial cancer and/or hyperplasia [15 studies, OR 6.01 (3.38 – 10.70)] and higher odds of endometrial cancer [10 studies, OR 7.08 (4.05 – 12.38)] than women without PCOS. The quality of evidence of these outcomes was very low to moderate due to the observational design of included studies and evidence quality being upgraded for their large effect size.

Four longitudinal studies examined endometrial cancer in women with and without PCOS, two with low risk of bias and two high risk of bias. Outcomes were not suitable for meta-analysis. All longitudinal studies reported higher risk of endometrial cancer in women with than without PCOS. Only two studies reported on endometrial hyperplasia alone and their results were non-consistent.

Recommendations

1.11		Endometrial hyperplasia and cancer	
1.11.1	EBR	Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer.	❖❖❖❖ ⊕○○○
1.11.2	PP	Women with PCOS should be informed about the increased risk of endometrial hyperplasia and endometrial cancer, acknowledging that the overall chance of developing endometrial cancer is low, therefore routine screening is not recommended.	
1.11.3	PP	Long-standing untreated amenorrhea, higher weight, type 2 diabetes and persistent thickened endometrium are additional to PCOS as risk factors for endometrial hyperplasia and endometrial cancer.	
1.11.4	PP	Women with PCOS should be informed of preventative strategies including weight management, cycle regulation and regular progestogen therapy.	
1.11.5	PP	When excessive endometrial thickness is detected, consideration of a biopsy with histological analysis and withdrawal bleed is indicated.	

Justification

Associations between PCOS and endometrial cancer are complex, with many potential confounders. Women with PCOS have an increased risk of endometrial cancer premenopause, consistent with anovulation and increased prevalence of higher weight. Routine screening for endometrial cancer in PCOS is not recommended as absolute risk remains low, despite much higher relative risks in PCOS, hence clinician vigilance and awareness of increased risk is important. Previous recommendations are strengthened here with greater evidence. A strong recommendation for the option is provided for 1.11.1 even though the certainty of the evidence was very low due to the nature of the appropriate study design being mainly observational.

1.12 Risks in relatives

What is the risk of PCOS and cardiometabolic outcomes (CVD, T2D) in relatives of women with PCOS?

Clinical need for the question

Women with PCOS have a 1.9-fold increased risk of metabolic syndrome[95] and clustering of cardiovascular risk factors; however, the risk of metabolic complications in first-degree relatives of PCOS women is unclear.[107,108] Other studies showed that first-degree relatives of women with PCOS had higher rates of glucose intolerance, hypertension and hyperlipidaemia.[109,110]

Family studies suggest a 2.3-fold increased risk for T2D and a 1.4-fold increased risk for metabolic syndrome in fathers of women with PCOS[111] and a 3.9-fold increased risk for dyslipidaemia in brothers of women with PCOS.[112] Studies suggest a genetically defined, ovarian-independent, male cardiometabolic equivalent for PCOS.[113] PCOS propensity risk scoring was associated with higher weight, T2D, dyslipidaemia, coronary artery disease, androgenic alopecia, FAI and SHBG in men, with the effect mediated by BMI.[113]

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 1.12.

Thirty-one studies were included in the systematic review and 27 in the meta-analysis with 25 cross-sectional and six cohort studies. One had low risk of bias, one high and all others were judged as moderate risk of bias.

Metabolic syndrome: Six studies were suitable for meta-analysis and all were moderate risk of bias. Higher weight with a BMI > 30 kg/m²; had two studies suitable for meta-analysis and both were moderate risk of bias.

Hypertension had two studies suitable for meta-analysis that were of moderate risk of bias.

Diabetes; Three studies were suitable for meta-analysis and were moderate risk of bias.

PCOS: Two studies were suitable for meta-analysis and were moderate risk of bias.

When compared to first-degree relatives of controls, first-degree relatives of those with PCOS were more likely to suffer from metabolic syndrome, hypertension, diabetes and PCOS. The certainty of evidence for these outcomes was low due to the small number of studies resulting in serious imprecision, with exception of metabolic syndrome, which was of moderate due to larger numbers of studies.

On subgroup analysis, despite limited studies, fathers of women with PCOS were more likely to suffer from metabolic syndrome with an OR of 1.76 [1.33, 2.34], hypertension (4.19 [1.06, 16.56]) and diabetes (14.54 [2.83, 74.71]), while mothers of women with PCOS were more likely to suffer from metabolic syndrome (3.24 [1.35, 7.80]). Brothers of women with PCOS were more likely to suffer from metabolic syndrome but not sisters. Offspring of women with PCOS did not appear to have higher incidence of diabetes, excess weight or metabolic syndrome. These analyses were moderate to low quality due to low numbers of participants and different ages and the cross-sectional nature of a majority of the studies. Additionally, not all studies captured the outcome of diabetes and hypertension (particularly for siblings and children of women with PCOS). When analysing by subgroup, daughters and sisters of women with PCOS did not appear to be at risk of PCOS, however this was confounded by serious imprecision with low numbers of participants.

Recommendations

1.12 #		Risks in relatives	
1.12.1	**EBR**	Healthcare professionals could consider that fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension.	❖❖❖ ⊕◯◯◯
1.12.2	**PP**	The cardiometabolic risk in female first-degree relatives of women with PCOS remains inconclusive.	

Justification

This clinical question and associated recommendations are new to the 2023 guideline and reflect consumers' and health professionals' priorities. First-degree relatives of women with PCOS had a moderately increased risk of metabolic syndrome, including male first-degree relatives. Whilst there was a significantly increased risk of hypertension, IGT and T2D in first-degree relatives of women with PCOS, the quality of evidence was either low or very low. Studies looking specifically at sisters of women with PCOS did not find any significantly increased metabolic risks. In studies looking at daughters of women with PCOS, most were young adolescents, with some studies including pre-menarcheal daughters. More longitudinal studies with follow-up from infancy to adulthood are required to thoroughly capture the cardiometabolic risk for first-degree relatives of women with PCOS. Based on emerging evidence only, no routine recommendations are made for screening relatives in clinical practice.

Chapter Two

Prevalence, screening, and management of psychological features and models of care

		General principles
	PP	Psychological features are common and important component of PCOS that all health professionals should be aware of.
	PP	Funding bodies should recognise that PCOS is highly prevalent, has significantly higher psychological disorders which should be prioritised and funded accordingly.

2.1 Quality of life

In women with PCOS, what is the prevalence and severity of reduced quality of life?

Clinical need for the questions

Quality of life 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.[114,115] 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 as does the role of QoL assessment in clinical care and the optimal methods to assess QoL in PCOS.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 2.1.

In adults, a multitude of studies were identified with highly variable endpoints, reporting and populations studied. Most studies found that menstrual irregularity, weight and hirsutism were the most serious concerns followed by emotional wellbeing, on the PCOSQ. It is noted that generic patient-reported outcome measures underestimate the impact of PCOS on HRQoL. However, the majority of self-perceived health status literature around PCOS, concerns fertility specific or PCOS specific measurement scales, rather than generic scales and involves those recruited from infertility clinics. This limits comparisons and generalisability.

Three common questionnaires were used to assess QoL in adults.

SF36: Data from 8 studies were pooled in our meta-analysis. Results showed that women with PCOS scored lower than women without PCOS in all domains assessed with low to very low certainty of evidence: Physical component summary (Standard mean difference (SMD) -1.28, [-2.38, -0.17]); mental component summary (SMD -1.63 [-3.15, -0.11]); physical function (SMD -0.52 [-0.86, -0.17]); physical role function (SMD -0.74 [-1.28, -0.19]); bodily pain (SMD -0.80 [-1.52, -0.08]); general health (SMD -1.02 [-1.93, -0.11]); vitality (SMD -0.80 [-1.07, -0.53]); social function (SMD -0.77 [-1.68, 0.13]); emotional role (SMD -0.86 [-1.27, -0.46]); and mental health (SMD -1.56 [-2.66, -0.46]).

WHO QoL BREF: Data from 7 studies were pooled in our meta-analysis. Results showed that women with PCOS scored lower scores than women without PCOS in all domains assessed, with low certainty of evidence: Physical health (SMD -0.28 [-0.52, -0.04]); psychological health (SMD -0.46 [-0.79, -0.12]); social relationships (SMD -0.32 [-0.62, -0.03]); and environmental (SMD -0.34 [-0.73, 0.05]).

PCOSQ: Data from 3 studies were pooled in our meta-analysis. Except for total scores where there is no significant difference, women with PCOS scored lower scores than women without PCOS in other domains assessed with very low certainty of evidence: emotions (SMD -1.65 [-2.93, -0.36]), hirsutism (SMD -2.09 [-3.49, -0.70]); body weight (SMD -1.79 [-3.45, -0.13]); infertility (SMD -1.66 [-3.44, -0.11]); and menstrual disorders (SMD -1.63, [-3.45, 0.19]).

In adolescents the Pediatric Quality of Life Inventory (PedsQL) questionnaires have been applied in PCOS.[116] Meta-analysis in Physical Function, with a P=0.04 and a heterogeneity of 76%, suggests that scores for the PEDSQoL domain of Physical Function are lower in adolescents with PCOS compared to those without PCOS, with high heterogeneity. Measured by PedsQL, psychosocial function and overall QoL based on data in 2 studies, was not different in PCOS.[117,118]

Recommendations

2.1		Quality of life	
2.1.1	EBR	Healthcare professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults.	❖❖❖❖ ⊕⊕◯◯
2.1.2	PP	Women with PCOS should be asked about their perception of PCOS related symptoms, impact on quality of life, key concerns and priorities for management.	

Justification

HRQoL is reduced in women with PCOS across multiple dimensions, acknowledging high heterogeneity, challenges with appropriate tools and diverse populations studied to date. This diverse condition varies across the lifespan, and presentations and is influenced by sociocultural 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. Population level differences in dimension scores were unable to be assessed. 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, healthcare 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. The gaps in adequate data in adolescents were noted. Previous recommendations are strengthened here with increased evidence.

2.2 Depression and anxiety

In women with PCOS, what is the prevalence and severity of depression and anxiety?

Clinical need for the question

Anxiety and depression are both common among women, especially young women. Any increase in prevalence and severity is likely to have significant impact. 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.[119] A large international survey has shown that most women report that psychological issues are under-recognised in PCOS[118] 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. Effective, readily available psychological screening tools are available for clinical practice, yet uptake and recognition of psychological symptoms in PCOS appears limited internationally hence the GDG also considered tools used to assess depressive and anxiety symptoms.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further details can be found in the technical report in Section 2.2.

Overall, 80 studies were included in our systematic review examining depression and anxiety in PCOS.

Depression: 47 studies compared the prevalence of depression between women with and without PCOS of which only 7 studies were of low risk of bias and the remaining were either moderate or high risk of bias, All 47 studies were included in the meta-analysis on depression prevalence. 73 studies examined depression scores between women with and without PCOS. However, only 45 studies were suitable for meta-analysis, and only 4 of the included studies were of low risk of bias.

Reported prevalence of depression was up to 80.0% in women with PCOS in the included studies and there was a definitively higher risk of depression in PCOS (OR 2.59 [2.11-3.16]), compared to those without PCOS, with similar results in adults and adolescents with low to moderate certainty. Depressive scores were lower in PCOS at standard mean difference of 0.71 [0.55-0.87] overall, 0.76 [0.58-0.94] in adults and 0.41 [0.13-0.70] in adolescents with low certainty of evidence.

Anxiety: 27 studies compared prevalence of anxiety between those with versus without PCOS and all were included in the meta-analysis. Six studies were of low risk of bias and the remaining were either moderate or high risk of bias. 50 studies reported anxiety scores between groups, however, only 28 could be included in the meta-analysis. Nine of those were of low risk of bias and the rest were either moderate or high risk of bias.

Reported prevalence of anxiety was up to 76.7% in women with PCOS in our included studies and there was a definitively higher risk of anxiety in PCOS (OR 2.68 [2.08-3.44]) compared to those without PCOS, but no clear increase in the 3 studies in adolescents 0.92 [0.11-7.96] with low to moderate certainty of evidence. Anxiety scores were lower in PCOS at standard mean difference of 0.52 [0.36-0.68] overall, 0.58 [0.41-0.76] in adults and 0.23 [-0.19-0.64] in adolescents with very low to low certainty.

Screening: A narrative summary of the evidence on tools used to screen for depressive and anxiety symptoms in PCOS was completed capturing tools used in the systematic review on prevalence, other relevant sources of information for the general population, multidisciplinary GDG expertise and consumer perspectives. National guidelines do vary with US and UK guidelines recommending routine screening for common mental health disorders for all adults and adolescents, particularly with chronic physical health problems and in the perinatal period.[120-124] US guidelines conclude moderate benefit of depression screening in the general adult population.[123] Australian guidelines for the general population do not recommend routine screening, except during the perinatal period.[125,126] Mental health guidelines generally do not recognise PCOS as a condition with a high risk of depression and anxiety.

Recommendations

2.2		Depression and anxiety	
2.2.1	**EBR**	Healthcare professionals should be aware of the high prevalence of moderate to severe depressive symptoms and depression in adults and adolescents with PCOS and should screen for depression in all adults and adolescents with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.2.2	**EBR**	Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools.	❖❖❖❖ ⊕⊕⊕⊕
2.2.3	**CR**	If moderate or severe depressive or anxiety symptoms are detected, practitioners should further assess, refer appropriately or offer treatment.	❖❖❖❖
2.2.4	**PP**	Severity of symptoms and clinical diagnosis of depression or anxiety should guide management. The optimal interval for anxiety and depression screening is not known. A pragmatic approach could include screening at diagnosis with repeat screening based on clinical judgement, risk factors, comorbidities and life events, including the perinatal period. Screening for mental health disorders comprises assessment of risk factors, symptoms, and risk of self-harm and suicidal intent.	

Justification

Women with PCOS have definitively greater depressive and anxiety symptoms and prevalence of depression and anxiety compared to those without PCOS. These symptoms may be related to the distress associated with PCOS. Overall in PCOS, where prevalence and severity of depression and anxiety are higher, the GDG deemed that it was the responsibility of all healthcare professionals partnering with women with PCOS to understand the increased prevalence of and the impact of PCOS on psychological health. Routine screening for depressive and anxiety symptoms was recommended. In the context of PCOS, identification of psychological features and mental health disorders is crucial to address gaps in care identified by affected women, and to provide opportunities to improve wellbeing and QoL, facilitate appropriate referral and care and optimise engagement with lifestyle and preventive strategies. 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 whilst this aligns with the 2018 guideline and here is based on greater evidence, this is still expected to change practice. Time, resources and access issues were considered, yet with such definitive evidence on prevalence and severity, and based on consumer reports on priority and on lack of health professional engagement around the psychological features of PCOS, screening was recommended, aligned with international, broadly validated screening approaches in general populations. Reciprocally, the GDG also considered the balancing factors of risk of over-diagnosis of clinical depression and anxiety, which should also be avoided as well as potential for increases distress with another potentially stigmatising diagnosis. While the optimal timing and interval for screening is unknown, a pragmatic approach was recommended to screen all women and adolescents at the time of PCOS diagnosis and to use clinical judgment considering an individual woman's risk factors and life events to inform additional screening. Targeted screening during the antenatal and postnatal periods in PCOS is aligned with recommendations in the general population. Previous recommendations are strengthened here with increased evidence.

2.3 Psychosexual function

In women with PCOS, what is the prevalence and severity of psychosexual dysfunction?

Clinical need for the question

Psychosexual dysfunction refers to sexual problems or difficulties that have a psychological origin, based on cognitions and/or emotions such as depression, low self-esteem and negative body image.[127] These risk factors for psychosexual dysfunction are increased in PCOS and may impact QoL and relationships. 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 also affect psychosexual function in the general population although data in PCOS is limited.[128] Hence, this question was prioritised.

Summary of systematic review evidence

Given the extensive studies included and the meta-analyses, further information, including detailed references and study characteristics, can be found in the technical report in Section 2.3.

Twenty-seven studies compared psychosexual function in those with PCOS versus controls. Six studies were of low risk of bias and the remaining were moderate risk of bias.

Pooled analysis showed that there were no differences in sexual desire or pain between women with and without PCOS. However, those with PCOS had lower total sexual function in 17 studies (OR -2.42 [-3.26, -1.58]), sexual arousal in 14 studies (-0.36 [-0.59, -0.13]), lubrication (-0.47 [-0.75, -0.20]), orgasm (-0.35 [-0.52, -0.17]) and satisfaction. The four studies that employed the visual analogue scale tool could not be pooled due to using the same control group, but comparisons within each study showed that women with PCOS had reduced sex life satisfaction and perceptions of sexual attractiveness, while reporting a higher impact of excessive body hair on sexuality and greater difficulties in engaging in social contact due to appearance. No differences were found in the reported frequency of sexual thoughts and fantasies, importance of sexual satisfaction or pain during intercourse between women with PCOS and controls. Psychosexual dysfunction requires both altered psychosexual function and related distress. As no studies explored related distress, this limited evidence interpretation. Evidence for all outcomes was low certainty.

Recommendations

2.3		Psychosexual function	
2.3.1	CR	Healthcare professionals could consider the multiple factors that can influence psychosexual function in PCOS including higher weight, hirsutism, mood disorders, infertility and PCOS medications.	❖❖❖
2.3.2	CR	Permission to discuss psychosexual function should be sought noting that the diagnosis of psychosexual dysfunction requires both low psychosexual function, combined with related distress.	❖❖❖❖

Justification

The prevalence and severity of low psychosexual function and related distress is unclear in individuals with PCOS. Whilst those with PCOS score statistically significantly lower on psychosexual function questionnaires than those who do not have PCOS, clinical relevance is unclear as we lack the corresponding distress scores which are required to meet the criteria for psychosexual dysfunction. The impact of infertility, higher weight and other factors also cannot be ascertained on the current evidence and the independent impact of PCOS is unclear. Screening and assessment (after seeking permission to discuss) could be considered in sexually active women to facilitate appropriate intervention aiming to optimise sexual function, limit the social impact of PCOS and improve QoL. Future studies assessing psychosexual distress scores are needed.

2.4 Body image

In women with PCOS, what is the prevalence and severity of body image distress?

Clinical need for the question

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 and was prioritised.

Summary of systematic review evidence

Nine studies were included[129-136] from various countries and all were case-control design with moderate risk of bias. Multiple methods of measuring body image were used but the psychometric analyses generally related to the same construct, yet this limited meta-analyses. The broader body of evidence across tools and domains for each tool, informed these recommendations as captured in technical report in Section 2.4.

Recommendations

2.4		Body Image	
2.4.1	EBR	Healthcare professionals should be aware that features of PCOS can have a negative impact on body image.	❖❖❖❖ ⊕⊕○○

Justification

Given that negative body image in PCOS appears to be increased and may result in increased depression and poorer QoL, 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, keeping in mind that unnecessary use of extensive screening tools may be burdensome for women and healthcare professionals. 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 should also be considered in all clinical, health services and population health research in PCOS. Previous recommendations are strengthened here with increased evidence.

2.5 Eating disorders and disordered eating

In women with PCOS, what is the prevalence and severity of disordered eating?

Clinical need for the question

Diagnosable eating disorders include anorexia nervosa; bulimia nervosa, binge-eating disorder, other specified eating disorders, and unspecified eating disorders that do not meet the full criteria for any of the eating disorder diagnoses, but are clinically significant. 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 features. 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. Eating disorders and disordered eating risk factors and prevalence are increased in PCOS.[114] 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 hence this question was prioritised.

Summary of systematic review evidence

Given the extensive studies included and the multiple meta-analyses informing this question, further information, including detailed references and study characteristics, can be found in the technical report in Section 2.5.

Eleven cross-sectional studies reported the risk of at least one eating disorder including bulimia nervosa, binge eating disorder, anorexia nervosa, or night eating syndrome in adults with PCOS compared to controls. One study had a low risk of bias and ten studies had a moderate risk of bias. One study restricted inclusion to adolescents.

In the meta-analysis of all studies of adults, the odds of any eating disorder are increased in women with PCOS (OR 1.53 [1.29-1.83], moderate certainty), bulimia nervosa (1.34 [1.17-1.54], very low certainty), and binge eating (2.0 [1.18-3.72]. low to moderate), however other conditions were not increased in PCOS. Certainty in these results is moderate. One study reported the odds of any eating disorder in adolescents with PCOS and did not find an increased risk.

Recommendations

2.5		Eating disorders and disordered eating	
2.5.1	**EBR**	Eating disorders and disordered eating should be considered in PCOS, regardless of weight, especially in the context of weight management and lifestyle interventions (see sections 2.4 and 3.6).	❖❖❖ ⊕⊕◯◯
2.5.2	**PP**	If disordered eating or eating disorders are suspected, appropriately qualified practitioners should further assess via a full diagnostic interview. If an eating disorder or disordered eating is detected, appropriate management and support should be offered.	

Justification

Women with PCOS have a higher prevalence of experiencing many of the identified risk factors for eating disorders. They are at increased risk of excess weight, depression, anxiety, self-esteem and poor body image. They are also more likely to be highly motivated for weight loss and to be prescribed dietary restriction. The increased risk factors, the 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 PCOS. Many women with eating disorders are undiagnosed and unaware. 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, hence routine screening is not recommended, but heightened awareness is recommended. Previous recommendations are strengthened here with increased evidence.

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

2.6.1 What are the information, resource and education needs of women, adolescents, culturally and linguistically diverse groups and healthcare providers regarding PCOS?

Clinical need for the question

PCOS can involve diverse clinical features that change across the life course. In PCOS, there is a well-demonstrated gap and compelling need for improved information provision.[14,137,138] Internationally, there are reports of delayed diagnosis, inadequate information and variation in care. Provision of information also improves satisfaction with care and patient experience. PCOS is a common disorder worldwide with psychosocial impacts and cultural differences in perception of features such as hirsutism, infertility and other complications. Therefore, cultural awareness is important, as is culturally and linguistically appropriate care and information. The majority of consumer information is in English, presenting language barriers and resources should be framed and provided in a culturally appropriate way.[139] Barriers to accessible and culturally appropriate information provision were identified, such as information not matched to health literacy, and unavailability of female physicians. For healthcare professionals, surveys have shown globally the lack of awareness, knowledge gaps and information needs of healthcare professionals in PCOS.[140,141,142] Given current dissatisfaction in care and information provision noted internationally, the cultural and linguistic considerations in PCOS care, and the evidence that healthcare professionals do not adequately address the diverse features of PCOS, this question was prioritised.

Summary of systematically searched evidence

Given the extensive studies included, please see the technical report for detailed references and study characteristics in Section 2.6.1.

This systematic review captured 41 studies focused on information needs of healthcare professionals and those with PCOS including adolescents and culturally and linguistically diverse populations. Given the nature of the data, which included quantitative, qualitative and mixed methods, a narrative analysis was completed. Quality was variable with four studies being high quality and the majority being low to moderate.

Lack of priority, limited education and awareness all resulted in inconsistent care and patient dissatisfaction. For patients, clear gaps emerged in evidence-based information provision at the time of diagnosis and ongoing, including for underserved groups.

QoL Physical

Measured by Paediatric Quality of Life Inventory (PedsQL) Physical Function- With a P=0.04 and a heterogeneity of 76%, evidence suggests that while scores for the PedsQL domain of Physical Function are lower in adolescent women with PCOS compared to adolescent women without PCOS, moderate heterogeneity means the results should be interpreted with caution.

QoL Psychosocial

Measured by PedsQL Psychosocial function and based on data from 169 patients in 2 studies. With a P=0.83 and a heterogeneity of 0%, evidence suggests that scores for the PedsQL quality of life domain of psychosocial function are lower in adolescent women with PCOS compared to adolescent women without PCOS.

QoL Total (adolescence)

Measured by the PedsQL Total and based on data from 169 patients in 2 studies. With a P=0.47 and a heterogeneity of 0%, evidence suggests that while scores for the PedsQL total quality of life domain are lower in women with PCOS compared to women without PCOS, however this is not statistically significant.

Recommendations

2.6		**Information resources, models of care, cultural and linguistic considerations**	
2.6.1		**Information needs**	
2.6.1.1	**EBR**	Tailored information, education and resources that are high-quality, culturally appropriate and inclusive should be provided to all with PCOS.	❖❖❖❖ ⊕⊕⊕◯
2.6.1.2	**EBR**	Information, education and resources are a high priority for patients with PCOS and should be provided in a respectful and empathic manner.	❖❖❖❖ ⊕⊕⊕◯
2.6.1.3	**CR**	Entities responsible for health professional education should ensure that information and education on PCOS is systemically embedded at all levels of health professional training to address knowledge gaps.	❖❖❖❖
2.6.1.4	**PP**	The diversity of the population should be considered when adapting practice paradigms. Healthcare professional opportunities should be optimised at all stages of graduate and postgraduate training, continuing professional development and in practice support resources.	
2.6.1.5	**PP**	Women should be counselled on the risk of misinformation and guided to evidence-based resources.	

Justification

The GDG recognised the plethora of evidence internationally that, despite being a common condition, PCOS was much neglected, PCOS care dissatisfaction is high and information needs are significant for those affected and for their healthcare providers. Based on this evidence, the expertise of the GDG and consumer input, and the importance of access to evidence-based accessible information to promote shared decision making and self-management, strong recommendations were made by the GDG to enhance awareness, education and information provision for healthcare professionals and for those with PCOS. In the 2023 guideline, the narrative review is upgraded to a systematic review and the recommendations are strengthened here. Strong consumer engagement influenced the change in focus of these recommendations aiming to better meet the needs of those affected by PCOS.

2.6.2 What are the characteristics of available models of care implemented in PCOS clinics or services?

Clinical need for the question

PCOS is associated with delayed diagnosis and poor satisfaction with inconsistent care[143] Those affected by PCOS may consult multiple healthcare professionals and multidisciplinary care is increasingly required in chronic disease management, with improvements in health related outcomes.[144] 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-centered principles. Models of care have core components including being co-developed with stakeholders and end users, adhering to best practice or guideline recommendations and integration of care[145] With such a prevalent condition, primary care providers will need to improve education, awareness and care in PCOS and dedicated services will likely also be required. Given patient dissatisfaction with care this question was prioritised.

Summary of systematic review evidence

Five studies evaluated outcomes from four PCOS health services.[146-149] These were only from developed countries and were dedicated multidisciplinary services, rather than integrated care models. Study designs included cross-sectional and mixed-method evaluation. Two studies were rated low risk of bias and three as moderate risk of bias. Service evaluation was reported by two studies, patient outcome evaluation was reported by four studies. Three of the services were within tertiary hospitals with one in a primary care clinic setting. Some form of structural lifestyle management, cardiometabolic risk assessment or management, emotional well-being screening and reproductive health management were provided in all services. Evaluation of the PCOS health services and patient outcomes were heterogeneous, precluding meta-analysis.

Recommendations

2.6.2 #		Models of care	
2.6.2.1	**CR**	Models of care should prioritise equitable access to evidence-based primary care with pathways for escalation to integrated specialist and multidisciplinary services as required.	❖❖❖❖
2.6.2.2	**PP**	Strategies to deliver optimal models of care could include health professional education, care pathways, virtual care, broader health professional engagement (e.g. nurse practitioners) and coordination tools.	

Justification

The diverse nature of PCOS, the complexity of clinical features and the extensive evidence on inconsistent care, delayed diagnosis and dissatisfaction with care informed the recommendations here as did broader literature on models of care in other chronic conditions that was also considered. However, given the limited PCOS specific evidence, especially the lack of consideration of primary care (frontline care vital in a chronic condition with an 8-10% prevalence), consideration of integrated models of care or models of care in more diverse settings, health systems and populations, a consensus recommendation was made by the GDG. Given the prevalence and needs here, this recommendation was strongly rated by the GDG.

2.6.3 How can we best support women to navigate the impact of PCOS on family and interpersonal relationships?

Clinical need for the question

It is well established that PCOS has an impact on physical and psychological health. PCOS is associated with increased rates of anxiety, depression and a lower quality of life[150] and can disrupt social, family and interpersonal relationships in the social domain.[151] PCOS can affect interactions and relationships with partners, family, friends, colleagues, and others with whom people with PCOS have social relations. These can create challenges in personal and social interaction which, in turn, can impact interpersonal relationships in a way that varies across the lifespan and cultures.[152] Currently, there is a paucity of reliable data on the impact of PCOS in the social domain. Some evidence suggests a positive effect of social and family support on healthy eating and participation in exercise. Family and peer support can reduce stress, increase confidence and provide a sense of security but many experience distress and pressure around having children. Immediate family tend to be more supportive in comparison to extended family members. Consumer consultation, especially from South Asian regions, prioritised this question on social, family, and interpersonal relationships including life stage and cultural variations.

Summary of narrative review evidence

Given this involved an extensive narrative review, further information, including detailed references, study characteristics and core themes, can be found in the technical report in Section 2.6.3.

The narrative review identified that few well-controlled studies examine the effects of PCOS in the social domain or optimal choice of interventions for managing effects on family and interpersonal relationships. Social and peer support, family and relationship satisfaction, marginalisation and future directions were explored as themes that emerged from the literature. Cultural issues, including those related to fertility and stigma of having PCOS emerged as important. Support needs and experiences of family and interpersonal relationships of women and people with PCOS varies and the need for much greater research on social topics was recognised. Social and cultural expectations impact interpersonal relationships as the features of PCOS are at odds with some socio-cultural constructs of attractiveness, motherhood or femininity. Specific challenges, the need for greater support and the role of families in adolescence also emerged as important.

Recommendations

2.6.3		Support to manage PCOS	
2.6.3.1	**CR**	Public health actors should consider increasing societal awareness and education on PCOS to reduce stigma and marginalisation.	❖❖❖
2.6.3.2	**PP**	Culturally appropriate resources and education on PCOS across the life span for families of those with the condition, should be considered.	

Justification

This new consensus recommendation was made by the GDG understanding that this issue was highly prioritised in consumer consultation for the guideline. The need for greater education was again recognised at a societal level as well as for health care providers and those affected by PCOS and their families. The importance of culturally appropriate resources was also prioritised and this will inform the guideline translation program. Research recommendations were also generated here to address key knowledge gaps in social aspects that were identified.

2.6.4 What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?

Clinical need for the question

Interactions between patients, their doctors and the wider healthcare team about PCOS are important to enhance knowledge, self-management, outcomes of care, shared decision making and support to achieve health outcomes that matter to them. As outlined there is also wide spread dissatisfaction with PCOS care.[143] PCOS is heterogeneous and varies across populations, individuals and across the life span. It affects physical and mental health and has sociocultural implications as noted above. It is also a chronic disease in which self-management is important, requiring information, education and knowledge. This makes clinical care challenging and women describe falling through the cracks of increasingly compartmentalised or specialty care. Hence this question was prioritised from consumer consultation for the current guideline.

Summary of systematic review evidence

Given the extensive studies included, further information, including detailed references and study characteristics, can be found in the technical report in Section 2.6.4.

A systematic review was completed and 28 studies were captured. Two studies were high risk of bias, six moderate and the rest were low risk of bias. All were qualitative or mixed methods studies. Very limited research focused on adolescents.

Three main themes emerged from synthesis of qualitative and mixed-methods studies on challenges for patients interacting with healthcare professionals. Here data describing patient perspectives on key challenges was prioritised and extracted, which by design identified problematic areas of care.

Healthcare providers' knowledge and practices: Aligning with patients' experience, and surveys of healthcare professionals in Europe/Asia and North America and Nordic European countries,[140-142] clinician awareness of broader features and psycho-social morbidities associated with PCOS is low. For PCOS diagnostic criteria, understanding was variable and diagnostic approaches and treatments varied by health professional group.

Health care professional interactions: Of the twenty-eight studies identified, all provided data on key challenges for those with PCOS when interacting with healthcare professionals. Of these studies three were mixed methods designs, one a systematic review, one a comparative design of people with and without PCOS and remaining studies qualitative designs.

Qualitative data synthesised participant narrative and author interpretation, and informed descriptive analysis. First, interactions were challenging when potentially bad news (PCOS diagnosis, management, or long-term risks) was shared in a way that was not empathic and that did not safeguard patient wellbeing. PCOS news can be shared in a suboptimal way due to lack of appropriate setting, limited time or preparation (by healthcare professionals, of the patient) or by use of unhelpful strategies (normalising, minimising). Lack of knowledge and resources or a well-formulated strategy for management emerged as important. Healthcare professionals that acknowledged limited expertise and who took the time to research and support patients with a new diagnosis were perceived positively.

Second, shared decision making was important yet limited as interactions were often too abbreviated with limited information and options presented, patient preferences were often not elicited, and too little time was available. Hence patients felt excluded from decision making, whereas use of shared decision making was positively regarded.

Third, interactions were challenging when healthcare professionals did not support patient agency, that is, patients' ability to take independent actions to manage their health and care. Patients reported that their perspectives and self-management were not valued. Healthcare professionals that were validating, supported patients and having consultations that were patient led and informed, were viewed positively.

Recommendations

2.6.4		Patient care	
2.6.4.1	EBR	Healthcare professionals should employ shared decision making and support patient agency or ability to take independent actions to manage their health and care.	❖❖❖❖ ⊕⊕⊕◯
2.6.4.2	EBR	The importance of being knowledgeable about PCOS, of applying evidence-based practices when sharing news on diagnosis, treatment and health implications, and of ascertaining and focusing on patient priorities, should be recognised.	❖❖❖❖ ⊕⊕⊕◯
2.6.4.3	CR	Healthcare system leaders should enable system wide changes to support health professional training, knowledge and practice in sharing news optimally, shared decision making and patient agency, including ensuring adequate consultation time and accessible resources.	❖❖❖❖
2.6.4.4	PP	Evidence-based strategies for shared decision making and for sharing news (such as the SPIKES framework) are readily available and should be used to inform PCOS care. All healthcare professionals partnering with women with PCOS should be knowledgeable in sharing news, in shared decision making and in supporting patient self-management. Evidence-based strategies and resources can be used to support patient activation, which refers to modifiable knowledge, skills, ability, confidence and willingness to self-manage one's own health and care.	

Justification

Given the three emergent themes on patient specific areas to improve patient healthcare provider interactions, again education and knowledge on PCOS were important alongside support, empathy, shared decision making and patient agency. Given the complexity of PCOS, evidence-based accessible and culturally appropriate resources recommended above could assist in PCOS care. The emergent themes informed recommendations in PCOS care and whilst implementation may present challenges in terms of time required, models of care and information resources may assist. These new recommendations emerged from strong consumer priority and evidence and are likely to impact on practice with better alignment to patient expectations and needs.

2.7 Psychological therapy

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?

Clinical need for the question

Women with PCOS have a higher prevalence of clinically significant self-reported symptoms of depression, anxiety and eating disorders and of depressive disorders, anxiety disorders and eating disorders diagnosed using structured clinical interview. Numerous empirically supported treatments (e.g. cognitive behavioural therapy (CBT), behavioural therapy, interpersonal therapy) are available for the treatment of these disorders in the general population.[153 154] These treatments result in clinically significant improvements of the mental health condition and associated distress and impairment, as well as broader improvements including QoL and psychosocial wellbeing. Of note, a systematic review has shown increasing evidence of the effectiveness of treatment delivered via telehealth (videoconference and telephone), as well as online programs,[156] particularly if they are delivered with the assistance of a therapist or guide/coach. The choice of treatment is dependent on participant characteristics (e.g. age), diagnosis and symptoms severity, and available resources.

Summary of narrative review evidence

Given the limited evidence specifically in PCOS, this question was allocated as a narrative review and therefore a systematic literature review was not conducted. General population guidelines were accessed including

- National Institute for Health and Care Excellence: www.nice.org.uk/guidance/published?type=csg,cg,mpg,ph,sg,sc
- National Institute of Mental Health: www.nimh.nih.gov/health/index.shtml
- American Psychiatric Association: www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines
- National Health and Medical Research Centre: www.clinicalguidelines.gov.au

Women with PCOS have higher levels of body image distress, lower levels of self-esteem, loss of feminine identity and lower psychosexual function, all common comorbidities of depressive, anxiety and eating disorders. There are no broadly accepted guidelines for the treatment of body image distress, self-esteem or feminine identity. Therefore, psychological treatment should be guided by the results of systematic reviews and meta-analyses where available, or where they are not available high quality RCTs and evidence-based guidelines. Available research suggests that psychological treatment, particularly CBT, is effective in improving body image distress on systematic review[157] and low self-esteem. These treatments have been shown to improve the condition and associated distress and impairment. An RCT in PCOS on acceptance and commitment therapy improved self-esteem and body image compared to controls.[158]

A systematic review on psychosocial interventions in PCOS included seven RCTs,[159] covering psychological interventions (two studies) and lifestyle interventions (i.e. diet, exercise) with behavioural/cognitive behavioural components, primarily targeting lifestyle change and including mental health measures as secondary outcomes (five studies). While significant pre-post intervention effects were evident, between group effects were inconsistent with greater impact short-term. Only two studies found long term effects for body image and stress. There were no significant effects for anxiety (at any time point), and no significant long-term effects for anxiety, depression or QoL. One study included participants with mental health concerns and the others excluded such participants. Another systematic review and meta-analyses examined psychological CBT interventions and depressive symptoms in PCOS, with a large effect in favour of CBT (Cohen's d = 1.16; 0.31-2.01).[160]
This literature, other guidelines and evidence on psychological therapy in the general population informed consensus recommendations.

Recommendations

2.7		Psychological therapy	
2.7.1	CR	Women with PCOS diagnosed with depression, anxiety, and/or eating disorders should be offered psychological therapy guided by regional general population guidelines and the preference of the woman with PCOS.	❖❖❖❖
2.7.2	CR	Women with PCOS with disordered eating, body image distress, low self-esteem, problems with feminine identity, or psychosexual dysfunction should be offered evidence-based treatments (e.g. cognitive behaviour therapy) where appropriate.	❖❖❖❖

Justification

Treatment of depression, anxiety, eating disorders/disordered eating should be guided by regional general population guidelines on identification, assessment and treatment. There are no broadly accepted guidelines for the treatment of body image distress, self-esteem, feminine identity or psychosexual dysfunction. Limited available research suggests that CBT is effective in the treatment of body image distress, self-esteem, feminine identity or psychosexual dysfunction, with a clear need for further research in this area. These new consensus recommendations reflect general population guidelines. Given the high prevalence of psychological disorders, these consensus recommendations were made with the understanding that they are likely to impact on practice, but at a minimum reflect care that should be provided for all those with psychological disorders.

2.8 Antidepressant and anxiolytic treatment

Are antidepressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?

Clinical need for the question

Depression and anxiety are exceptionally common globally with higher prevalence in women. Psychoeducation, CBT, and combinations of psychotherapeutic approaches are considered to be the preferred treatment options for depression and anxiety.[153 154] Lifestyle and other therapies that target PCOS features have shown improvement in psychological symptoms in PCOS. Depression can be treated with psychotherapy and if moderate to severe, Major Depressive Disorder occur, additional antidepressant pharmacotherapy may be required. Anxiety disorders are common in women with PCOS. Generalised Anxiety Disorder, Social Anxiety Disorder, Panic Disorder and the phobias as described in the DSM 5 (Diagnostic and Statistical Manual of Mental Disorders), can be present in PCOS but are often in a subsyndromal manner with many having anxiety symptoms without meeting DSM 5 criteria. In clinical practice, many women with PCOS present feeling anxious, with intermittent exacerbation of anxiety symptoms and even panic. Psychological therapy can be very helpful in this condition; however, the role/efficacy of antidepressants and/or anxiolytics is unclear.

Summary of systematic and narrative review evidence

One study compared Sertraline versus placebo in women with PCOS.[155] Relevant outcomes included depression scores using the Hamilton Depression Rating Scale. This study was judged as moderate risk of bias. Sertraline was more effective than placebo in reducing depression scores in women with PCOS. Evidence for this outcome was of low quality due to being derived from a single small study with a moderate risk of bias. Otherwise general population guidelines informed these recommendations.[153 154]

Recommendations

2.8		Antidepressant and anxiolytic treatment	
2.8.1	CR	Psychological therapy could be considered first-line management, and antidepressant medications considered in adults where mental health disorders are clearly documented and persistent, or if suicidal symptoms are present, based on general population guidelines.	❖❖❖
2.8.2	PP	Lifestyle intervention and other therapies (e.g. COCP, metformin, laser hair removal) that target PCOS features should be considered, given their potential to improve psychological symptoms. Where pharmacological treatment for anxiety and depression is offered in PCOS, healthcare professionals should apply caution: • to avoid inappropriate treatment with antidepressants or anxiolytics • to limit use of agents that exacerbate PCOS symptoms, including weight gain. Healthcare professionals should be aware that not managing anxiety and depression may impact adherence to PCOS treatment/management.	

Justification

There was limited literature to answer this question. We only found one study that compared Sertraline versus placebo in women with PCOS.[155] Relevant outcomes included depression scores using the Hamilton Depression Rating Scale and this study was judged as moderate risk of bias. The recommendation is new and based on general population guidelines for treatment of anxiety and depression. Given the high prevalence of psychological disorders, these consensus recommendations were agreed with the understanding that they are likely to impact on practice but at a minimum reflect care that should be provided for all those with psychological disorders.

Chapter Three
Lifestyle management

3.1 Effectiveness of lifestyle interventions

In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for improving anthropometric, 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 increasing in the general population and are further increased in adolescents and adults with PCOS. The potent combination of excess weight and PCOS, adversely effects reproductive, metabolic and psychological health, presenting a major public health challenge. This highlights the need for both prevention and treatment. Insulin resistance affects 75% of lean women and 95% of those with a BMI > 25 kg/m² with PCOS[161] and is further exacerbated by excess weight.[100,162] Those with PCOS internationally report that excess weight causes significant distress and that there is inadequate information and support around lifestyle change.[14] Weight was also a highly ranked and prioritised outcome by both healthcare professionals and women during the guideline development process. Overall, in women with PCOS and excess weight, lifestyle interventions which reduced total body weight by as little as 5%, have shown metabolic, reproductive and psychological benefits.[163-186] Given the uncertainty on effectiveness and optimal components of lifestyle intervention in PCOS, this clinical question was prioritised.

Summary of systematic and narrative review evidence

Given the extensive studies included and the meta-analyses, further information, including detailed references and study characteristics, can be found in the technical report in Section 3.1.

Eighteen RCTs (7 new and 11 from the last guideline) were captured and mainly had a high risk of bias. One study assessed fertility with the primary outcome being pregnancy rate, whilst others included ovulation rate and menstrual regularity as secondary outcomes. Lifestyle included exercise and diet interventions versus minimal interventions, which contributed to heterogeneity in results around anthropometric measures. Lifestyle overall improved anthropometric outcomes; waist circumference (12 studies, mean difference: -1.32cm [-2.46; -0.18]), waist/hip ratio (WHR) (6 studies: -0.03; [-0.05; -0.01]), mFG score (6 studies -0.97; [-1.90; -0.03]); fasting insulin (14 studies -1.8 pmol/L 7; [-3.10; -0.65]); total cholesterol (12 studies -0.15 mmol/L; [-0.26; -0.03]) and low density lipoprotein cholesterol (LDL-C) (12 studies -0.15 mmol/L; [-0.28; -0.02]). Other measures including body weight (-1.02 kg, [-2.08, 0.04]), BMI, SHBG, total testosterone, FAI, glucose regulation (fasting and 2-hour postprandial glucose levels), high density lipoprotein cholestoral (HDL-C), and triglyceride (TG) levels did not differ between groups. There was a moderate certainty of evidence for BMI, weight circumference (WC), HDL-C, LDL-C, and TG or low certainty for weight, WHR, mFG score, SHBG, and total cholesterol and very low for testosterone and FAI. Few studies looked at the impact of lifestyle intervention on pregnancy, ovulation rate, or menstrual cyclicity, and no study evaluated miscarriage.

Given the relatively small number of participants across these 18 studies (634), evidence and guidelines for the general population were also considered.

Recommendations

3.1		Effectiveness of lifestyle interventions	
3.1.1	EBR	Lifestyle intervention (exercise alone or multicomponent diet combined with exercise and behavioural strategies) should be recommended for all women with PCOS, for improving metabolic health including central adiposity and lipid profile.	❖❖❖❖ ⊕◯◯◯
3.1.2	CR	Healthy lifestyle behaviours encompassing healthy eating and/or physical activity should be recommended in all women with PCOS to optimise general health, quality of life, body composition and weight management (maintaining weight, preventing weight gain and/or modest weight loss).	❖❖❖❖
3.1.3	PP	Healthcare professionals should be aware that lifestyle management is a core focus in PCOS management.	
3.1.4	PP	Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS, and value women's individualised preferences.	
3.1.5	PP	There are benefits to a healthy lifestyle even in the absence of weight loss.	
3.1.6	PP	In those with higher weight, weight management can be associated with significant clinical improvements and the following key points need to be considered including: • a lifelong focus on prevention of further weight gain • if the goal is to achieve weight loss, a tailored energy deficit could be prescribed for women, considering individual energy requirements, body weight and physical activity levels • the value of improvement in central adiposity (e.g. waist circumference, waist-hip ratio) or metabolic health • the need for ongoing assessment and support.	
3.1.7	PP	Healthcare professionals should be aware of weight stigma when discussing lifestyle management with women with PCOS [see 3.6].	
3.1.8	PP	Healthy lifestyle and optimal weight management, in the context of structured, intensive and ongoing clinical support, appears equally effective in PCOS as in the general population.	
3.1.9	PP	In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain.	
3.1.10	PP	Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care (refer to 1.9.12).	

Justification

The updated systematic review for this question identified new studies since the 2018 guideline. Studies were focused on adults and were predominantly in academic medical centres rather than being community-based. Given the high prevalence and important adverse impact of excess weight in PCOS and the apparent efficacy of lifestyle interventions in PCOS and in other populations, healthy lifestyle behaviours were deemed important in this high-risk group. Women with PCOS, had prioritised weight management and also emphasised the need to optimise healthy lifestyle in all women with PCOS, independent of weight loss goals. Despite certainty of evidence being rated very low, the strength of the recommends are strong as the recommendations and practice points were informed by general population guidelines, together with the evidence identified in PCOS and the input of the multidisciplinary health professional and consumers on the GDG. They are intended to reduce variation in practice, improve lifestyle advice, optimise support to target weight gain prevention, and where appropriate and desired, to target weight loss. The GDG recognised the challenges with changing and maintaining a healthier lifestyle, and the environmental, policy and sociocultural drivers behind lifestyle and excess weight. The need for adequate training of healthcare professionals in empathetic partnering with women to develop realistic lifestyle management goals and to encompass a broader focus beyond weight, to the many dimensions of healthy lifestyle. The recommendations also consider important psychosocial, cultural and ethnic aspects in relation to lifestyle interventions, informed by evidence generated for other clinical questions. Substantial resources are likely needed to implement these recommendations which may increase consultation times, referral to allied healthcare 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. The main update from the last guideline related to greater awareness of weight stigma and its impact.

3.2 Behavioural strategies

In women with PCOS, are behavioural interventions in addition to diet and/or exercise (compared to diet and/or exercise alone) effective for improving anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?

Clinical need for the question

Lifestyle intervention is important in PCOS, with a strong focus on preventive strategies,[187] given the increased rates of weight gain in the general population and the higher rates of weight gain in PCOS.[187,188,189,190] Retention and sustainability of lifestyle interventions in PCOS are generally suboptimal, with behaviour change interventions and support prioritised in this condition. Behavioural and cognitive behavioural interventions are the most commonly used psychological approaches in lifestyle interventions with evidence of efficacy especially where these interventions are more intensive.[191] Behavioural and cognitive behavioural intervention approaches target the behaviours (and their antecedents and consequences) and cognitions thought to be responsible for maintaining a positive energy balance,[192] and are recommended by international general population guidelines. Given the need to improve adherence and impact of lifestyle interventions in PCOS, this question was prioritised.

Summary of systematic and narrative review evidence

We did not identify any evidence in women with PCOS to answer the question and therefore the literature has been reviewed narratively. Five studies were identified in the systematic search, but all were excluded from systematic review due to lack of direct alignment to the PICO. Intervention duration was 4 months (2 studies) or 12 months (3 studies). Risk of bias was moderate in four studies) or high. Overall, studies included overweight women. One study utilising CBT, recruited women with a depression score ≥ 14.[193] All results were heterogeneous and provided limited support for specific benefits of behavior change interventions. Hence consensus recommendations were made aligned to general population evidence and guidelines such as those produced by the NHMRC www.nhmrc.gov.au/about-us/publications/clinical-practice-guidelines-management-overweight-and-obesity[194]

Recommendations

3.2		Behavioural strategies	
3.2.1	**CR**	Lifestyle interventions could include behavioural strategies such as goal-setting, self-monitoring, problem solving, assertiveness training, reinforcing changes and relapse prevention, to optimise weight management, healthy lifestyle and emotional wellbeing in women with PCOS.	❖❖❖
3.2.2	**PP**	Behavioural support could include: goal-setting, problem solving, self-monitoring and reviewing, or SMART goals (Specific, Measurable, Achievable, Realistic and Timely).	
3.2.3	**PP**	Comprehensive healthy 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

Overall, there remains a paucity of evidence to definitively support implementation of behavioural therapy in addition to lifestyle management in PCOS. High-quality RCTs evaluating the efficacy of behavioural interventions to optimise health behaviour change and/or weight management are required in this population, exploring anthropometric, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes. In other high cardiometabolic risk populations, behavioural change strategies and/or behavioural/cognitive interventions in combination with diet and exercise, potentiates weight loss compared with diet and/or physical activity alone and this evidence was considered here. Self-management strategies have been shown to enhance weight loss and healthy lifestyle behaviour change when incorporated into advice on lifestyle interventions for the general population. Skill levels among healthcare professionals may vary, presenting implementation challenges and greater research is needed in this area.

3.3 Dietary interventions

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

Clinical need for the question

Specific dietary composition in lifestyle interventions remains controversial.[195] Given the general recommendations to reduce caloric (energy) intake, rather than modifying macronutrient composition in the 2018 guideline, the widespread misinformation and 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

Given the extensive studies included and the meta-analyses, further information, including detailed references and study characteristics, can be found in the technical report in Section 3.3.

Twelve RCTs were identified with 496 participants, ten with a parallel design and two crossover studies. The majority of studies were in adults with one in adolescents and the majority of participants had an elevated BMI. Duration of the studies was 4 weeks to 6 months.

Dietary interventions included the DASH (Dietary Approaches to Stop Hypertension) diet (3 studies), higher protein/lower carbohydrate diets (5 studies), higher fat/lower carbohydrate diets (3 studies) and a pulse-based low glycaemic index diet (1 study). Where specified, macronutrient composition ranged from 40-55% carbohydrate, 15-30% protein and 25-40% fat and control diets 50-55% carbohydrate, 15-20% protein and 25-30% fat.

A meta-analysis of five studies comparing a hypocaloric high protein/low carbohydrate diet (40% carbohydrate, 30% protein, 30% fat) versus a control diet (55% carbohydrate, 15% protein, 30% fat) showed no significant differences in anthropometric or metabolic outcomes apart from HDL-C, which favoured the control diet.

For the remaining studies, a meta-analysis was not conducted due to heterogeneity in dietary composition and energy restriction. Instead, a narrative analysis has been provided.

Three studies compared a DASH diet to a control (traditional) diet-macronutrient composition was 50-55% carbohydrate, 15-20% protein and 25-30% fat and energy was restricted in both the intervention and control groups. Analysis showed greater improvements in BMI (2 of 2 studies), waist circumference (1 of 1 study), fasting insulin (2 of 2 studies) and homeostatis model of assessment - insulin resistance (HOMA-IR) (2 of 2 studies) and mixed findings for weight (2 of 3 studies) and FAI (1 of 2 studies) with the DASH diet versus a control diet. No differences were seen for total testosterone, fasting glucose and blood lipids (HDL, LDL and TG). These findings were of low to very low certainty. Due to notices of concerns published in relation to several of the studies in this area, and to concerns around integrity of the studies, these studies were captured in the literature review, but had limited influence on the recommendations.

Importantly, it was noted that multiple studies by this group (including studies in this analysis) are issued with Notices of Concern due to serious issues around integrity and methods, results and analysis. As such this was considered by the GDG experts in making recommendations.

One study showed greater improvements in lipids, with a eucaloric low glycaemic index pulse-based versus a control diet, with no differences between the diets for anthropometric measures (weight, BMI and WC), fasting glucose, fasting insulin, HOMA-IR, total testosterone or FAI. Energy wasn't restricted here. Two studies compared a eucaloric higher fat/lower carbohydrate diet with a control diet with no differences between groups for fasting insulin and glucose. For other outcomes, between group comparisons were not reported. One study in adolescence compared a hypocaloric low carbohydrate, higher fat diet (45% carbohydrate, 20% protein, 35% fat) versus a low-fat diet (55% carbohydrate, 20% protein, 25% fat). A greater reduction in BMI was seen in the low-fat diet group with no significant differences in other outcomes.

Together these findings suggest that diets with a range of macronutrient compositions could be recommended for women with PCOS. This is consistent with research in the general population with a systematic review and network meta-analysis of 121 RCTs and 22000 participants, finding modest weight loss and improved CVD risk factors over 6 months, with diets of varying macronutrient compositions, although these outcomes were not maintained at 12 months.[196] Compared to usual diets, low carbohydrate and low-fat diets had similar effects on weight loss at six months. Furthermore, evidence doesn't suggest a benefit of modifying the macronutrient composition of the diet based on insulin secretion.

Rather than restricting carbohydrate, research in other populations suggests that the quality of carbohydrates in the diet is important, and diets containing carbohydrate foods which are high in fibre with a lower glycaemic index, including wholegrains, pulses/legumes and fruit, appear to reduce CVD risk factors and are associated with weight loss and a lower incidence of diabetes, cardiovascular disease and cardiovascular mortality[197] [198] and the mediterranean diet is associated with improved metabolic health.[199]

Recommendations

3.3		Dietary Interventions	
3.3.1	EBR	Healthcare professionals and women should consider that there is no evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	❖❖❖ ⊕◯◯◯
3.3.2	CR	Any diet composition consistent with population guidelines for healthy eating will have health benefits, and within this, healthcare professionals should advise sustainable healthy eating tailored to individual preferences and goals.	❖❖❖❖
3.3.3	PP	Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals and avoiding unduly restrictive and nutritionally unbalanced diets, are important, as per general population guidelines.	
3.3.4	PP	Barriers and facilitators to optimise engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, as well as personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimising their diet.	

Justification

Given that consumer targeted information about PCOS often purports the benefit of specific macronutrient composition, this recommendation is important to ensure that women and healthcare professionals are informed on the evidence on dietary composition and efficacy. Emphasis should be on individual preferences and cultural needs of individuals, and on an overall balanced and healthy dietary composition to achieve personalised nutritional goals. Education for both women and healthcare 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 likely benefits in PCOS. The recommendations are strengthened here with increased evidence.

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.[200,201] 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 advice around exercise and physical activity and the specific efficacy of different types and intensity of exercise is unclear, hence this clinical question was prioritised.

Summary of systematic review evidence

High-intensity interval training versus moderate-intensity continuous training: Three studies[202] [203] [204] compared high-intensity interval training versus moderate-intensity continuous training for a range of anthropometric, metabolic and hormonal/reproductive outcomes and were deemed to have low risk of bias. Meta-analyses
of two to three pooled studies, showed no differences, with low to very low certainty of evidence. In descriptive analysis, high-intensity training was more effective for menstrual regularity (OR 0.13 [0.02, 0.91]) with
very low certainty.

High-intensity interval training versus resistance training: One study compared high-intensity training with resistance training on a range of outcomes with no differences between groups, unclear risk of bias and very low certainty.[205]

Diet plus combined aerobic and resistance training versus diet plus aerobic exercise: One study with a high risk of bias found no differences between these interventions with very low certainty of evidence.

Recommendations

3.4		Exercise Interventions	
3.4.1	EBR	Healthcare professionals and women could consider that there is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.	❖❖❖ ⊕◯◯◯
3.4.2	CR	Any physical activity consistent with population guidelines will have health benefits and within this, healthcare professionals should advise sustainable physical activity based on individual preferences and goals.	❖❖❖❖

3.4.3	**CR**	Healthcare professionals should encourage and advise the following in concordance with general population physical activity guidelines: • All adults should undertake physical activity as doing some physical activity is better than none. • Adults should limit the amount of time spent being sedentary (e.g. sitting, screen time) as replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits. For the prevention of weight gain and maintenance of health, adults (18-64 years) should aim for a minimum of 150 to 300 minutes of moderate-intensity activities or 75 to 150 minutes of vigorous-intensity aerobic activity per week or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week. For promotion of greater health benefits including modest weight loss and prevention of weight regain, adults (18-64 years) should aim for a minimum of 250 min/week of moderate-intensity activities or 150 min/week of vigorous intensities or an equivalent combination of both, plus muscle strengthening activities (e.g. resistance/flexibility) ideally on two non-consecutive days per week. Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day including activities that strengthen muscle and bone, at least three times per week.	❖❖❖❖
3.4.4	**PP**	Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. It includes leisure time physical activity, transportation (e.g. walking or cycling), occupational (i.e. work), household chores, playing games, sports or planned exercise, or activities in the context of daily, family and community activities.	
3.4.5	**PP**	Aerobic activity is best performed in bouts of at least 10 minutes duration, aiming to achieve at least 30 minutes daily on most days.	
3.4.6	**PP**	Barriers and facilitators to optimise engagement and adherence to physical activity should be discussed, including psychological factors (e.g. body image concerns, fear of injury, fear of failure, mental health), personal safety concerns, environmental factors, physical limitations, socioeconomic factors, sociocultural factors, and personal motivators for change. The value of broader family engagement should be considered. Referral to suitably trained allied healthcare professionals needs to be considered for optimising physical activity in women with PCOS.	
3.4.7	**PP**	Self-monitoring including with fitness tracking devices and technologies for step count and exercise intensity, could be considered as an adjunct to support and promote active lifestyles and minimise sedentary behaviours.	

Justification

With limited number and quality RCTs on exercise programs in PCOS, the GDG also considered high quality mechanistic literature in PCOS and international exercise/physical activity recommendations for the general population. Exercise should be encouraged and advised in PCOS and 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, with ease of access in groups and with minimal equipment. Low cost e-health (electronic health) and m-health (mobile health) options may also be relevant. Where available and affordable, and where there is risk from injury, due consideration should be given to involvement of exercise physiologists/specialists in structured exercise interventions. The recommendations are strengthened here with an increase in evidence.

3.5 Factors affecting weight gain in PCOS

Why are women with PCOS at increased risk of weight gain (intrinsic and extrinsic factors)?

Clinical need for the question

Weight excess affects the majority of women in PCOS although this varies across populations and geography, related to factors including environmental, policy and sociocultural factors, and the complex pathophysiology and clinical heterogeneity of PCOS. There is a lack of understanding of interactions between PCOS, excess body weight and body fat distribution. A BMI > 30 kg/m², particularly with excess central weight, increases insulin resistance and hyperandrogenism, increases PCOS prevalence and exacerbates clinical features. It is also of significant concern to women with PCOS and a key target for prevention and management. Excess weight is a common feature of PCOS;[206] and those with PCOS commonly experience the additional burden of weight-associated insulin resistance. In a comprehensive systematic review and meta-analysis of the prevalence of excess weight in those with and without PCOS,[207] those with PCOS had a significantly increased risk for adiposity when compared with controls. Pooled estimated prevalence of a BMI above 25 kg/m², above 30 kg/m², or with higher central adiposity in PCOS is 61% (95% confidence interval (CI): 54–68%), 49% (42–55%) and 54% (43– 62%) respectively. The risk of a BMI above 25 kg/m², above 30 kg/m², or central adiposity, had relative risks (RR) of 1.95 (1.52-2.50), 2.77 (1.88, 4.10) and 1.73 (1.31, 2.30) respectively. This increased risk was independent of the PCOS diagnostic criteria (NIH versus. Rotterdam), age and geographic region of the affected subjects. Caucasian women with PCOS had a greater prevalence of BMI > 30 kg/m² than Asian women with PCOS, whether using the same criteria for excess weight categories or ethnic specific criteria. The temporal trends of the prevalence of a BMI above 30 kg/m² among women with PCOS, shows an increase from 51% in the 1990s to 74% in the following decades.[206]

Consumer surveys to help prioritise clinical questions for the 2022 PCOS guideline update found that 27% of responders ranked difficulty losing weight as the number one symptom of concern and 16% ranked it as the second. When asking women to rank the top 5 areas they would like more research to focus on, 21% ranked difficulty losing weight as the top priority and 12% ranked it as the second. As such, the focus of the clinical question in these guidelines was to examine the factors contributing to challenges in weight management.

Extrinsic factors potentially contributing to increased risk of weight gain in women with PCOS

Suboptimal diet and physical activity are modifiable environmental factors (extrinsic factors) that contribute to weight gain. Poorer dietary intake (including excess energy intake or poor diet quality including reduced core food group and increased discretionary food intake) and reduced physical activity have been proposed to contribute to increased weight in PCOS. However, this evidence is currently conflicting with deteriorating lifestyle behaviours,[208-212] improved lifestyle behaviours[213] or no differences in lifestyle behaviours groups[214-217] reported between women with and without PCOS. It is crucial to understand differences in lifestyle behaviours (extrinsic factors) in women with and without PCOS that could be related to the observed increased weight gain and higher weight prevalence in PCOS and therefore be targeted for lifestyle interventions to optimise weight management.

Intrinsic factors potentially contributing to increased risk of weight gain in women with PCOS

In addition to potential differences in extrinsic factors, potential mechanisms for excess weight gain in PCOS may be related to underlying hormonal abnormalities including insulin resistance and hyperandrogenism or specific barriers which are intrinsic to maintaining healthy weight, such as appetite dysregulation,[218] altered metabolic rate,[219] or postprandial thermogenesis.[220] However, the research to date is limited and inconsistent. It is crucial to understand the pathophysiological mechanisms that may be altered in PCOS and associated with impaired weight management to guide realistic weight management goals and to aid investigation of future pharmacological targets.

Summary of systematic review evidence

Given the extensive studies included and the meta-analyses, further information, including detailed references and study characteristics, can be found in the technical report in Section 3.5.

Extrinsic factors potentially contributing to increased risk of weight gain in women with PCOS

Forty studies examined total energy intake of women with and without PCOS and thirty studies were suitable to be included in the meta-analysis. Four studies were judged as high risk of bias while the rest were of low to moderate risk of bias.

Thirty-seven studies examined total carbohydrate intake of women with and without PCOS and thirty studies were suitable to be included in the meta-analysis. Twenty-three studies were included in meta-analysis for total gram/day of carbohydrate intake while thirteen studies were included in the meta-analysis for percentage of carbohydrate intake over total energy intake. Only three studies were judged as high risk of bias while the rest were of low to moderate risk of bias.

Thirty-seven studies examined total protein intake of women with and without PCOS and thirty studies were suitable to be included in the meta-analysis. Twenty-five studies were included in meta-analysis for total gram/day of protein intake while thirteen studies were included in the meta-analysis for percentage of protein intake over total energy intake. Only three studies were judged as high risk of bias while the rest were of low to moderate risk of bias.

Thirty-six studies examined total fat intake of women with and without PCOS and twenty-eight studies were suitable to be included in the meta-analysis. Twenty-two studies were included in meta-analysis for total gram/day of fat intake while thirteen studies were included in the meta-analysis for percentage of fat intake over total energy intake. Only three studies were judged as high risk of bias while the rest were of low to moderate risk of bias.

Nine studies examined dietary glycaemic index of women with and without PCOS and seven were included in the meta-analysis. Two studies were judged as high risk of bias and the rest were of low to moderate risk of bias.

Eight studies examined dietary glycaemic load of women with and without PCOS and four were included in the meta-analysis. Two studies were judged as high risk of bias, the other two studies were of moderate risk of bias.

Forty-nine studies examined physical activity of women with and without PCOS and nine were included in the meta-analysis. Three studies were judged as high risk of bias, the other two studies were of moderate risk of bias.

Intrinsic factors potentially contributing to increased risk of weight gain in women with PCOS

A total of twenty studies compared energy intake homeostasis in women with and without PCOS. Outcomes examined included appetite stimulating gut hormones, appetite suppressing gut hormones, subjective hunger and subjective satisfy post meal or glucose intake. Four studies were judged as being moderate risk of bias while the rest were judged as being low risk of bias.

A total of nine studies examined energy expenditure homeostasis in women with and without PCOS. Outcomes examined included meal induced thermogenesis and resting energy expenditure, the latter of which was the only outcome amenable to meta-analysis (for five of the nine studies).

Appetite stimulating gut hormones

Adiponectin and ghrelin were compared between women with and without PCOS post oral glucose tolerance test (OGTT) or mixed meal test (MMT). Meta-analysis was not possible due to heterogeneity between the studies and narrative evidence synthesis was conducted.

Two out of two studies which examined post stimulation adiponectin area under the curve (AUC) both reported significantly lower AUC in women with PCOS than controls.

Three out of seven studies reported lower ghrelin AUC post MMT in women with PCOS than controls. All three studies post OGTT reported lower ghrelin AUC in women with PCOS than controls.

Overall, women with PCOS may have lower increase in appetite stimulating gut hormones (adiponectin and ghrelin) after meal or glucose intake than women without PCOS; however, the evidence is of very low certainty due to the observational nature of the studies, as well as inconsistency and imprecision.

Appetite supressing gut hormones

Glucagon-like peptide-1 (GLP-1), Peptide YY (PYY) and amylin were compared between women with and without PCOS post OGTT or mixed meal test (MMT). Meta-analysis was not possible due to heterogeneity between the studies and narrative evidence synthesis was conducted.

Nine studies examined post OGTT or MMT GLP-1 AUC in women with and without PCOS. Three studies reported GLP-1 AUC was lower in women with than without PCOS, one study reported GLP-1 AUC was higher in women with than without PCOS while the rest did not show any significant difference.

Four studies examined post OGTT or MTT PYY AUC in women with and without PCOS. Only one study reported that PYY AUC was lower in women with than without PCOS, the rest did not show any significant difference.

Only one study examined post OGTT or MMT amylin AUC in women with and without PCOS and it reported higher AUC in women with than without PCOS.

Overall, results of studies comparing appetite supressing gut hormones (GLP-1, PYY and amylin) after meal or glucose intake in women with and without PCOS are conflicting, with very low certainty evidence supporting no difference between the groups.

Subjective hunger

One study examined subjective hunger post MMT in women with and without PCOS and found that women with PCOS had more hunger than women without PCOS. Overall quality for this evidence is very low due to being only one study and low sample size.

Subjective satiety

Four studies examined subjective satiety post MMT in women with and without PCOS and only one study reported that women with PCOS had lower satiety than women without PCOS. The other three did not find any significant difference. Overall, evidence suggest that women with and without PCOS do not have any difference in subjective satiety post meal intake. Certainty of evidence for this finding is very low due to conflicting results.

Meal induced thermogenesis

Two studies examined meal induced thermogensis (MIT) in women with and without PCOS and their results were conflicting. It is unclear if meal induced thermogenesis differs between women with and without PCOS.

Resting energy expenditure

Nine studies examined resting energy expenditure (REE) in women with and without PCOS, of which five were suitable for meta-analysis. The remaining studies either did not report results for REE, or they reported outcomes in median (IQR) or using inconsistent units. In meta-analysis, there was no difference in REE between women with PCOS and controls (WMD=-38.61 [95%CI= -301.48, 224.26]; p=0.8). Certainty in the evidence was very low due to high and statistically significant heterogeneity (I^2= 98%, $p < 0.0001$), inconsistent direction of effect and variable effect sizes, and imprecision evidences by the wide CI. The observational nature of the data precludes causality and we cannot rule out residual confounding, further downgrading certainty in the evidence.

Recommendations

3.5		Factors affecting weight gain in PCOS	
3.5.1	EBR	Healthcare professionals and women with PCOS could consider that there is a lack of consistent evidence of physiological or behavioural lifestyle differences, related to weight, in women with PCOS compared to women without PCOS.	❖❖❖ ⊕○○○
3.5.2	PP	Whilst the specific mechanisms are unclear, it is recognised that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain and higher BMI which may: • underpin greater challenges with weight management • highlight the importance of lifelong healthy lifestyle strategies and prevention of excess weight gain • assist women with PCOS and healthcare professionals in forming realistic, tailored lifestyle goals.	

Justification

These new recommendations were prioritised by patients and health professionals. Rate of weight gain and excess weight is more prevalent in women with PCOS, compared to women without PCOS, and causes considerable concern among affected women. A BMI above 30 kg/m² 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 is vital, consistent with international public health recommendations. There is very low quality evidence that women with PCOS may have some differences in lifestyle behaviours (higher total dietary fat intake and lower physical activity on self-report) and may have some differences in appetite related hormones after a mixed meal tolerance test (MMTT). There is no evidence of certainty for other outcomes including energy intake (on pooled analysis), other macronutrients (carbohydrate, protein), glycaemic index, glycaemic load, subjective hunger or satiety, meal induced thermogenesis or resting energy expenditure. Most outcomes are self-reported and prone to recall bias and misreporting. It is acknowledged that women with PCOS have higher rates of weight gain and excess weight; however, the mechanisms contributing to this are not well understood. More research in this priority area is needed.

3.6 Weight stigma

What is the burden of weight stigma in women with PCOS?

Clinical need for the question

Weight stigma is the social devaluation of individuals because of their weight.[221] Weight stigma is the combination of negative attitudes, stereotypes, and prejudice about high body weight and for the individuals targeted, their weight stigma experiences/perceptions can include internalisation (i.e. applying negative stereotypes e.g. believing you are not worthy of love because of your weight). Weight stigma is pervasive, and is arguably the last form of acceptable stigma.[222] Weight-related attitudes are negative and are not improving over time. It is common in many settings, including healthcare, workplace, education, and the home.[223] A systematic review found that 19-41% of individuals with higher weight experienced blatant weight discrimination, and women more commonly experience this with US data suggesting weight-related mistreatment in ~40% of adults.[224] Perpetration of weight stigma is common across healthcare disciplines.[221] In weight management programs over 50% of participants reported weight stigma.[225,226]

Summary of systematic and narrative review evidence

Given the studies included here on both systematic and narrative review, further information, including detailed references and study characteristics can be found in the technical report in Section 3.6.

We systematically reviewed all published studies that assessed the burden of weight stigma in women with PCOS. We also reviewed studies that assessed healthcare professionals working with those with PCOS and weight stigma. Seven studies identified, were qualitative, with four central findings – women with PCOS reported: experiencing weight stigma from doctors, experiencing weight stigma from family members, internalising weight stigma from a variety of societal sources, and anticipating weight stigma from the general public. Both women with PCOS and healthcare professionals report weight stigma in healthcare.

Our analysis was descriptive and preliminary in PCOS, given the limited evidence overall. Hence, we also reviewed evidence from the general population. Overall, systematic review findings are consistent with other populations, showing that weight stigma is pervasive, detrimental to mental health, profoundly affected by societal attitudes toward weight, and perpetrated in everyday settings by family members in the home and health and medical professionals in healthcare settings.

Weight stigma is associated with negative biopsychosocial outcomes, including poorer health behaviours. Specifically, weight stigma is associated with exercise avoidance in undergraduate women (controlling for BMI; 227), and experimental evidence shows that those exposed to weight stigmatising material had greater food consumption in higher weight individuals (compared to controls;[228]). Further, weight stigma is associated with many of the negative biopsychosocial outcomes associated with higher weight. Longitudinal evidence from the U.K. (n = 3,609) found [229] that, from baseline to a 4-year follow-up, weight stigma accounted for 27% of the prospective association between BMI and physiological dysregulation as per (i.e. biomarkers of health, such as inflammation, cardiovascular health and lipid/metabolic regulation). In other words, weight stigma explained nearly a quarter of the relationship between weight and physiological health. Experienced/perceived weight stigma is also moderately and significantly (r = -0.33; k = 241) associated with adverse mental health correlates such as depression, anxiety, disordered eating, body image disturbance [230]. There are proposed mechanisms that may explain the relationship between experienced weight stigma and adverse psychosocial correlates, such as the extent to which individuals internalise weight stigma [231,232]. A recent systematic review found that internalised weight stigma mediated the relationship between experienced/perceived weight stigma and biopsychosocial correlates, such as disordered eating, body shame, and exercise behaviour [233].

Recommendations

3.6 #		Weight stigma	
3.6.1	**EBR**	Many women with PCOS experience weight stigma in healthcare and other settings and the negative biopsychosocial impacts of this should be recognised.	❖❖❖❖ ⊕⊕○○
3.6.2	**CR**	Healthcare professionals should be aware of their weight biases and the impact this has on their professional practice and on women with PCOS.	❖❖❖❖
3.6.3	**CR**	Health policy makers, managers and educators should promote awareness of weight stigma and invest in weight stigma education and minimisation strategies.	❖❖❖❖
3.6.4	**PP**	Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes. In PCOS this includes: • acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only one indicator of health and broader factors should be assessed • asking permission to discuss and measure weight and using strategies to minimise discomfort (e.g. blind weighing) • recognising that the terms 'overweight' and 'obese/obesity' can be stigmatising with suggested alternatives including 'higher weight' • if weighing, explaining how weight information will be used to inform risks prevention and treatment and how not knowing may impact on recommendations • ensuring appropriate equipment is available for women of all sizes • offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without focusing on intentional weight loss) tailored to individual goals and preferences • offering all women best practice assessment, treatment and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone.	
3.6.5	**PP**	Increasing awareness of weight stigma among family members of women and adolescents with PCOS should be considered.	

Justification

These new recommendations were prioritised by patients and health professionals. Available evidence indicates that women with PCOS experience weight stigma from healthcare professionals and family members, internalise weight stigma, and anticipate weight stigma. Weight stigma is associated with negative biopsychosocial outcomes, including poorer health behaviours (e.g. exercise avoidance, higher food consumption). Further, weight stigma is independently associated with many of the negative biopsychosocial outcomes associated with higher weight. Weight-neutral/weight-inclusive care targeting health behaviours and outcomes, rather than weight loss, and providing best practice care regardless of weight, is less likely to result in weight stigma.

Most studies are conducted in Caucasian populations. The following subgroups needs to be considered in future research: (i) cultural and ethnic subgroups, and (ii) subgroups across the lifespan – including adolescents (only considered in one study), prepregnancy, pregnancy, post-partum, menopause. Weight stigma is pervasive and entrenched. Weight-centric/weight-normative care is the norm in most health services. Many healthcare professionals are unaware of their own weight-stigmatising beliefs and behaviours. Even healthcare professionals who are aware of weight stigma and its impacts can find it difficult to provide weight-neutral/weight-inclusive care.

Practicing weight-inclusive care will likely significantly change practice and may require increasing consultation time. Other potential causes for increased cost are training, education, equipment, resources, furniture. Increased allied health referral to assist with weight-inclusive interventions may also increase cost. These factors were considered and the balance was determined to be desirable, hence the recommendations were generated with consensus across the GDG.

Chapter Four

Management of non-fertility features

4.1 Pharmacology 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 practice points to inform women and guide healthcare 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		Pharmacology treatment principles in PCOS
	PP	Shared decision making between the patient (and parent/s or guardian/s, if the patient is a child) and the healthcare professional is required.
	PP	An individual's characteristics, preferences and values must be elicited and considered when recommending any intervention alone or in combination.
	PP	Understanding how individual adults and adolescents value treatment outcomes is essential when prescribing medications.
	PP	Medical therapy is generally not approved for use specifically in PCOS and recommended use is therefore evidence-based, but off-label. Healthcare professionals need to inform adults, adolescents and their parents/s or guardian/s and discuss the evidence, possible concerns and side-effects. Regulatory agencies should consider approval of evidence-based medications for use in PCOS.

'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 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 an indication or patient group for any given drug.

4.2 Combined oral contraceptive pills

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

Clinical need for the question

Combined oral contraceptive pills (COCPs) are commonly prescribed for adults and adolescents with PCOS to ameliorate the hormonal disturbances and clinical features. The effects of COCPs on menstrual cycle, hirsutism, weight loss, waist/hip ratio (WHR), testosterone concentrations, lipid profile and blood sugar levels are variably reported and depend on preparation, duration of use, severity of presentation, and adherence among other factors. Different combinations of COCPs are available with heterogeneous estrogen [natural estrogen or synthetic ethinyloestradiol (EE)] and progestin preparations with varying pharmacological and clinical properties. Thus, efficacy and side-effects of COCPs in PCOS may vary. The optimal COCP preparation, formulation, or dosing regimen remains unclear.[234,235]

Consideration of adverse effects is required before prescribing COCPs. Absolute contraindications include women with history of migraine with aura, deep vein thrombosis/pulmonary emboli, known thrombogenic mutations, multiple risk factors for CVD, history of ischaemic heart disease, stroke, complicated valvular heart disease, breast cancer, neuropathy, severe cirrhosis and malignant liver tumours. Women up to 6 weeks postpartum with other risk factors for venous thromboembolism (VTE) (e.g. immobility, transfusion at delivery, BMI > 30 kg/m^2, postpartum haemorrhage, immediately post-caesarean delivery, preeclampsia, smoking), have additional risk factors for venous thrombosis that need to be considered.[236]

Current evidence suggests that COCPs containing levonorgestrel, norethisterone and norgestimate (1st, 2nd and 3rd generation progestins) are associated with the lowest relative risk of venous thrombosis. Moreover, 4th generation includes preparations with natural estrogens resulting in significant variation in this generation. Furthermore, COCPs with 35ug EE and cyproterone acetate should not be used first-line and are indicated for treating moderate or severe hirsutism or acne, due to higher risk for venous thrombosis.

Summary of systematic review evidence – COCP

Given the extensive studies included and the meta-analyses, further information, including detailed references and study characteristics, can be found in the technical report in Section 4.1.

COCP with low versus high ethinyloestradiol (EE) dose: Two RCTs compared COCPs with higher (≥ 30 µg) versus low (20 µg) EE dose for 12 months, both with a low risk of bias. A meta-analysis could not be performed. Hirsutism reported in both studies showed no difference, with a moderate certainty of evidence. Other outcomes (BMI, WHR, FAI, total testosterone and SHBG), were only reported by one study, with the only difference being a greater increase in SHBG, with 30 µg with a low certainty of evidence.

COCP with 1st versus 3rd generation progestins: One RCT with a high risk of bias was identified and had four arms. Chlormadinone acetate, a 1st generation progestin was compared with desogestrel and gestodene. The only difference in outcomes was a greater decrease in testosterone and androstenedione, and a greater increase in SHBG with the 1st generation progestin, with a very low certainty of evidence.

COCP with 1st versus 4th generation progestins: Four RCTs were identified, all with a high risk of bias. Chlormadinone acetate, a 1st generation progestin was compared with the 4th generation progestin drospirenone with durations of 3-24 months. Meta-analysis showed a greater decrease in DHEAS (low certainty) and androstenedione (very low certainty) with drospirenone. For the other reported outcomes, a meta-analysis could not be performed, but with very low certainty of evidence, free testosterone, cholesterol and CRP levels were lower after the drospirenone preparation, with no differences in other outcomes.

COCP with 2nd versus 3rd generation progestins: Two RCTs were identified, both with a high risk of bias. One crossover study, involved four arms for 6 months. Both studies included 2nd generation levonorgestrel versus 3rd generation desogestrel but meta-analysis could not be performed. The crossover study showed a greater decrease in FAI, and increase in SHBG, with the 3rd generation progestin, with a very low certainty of evidence. Other outcomes showed no difference.

COCP with 2nd versus 4th generation progestins: Two RCTs were identified, with a high risk of bias with 2nd generation levonorgestrel compared to 4th generation drospirenone in both studies. A meta-analysis could not be performed but a greater decrease in FAI, and a greater increase in SHBG, were seen with the 4th generation progestin, with a very low certainty of evidence. For the other reported outcomes, no differences were seen between groups.

COCP with 3rd versus 4th generation progestins; Five RCTs were identified in adults with 3rd generation desogestrel or gestodene, and 4th generation drospirenone or dienogest with four with a high risk of bias and one with a low risk of bias. Meta-analysis showed a lower BMI after treatment with 4th compared with 3rd generation progestins with a low certainty of evidence. Total testosterone levels and LDL were lower, and HDL higher, after treatment with a 4th generation progestin, with a very low certainty of evidence.

Other COCPs versus ethinly estradiol with cyproterone acetate (CPA); Ten RCTs were identified, six with a high risk of bias, one moderate and three low risk of bias. Two involved adolescents, and the duration was between 3-12
months. Meta-analysis showed that the combination EE/CPA, resulted in a lower BMI, and lower total testosterone with a low certainty of evidence and a higher cholesterol and LDL (very low certainty), with less hirsutism, with low certainty of evidence. Regarding adverse effects, the outcome was not assessed systematically.

COCP versus progestin alone: Two RCTs were identified with a high risk of bias. Meta-analysis showed BMI, WHR and total testosterone were no different, with low certainty of evidence. In one study lower FAI, insulin and triglyceride levels and higher SGBG were noted with the COCP, all with very low certainty of evidence.

COCP versus control: Three RCTs compared COCPs with control with a high risk of bias. Study duration was 6-24 months. A meta-analysis could not be performed. COCP was superior to controls in improving cycle regularity with low certainty of evidence. COCP treatment improved multiple domains of QoL, with very low certainty of evidence. Weight, testosterone, insulin levels were lower after COCP treatment, compared with controls, with very low certainty of evidence. For other key outcomes, no difference was seen between groups with very low certainty of evidence. COCP treatment was associated with more minor adverse effects than controls.

COCP versus placebo: One RCT involving adolescents was identified and had a moderate risk of bias. COCP treatment resulted in lower levels of testosterone, higher SHBG and lower FAI, with very low certainty of evidence.

COCP versus lifestyle: One RCT was found, with a moderate risk of bias. LDL and triglycerides were lower after lifestyle treatment, with very low certainty of evidence. Total testosterone was lower after COCP treatment, compared with lifestyle, with very low certainty.

Lifestyle ± anti-obesity treatment versus combined COCP and lifestyle ± anti-obesity treatment: One preconception RCT was identified with a moderate risk of bias. COCP induced lower weight, lower total testosterone and higher SHBG, with a very low certainty of evidence. OGTT showed higher glucose levels with COCP with a very low certainty of evidence. In the combined treatment arm, patients improved in sexual desire, but no difference
was seen in the COCP arm with no differences in QoL or depression with very low certainty of evidence.

COCP has also been compared to and studied with multiple other agents including anti-obesity agents with all comparisons including only one small study. This information can be found in the technical report but did not inform recommendations made here.

Recommendations

4.2		Combined oral contraceptive pills	
4.2.1	EBR	The combined oral contraceptive pill (COCP) could be recommended in reproductive age adults with PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕○○○
4.2.2	EBR	The COCP could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles.	❖❖❖ ⊕○○○
4.2.3	EBR	Health professionals could consider that there is no clinical advantage of using high dose ethinylestradiol (≥ 30 µg) versus low dose ethinylestradiol (< 30 µg) when treating hirsutism in adults with PCOS.	❖❖❖ ⊕○○○
4.2.4	EBR	General population guidelines should be considered when prescribing COCP in adults and adolescents with PCOS as specific types or doses of progestins, estrogens or combinations of COCP cannot currently be recommended.	❖❖❖ ⊕○○○
4.2.5	EBR	The 35 µg ethinyl estradiol plus cyproterone acetate preparations should be considered as second-line therapy over other COCPs, balancing benefits and adverse effects, including venous thromboembolic risks.	❖❖❖ ⊕○○○
4.2.6	EBR	Progestin only oral contraceptives may be considered for endometrial protection, based on general population guidelines, acknowledging that evidence in women with PCOS is limited.	❖❖❖ ⊕○○○
4.2.7	PP	When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS: • It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies. • Shared decision making (including accurate information and reassurance on the efficacy and safety of COCP) is recommended and likely to improve adherence. • Natural estrogen preparations and the lowest effective estrogen doses (such as 20-30 micrograms of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side-effects, cost and availability. • The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines • The relative and absolute contraindications and side-effects of COCPs need to be considered and be the subject of individualised discussion. • PCOS specific features such as higher weight and cardiovascular risk factors, need to be considered.	

Justification

Although relatively safe, COCPs have absolute and relative contraindications and risks and benefits in the general population that need consideration by healthcare 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 a higher BMI may yield the greatest benefit. The PCOS features, BMI, ethnicity and the informed preference of the individual with PCOS need to be considered when recommending pharmacological agents for treatment. COCPs are off-label treatments specifically for PCOS. However, use is evidence-based for the treatment of clinical features of PCOS and is generally not restricted. Women should be informed of the benefits and risks and the regulation status. Regulatory agencies should consider approving COCP for use in PCOS. Recommendation are similar to the 2018 Guideline with the additional recommendation on progestin only contraceptives added.

4.3 Metformin

Is metformin 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 T2D and for several decades in PCOS. Insulin resistance is documented on clamp studies in 75% of lean women and 95% of women with an higher BMI[237] in PCOS and addressing this has underpinned the now widespread use of metformin. 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 occur and use in PCOS is generally off-label. 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

Given the extensive studies included and the meta-analyses, further information, including detailed references and study characteristics, can be found in the technical report in Section 4.3.

Metformin versus placebo: Twenty three RCTs were identified with 22 included in meta-analysis with three having a low risk of bias, 16 moderate and four a high risk of bias. Meta-analysis showed metformin was superior in lowering BMI (certainty moderate), WHR and testosterone (certainty very low), fasting glucose (certainty moderate), total cholesterol and triglycerides (certainty low), CRP (certainty very low) and HOMA-IR (certainty moderate) compared to placebo. Sub analyses according to BMI in participants with a healthy weight (BMI < 25), showed metformin lowered FAI (certainty moderate) and fasting insulin (certainty low). For BMI > 25, metformin lowered BMI (certainty moderate), fasting glucose and total cholesterol (certainty moderate) and LDL (certainty low). There was one
study comparing metformin to placebo in adolescents, which found no differences in outcomes with metformin compared to placebo with very low certainty.

Metformin + lifestyle versus placebo + lifestyle: Eight RCTs were identified with four having a low and four a moderate risk of bias and only one study was in adolescents. Meta-analysis showed that metformin + lifestyle was superior in lowering testosterone (moderate certainty) and WHR with no differences for other outcomes with moderate to very low certainty of evidence. In adolescents, testosterone and FAI was significantly lower in participants treated with metformin + lifestyle compared to those who received placebo + lifestyle. Certainty for these findings was very low. Gastrointestinal side-effects seem to be more common in the metformin + lifestyle group.

Metformin versus lifestyle: Three RCTs were identified; two had a moderate risk of bias and one a high risk of bias. All studies were on patients with a higher BMI and one was in adolescents. Meta-analysis showed that metformin was superior in lowering testosterone with no difference for other outcomes, however, certainty in the evidence was very low for all outcomes. Higher gastrointestinal side-effects were reported with metformin.

Metformin versus metformin (different doses): One RCT with a high risk of bias, compared different doses of metformin and there was no difference between the two interventions with very low certainty of evidence.

Metformin versus metformin + medroxy progesterone acetate: One RCT with a moderate risk of bias found that metformin was superior for improving testosterone, free testosterone and HDL with very low certainty of evidence.

Recommendations

4.3		Metformin	
4.3.1	EBR	Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m² for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles.	❖❖❖ ⊕○○○
4.3.2	EBR	Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.	❖❖❖ ⊕○○○
4.3.3	CR	Metformin alone may be considered in adults with PCOS and BMI < 25 kg/m², acknowledging limited evidence.	❖❖❖
4.3.4	PP	Where metformin is prescribed the following need to be considered: • Shared decision making needs to consider feasibility and effectiveness of active lifestyle intervention. Women should be informed that metformin and active lifestyle intervention have similar efficacy. • Mild adverse effects, including gastrointestinal side-effects are generally dose dependent and self-limiting. • Starting at a low dose, with 500 mg increments 1-2 weekly and extended-release preparations may minimise side-effects and improve adherence. • Suggested maximum daily dose is 2.5 g in adults and 2 g in adolescents. • Use appears safe long-term, based on use in other populations, however indications for ongoing requirement needs to be considered. • Use may be associated with low vitamin B12 levels, especially in those with risk factors for low vitamin B12 (e.g. diabetes, post bariatric/metabolic surgery, pernicious anaemia, vegan diet etc.), where monitoring should be considered.	

Justification

A considerable number of studies were captured on systematic review; however, the quality and certainty of the evidence was limited. Inadequate evidence was found around BMI subgroups and adolescents. Metformin has clear benefits in other relevant populations including those with T2D, which also informed GDG recommendations. In PCOS, evidence indicated that metformin was effective overall and/or in specified subgroups, in improving weight, BMI, WHR, testosterone and triglycerides in PCOS including those defined by Rotterdam criteria. In providing these recommendations, the GDG considered that women with PCOS regarded BMI and weight 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 in Chapter five of this guideline. Gastrointestinal side-effects were noted, and whilst more frequent with metformin, appeared to be mild, self-limiting and could be minimised with lower starting doses, extended-release preparations or administration with food based on general population evidence. 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 favour metformin use in PCOS. Metformin is an off-label treatment specifically for PCOS. However, use is evidence-based for the treatment of clinical features of PCOS and is generally not restricted. Women should be informed of the benefits and risks of metformin in PCOS. Regulatory agencies should also consider approving metformin for use in PCOS. Overall these recommendations are similar to the 2018 Guideline.

4.4 Metformin and combined oral contraceptive pills

Is metformin versus the COCP with or without other agents effective for management of features of PCOS in adolescents and adults with PCOS?

Clinical need for the question

Metformin and COCP have different mechanisms of action and efficacy on various outcomes in PCOS, as a complex and heterogeneous condition. The comparative role of these agents and the role of combining these agents together and with other relevant agents remains unclear and has been prioritised.

Summary of systematic review evidence

Given the extensive studies included and the meta-analyses, further information, including detailed references and study characteristics, can be found in the technical report in Section 4.4.

COCP versus metformin: Twenty-five RCTs were captured with four RCTs in adolescents. Those reporting mean ± SD were included in meta-analysis, with subgroup analysis for adults and adolescents. Overall, there were no differences between treatments regarding BMI, weight or WHR, with very low certainty of evidence. No differences were seen in the subgroups. Menstrual cycle duration became shorter with COCP treatment compared with metformin, with moderate certainty of evidence. There was no difference in hirsutism (very low certainty of evidence), but COCP treatment resulted in lower FAI, total testosterone, androstenedione and higher SHBG levels (low certainty of evidence), and lower free testosterone and DHEAs (very low certainty).

In adolescents, similar results were seen with hyperandrogenism, but with very low certainty of evidence, except for total testosterone, which was lower after COCP treatment with moderate certainty of evidence. For free testosterone, no difference was seen between treatments, with very low certainty of evidence.

In adults, there was no difference in hirsutism with a very low certainty of evidence. FAI and total testosterone levels were lower after COCP treatment with low certainty and free testosterone lower with very low certainty. SHBG levels were higher (low certainty), androstenedione lower (moderate certainty) and DHEAS lower (very low certainty) after COCP, compared with metformin.

For metabolic outcomes, insulin was lower overall (low certainty), and in adults (moderate certainty) after metformin. In adolescents there was no difference in insulin (very low certainty of evidence). HOMA-IR was lower after metformin treatment both overall and in adults, with very low and low certainty of evidence respectively. Cholesterol levels were lower after metformin both overall (very low certainty) and in subgroups (low certainty). There were no differences in LDL, HDL or triglyceride levels, except for adolescents, where lower LDL levels were seen after metformin treatment (low certainty). CRP levels were lower after metformin treatment, overall (low certainty), in adults (low certainty), and in adolescents (very low certainty). Glucose levels did not differ, overall or in the subgroups.

COCP versus COCP + metformin: Eighteen RCTs were identified all in adults. Combined therapy resulted in lower FAI (moderate certainty), higher SHBG and lower DHEAS (low certainty) and lower androstenedione (very low evidence certainty). Combined therapy also reduced insulin and HOMA-IR with very low and low certainty respectively. With moderate certainty, the effect on total testosterone dis not differ between treatments. There were no differences in blood lipids, CRP or anthropometry (low or very low certainty). There was no difference in QoL. COCP + metformin seemed to be associated with more gastrointestinal side-effects.

COCP + metformin + lifestyle versus COCP with cyproterone + metformin + lifestyle: One study, with a high risk of bias was identified in insulin-resistant women with PCOS and higher weight. All received metformin and lifestyle modification and were randomised to different COCP groups with no difference between treatment in any of the reported outcomes, with very low certainty of evidence.

Metformin has been compared to and studied with multiple other agents including glitazones, saxagliptin, sodium-glucose transport protein 2 (SGLT-2) inhibitors, liraglutide, and inositol with all comparisons including only one small study and many being of limited clinical relevance such as comparison to glitazones where safety in reproductive aged women is not confirmed. This information can be found in the technical report but did not inform recommendations made here.

Recommendations

4.4		Metformin and combined oral contraceptive pills	
4.4.1	**EBR**	COCP could be used over metformin for management of hirsutism in irregular menstrual cycles in PCOS.	❖❖❖ ⊕○○○
4.4.2	**EBR**	Metformin could be used over COCP for metabolic indications in PCOS.	❖❖❖ ⊕○○○
4.4.3	**EBR**	The combination of COCP and metformin could be considered to offer little additional clinical benefit over COCP or metformin alone, in adults with PCOS with a BMI ≤30 kg/m².	❖❖❖ ⊕○○○
4.4.4.	**PP**	In combination with the COCP, metformin may be most beneficial in high metabolic risk groups including those with a BMI > 30 kg/m², diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.	
4.4.5	**PP**	Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles. For hirsutism, other interventions may be needed.	

Justification

A large number of studies were considerable on systematic review. However, the quality and certainty of the evidence was limited and recommendations were conditional. Inadequate evidence was found around BMI subgroups and adolescents. COCP and metformin have different mechanisms of action and efficacy in PCOS and hence recommendations reflect relevant outcomes and indications for treatment. These recommendations were similar to the 2018 Guideline.

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

Excess weight is a significant concern for adolescents and adults with PCOS and is more prevalent than in those without PCOS. Whilst healthy lifestyle intervention has a key 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 of lifestyle interventions appear to benefit from the addition of these agents to lifestyle interventions in the general population. Recent guidelines, systematic and Cochrane reviews have focused on the role of these agents in general and high-risk populations including in adolescents with a BMI > 30 kg/m². 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 used in adults for assistance with weight loss and weight maintenance in management of higher weight in other populations.[238] However, in PCOS and in reproductive aged women generally, the role of anti-obesity pharmacological agents remains unclear. Only agents approved for use by multiple regulatory agencies in weight management were the subject of recommendations here including exenatide, liraglutide, semaglutide and orlistat.

Summary of systematic review evidence

Given the extensive studies included and the meta-analyses, please see the technical report for detailed references and study characteristics in Section 4.5.

Eleven RCTs were identified and four were included in meta-analyses. All studies enrolled women with higher weight and/or insulin resistance and al were in adults. Five studies trialled exenatide,[239-243], three orlistat,[244-246], two liraglutide, [247,248] one semaglutide,[249] and one phentermine-topiramate as well as exenatide.[239] Four studies were placebo-controlled[245,247-249], four used metformin as a comparator,[240-242,250] two trials used the oral contraceptive pill (OCP) and lifestyle [244,246] alone, and one trial used metformin and lifestyle.[246] The majority of trials were at unclear risk of selection bias, mainly due to failure to specify if or how allocation was concealed. More than half of trials were at high risk of performance bias due to lack of blinding of participants and personnel, three quarters were at unclear risk of detection bias, and less than half were at low risk for reporting bias. More than a quarter of trials were at high risk of other bias, mainly due to conflicts of interest.

Exenatide versus metformin: There was no difference between exenatide and metformin for androgen related, metabolic, lipid and anthropometric outcomes. There was very low certainty evidence that metformin was superior to exenatide for fasting glucose, while exenatide was superior for area under the curve insulin and the Matsuda index. Nausea was more frequent with exenatide.

Exenatide + COCP versus metformin + COCP: Exenatide combinations were superior to metformin for most, but not all metabolic, anthropometric outcomes and reproductive outcomes, while there were no between-group differences for androgenicity and lipids. Gastrointestinal adverse events were more common with exenatide + COCP.

Exenatide + metformin (+/-COCP) and metformin alone (+/- COCP): There were no differences for most androgen related, metabolic and lipid outcomes. Metformin alone (+/- COCP) was superior to exenatide + metformin 120 minute insulin and LDL cholesterol. Exenatide + metformin + COCP was superior to MET + COCP for fasting glucose, 120 minute glucose, and 120 minute insulin. Exenatide + metformin + COCP was superior to MET + COCP for body weight, BMI and WC although there was no difference between these exenatide + metformin and metformin alone for weight and BMI. There was more bloating in the group with exenatide, but other gastrointestinal adverse events were comparable. Injection site reactions were reported with exenatide.

Exenatide versus phentermine/topiramate: There were no differences for androgenicity, metabolic, lipids, and anthropometric outcomes. Nausea was more common with exenatide while insomnia, rapid heart rate and dizziness were more common in the phentermine/topiramate group.

Liraglutide (+/- lifestyle) versus placebo (+/- lifestyle): Liraglutide was superior for menstrual cycles and some but not all androgen related and metabolic outcomes, but not for lipids. Liraglutide was superior to placebo for anthropometric outcomes including weight and fat mass. However, liraglutide alone resulted in more lean body mass loss than placebo, but this was not seen when liraglutide was combined with lifestyle interventions. Gastrointestinal adverse events and menstrual bleeding were more common with liraglutide. Gastrointestinal adverse events and abnormal menstrual bleeding were more common with liraglutide.

Semaglutide versus placebo: Semaglutide was superior for some but not all metabolic outcomes and lipid parameters, and anthropometric measures including visceral body fat. Nausea was more common with semaglutide

Orlistat versus placebo: Orlistat was superior to placebo for anthropometric and lipid outcomes but not for androgen related or metabolic outcomes.

Orlistat + lifestyle + COCP versus lifestyle + COCP alone: The first preparation was superior for some but not all androgen related, lipid and anthropometric outcomes, while there were no differences for metabolic outcomes. There was low certainty evidence that orlistat + lifestyle + COCP is superior to lifestyle + COCP alone for SHBG, LDL, and CRP and that there is no difference between groups for HDL, fasting insulin, and triglycerides. More than half of those taking orlistat reported urgency to go to the bathroom and 30% reported oily spotting in undergarments.

Orlistat versus metformin or orlistat + metformin versus metformin alone: There were no differences for androgens, metabolic, lipids and anthropometric outcomes. The only exception was that orlistat + metformin was superior to metformin alone for body fat reduction.

Recommendations

4.5 #		Anti-obesity pharmacological agents	
4.5.1	**CR**	Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.	❖❖❖
4.5.2	**PP**	Healthcare professionals should ensure concurrent effective contraception when pregnancy is possible, for women who take GLP-1 receptor agonists, as pregnancy safety data are lacking.	
4.5.3	**PP**	Gradual dose escalation for GLP-1 receptor agonists is recommended to reduce gastrointestinal adverse effects.	
4.5.4	**PP**	Shared decision making, when discussing GLP-1 receptor agonist use with women with PCOS, needs to consider side-effects, and the potential need for long-term use in weight management, given the high risk for weight regain after discontinuation, and the lack of long-term safety data.	

Justification

There was limited evidence identified in the PCOS population. 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, however the strong evidence in the general population and the increased prevalence of higher weight, led to high priority and strong recommendation for research with new anti-obesity agents. The evidence to support the consensus recommendation was informed by evidence and guidelines on the use of anti-obesity pharmacological agents in the management of higher weight in non-PCOS adults. There are known contraindications and side-effects of these medications that need to be considered and monitored. Concerns about cost effectiveness were also considered by the group, based on evidence in the general population. Recommendations will only apply to adults who are higher weight and not adolescents. There were no studies identified in adolescents. This is a high priority area for clinicians and those with PCOS and this is a high priority area for future research.

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 female pattern hair loss (see Chapter 1). Given the adverse impact of clinical hyperandrogenism on emotional wellbeing and QoL (see Chapter 2) a high priority was given to clinical hyperandrogenism outcomes and 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. Overall, the role of anti-androgens remains controversial and this question was prioritised across flutamide, finasteride and spironolactone.

Summary of systematic review evidence

Given the extensive studies included and the meta-analyses, please see the technical report for detailed references and study characteristics in Section 4.6.

Anti-androgen versus placebo: One RCT was identified in adolescents using finasteride with a high risk of bias. The mFG score and biochemical hyperandrogenism were lower at 3 and 6 months. Finasteride-treated participants reported positive subjective outcomes. Side-effects were not reported but the certainty of evidence was low.

Anti-androgens versus COCP, One RCT with a moderate risk of bias compared a cyproterone containing COCP with spironolactone, reporting lower hirsutism with COCP with a very low certainty of evidence.

Anti-androgen versus metformin: One RCT in adults compared finasteride, metformin or the combination and had high risk of bias. Fasting glucose improved in both finasteride and metformin groups at six months, but were not different at 12 months. The finasteride group had higher SHBG concentrations at 12 months with very low certainty of evidence.

Anti-androgen + COCP versus COCP +/- placebo: Six RCTs in adults all had moderate risk of bias. Meta-analysis showed total cholesterol, LDL and triglycerides were lower in COCP ± placebo. No differences in weight, BMI, testosterone, SHBG, HDL, and adverse events were noted. The certainty in the evidence ranged from very low to low, except for BMI which was moderate.

Anti-androgen + metformin versus COCP, One RCT was identified, including adolescents. With COCP treatment, SHBG levels were higher with very low certainty of evidence. Anti-androgen + metformin lowered triglycerides and LDL with very low certainty of evidence.

Anti-androgen + COCP versus metformin: Four RCTs in adults were included, two with a high risk of bias, one moderate and one low risk of bias. Highly variable preparations and doses were used with three of the studies using spironolactone and one using flutamide. Only two outcomes could be included in the meta-analysis. No differences were seen in BMI or HDL, with very low certainty of evidence. Narratively, FAI and androstenedione levels were lower after anti-androgen + COCP, with very low certainty. Fasting glucose levels were lower after metformin, with very low certainty. In all other outcomes, there were no differences.

Anti-androgen + lifestyle versus anti-androgen + metformin + lifestyle: Three RCTs were identified, two with low and one with high risk of bias. No differences were apparent for BMI, hirsutism, total testosterone, insulin resistance with evidence certainty varying between very low to low. Fasting glucose was lower in the intervention with metformin with a moderate certainty of evidence and the other combination was better for triglycerides, with a low certainty of evidence.

Anti-androgen + metformin + lifestyle versus metformin + lifestyle: Four RCTs in adults were identified, three with low risk of bias and one moderate risk of bias. Meta-analysis showed no differences in weight, BMI, WHR, hirsutism, SHBG, DHEAS, lipids and a range of markers of insulin resistance. Testosterone and fasting insulin were lower in antiandrogen + metformin + lifestyle group with low certainty of evidence.

Anti-androgen + metformin + pioglitazone versus COCP: One study in adolescents with moderate risk of bias showed that the group with pioglitazone had reduced hirsutism, SHBG, fasting insulin, HOMA-IR, LDL, CRP and FAI but higher androstenedione compared with the COCP group. Certainty in this evidence was low. In adolescents, five publications were identified, however they were all from on research group, and had overlapping populations. Hence, data was extracted from the publication with the largest sample size, which had a high risk of bias. Anti-androgen + metformin + pioglitazone improved ovulation but there were no differences for FG scores, testosterone, androstenedione, BMII, HOMA-IR, OGTT, or lipids. SHBG was higher in the COCP group and insulin measures were lower in the anti-androgen + metformin + pioglitazone group. Side-effects/adverse events were not discussed and certainty of the evidence was low for all outcomes.

Anti-androgen + lifestyle versus metformin + lifestyle: Four RCTs were identified, two had low risk of bias and two moderate risk. Meta-analysis showed that hirsutism, SHBG and fasting insulin improved with anti-androgens with no differences in testosterone, DHEAS, fasting glucose, QUICKI, androstenedione, HOMA-IR, or BMI. Certainty for fasting insulin, WHR, testosterone, and QUICKI was moderate (downgraded due to moderate risk of bias), while the remaining outcomes had low to very low certainty evidence

Multiple other combinations of COCP, anti-androgens, lifestyle and metformin were identified with one to two small RCTs for each comparison, significant risk of bias and very low certainty of evidence. These are detailed in the technical report but did not influence recommendations here.

Recommendations

4.6		Anti-androgen pharmacological agents	
4.6.1	**EBR**	In combination with effective contraception, anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.	❖❖❖ ⊕○○○
4.6.2	**CR**	Given the negative psychological impact of female pattern hair loss, anti-androgens in combination with COCP could be trialed, acknowledging the lack of evidence in the PCOS population.	❖❖❖
4.6.3	**PP**	Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/s or guardian/s, regarding the risks of incomplete development of external genital structures of male fetuses (undervirilisation) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counseled to use effective contraception (e.g. intrauterine device or COCPs).	
4.6.4	**PP**	Anti-androgens could be considered to treat hirsutism, in the presence of another effective form of contraception, for women with contraindications for COCP therapy or when COCPs are poorly tolerated.	
4.6.5	**PP**	When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that: • spironolactone at 25-100 mg/day appears to have lower risks of adverse effects • cyproterone acetate at doses ≥ 10 mg is not advised due to an increased risk including for meningioma • finesteride has an increased risk of liver toxicity • flutamide and bicalutamide have an increased risk of severe liver toxicity. The relatively limited evidence on anti-androgens in PCOS needs to be appreciated with small numbers of studies and limited numbers of participants.	

Justification

The GDG recognised plausible reasons for anticipating differences in the relative effectiveness of anti-androgens for different PCOS features, 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 and small samples sizes with a multitude of comparisons with significant risk of bias and low to very low certainty, limited the ability of the GDG to make clear evidence-based recommendations. 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 noted. Contraception is considered mandatory in reproductive age women when using anti-androgens. For these reasons, most anti-androgen use in PCOS is in combination with COCPs (see Section 4.3), however it is noted that use could be considered with other forms of effective contraception.
These recommendations are similar to the 2018 Guideline.

4.7 Inositol

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

Clinical need for the question

Insulin resistance and hyperinsulinaemia are underlying endocrine or hormonal features of PCOS, independent of BMI. Mild gastrointestinal side-effects with metformin, and concerns about glitazones, has meant that other options to address insulin resistance are needed in PCOS. Inositol acts as a secondary messenger with a role in insulin signaling transduction.[251] There are nine stereo-isomers of inositol of which myo-inositol (MI) is the most abundant in the human body. [252] MI promotes glucose uptake[253] and is also involved in FSH mediated pathways impacting proliferation and maturation of granulosa cells.[254] Under the stimulus of insulin, MI is converted to D-chiro-inositol (DCI),[255] which stimulates glycogen production and facilitates glucose uptake.[256] It is proposed that hyperinsulinaemia in PCOS enhances ovarian epimerase activity which enhances DCI synthesis at the expense of MI concentration. In women without PCOS, the ratio of MI to DCI conversion is 100:1 in follicular fluid whereas in women with PCOS, this ratio drops to 0.2:1.[257] MI is also postulated to enhance aromatase synthesis in granulosa cells and therefore reducing androgen production.[258] However, there are concerns about misinformation and potential conflict of interest and these supplements come at high cost, with a priority to ensure evidence-based information on inositol.

Summary of systematic review evidence

Given the extensive studies included and the meta-analyses, please see detailed references and study characteristics in the technical report in Section 4.7.

Forty-three studies were identified with fourteen not included after integrity check, related to GDG 5. The remaining 29 RCTs were included in the systematic review and 19 in the meta-analysis. Ten studies had high risk of bias, 16 low or moderate risk and three had unclear risk of bias. Interventions and comparators were heterogeneous and here selected important comparisons are presented.

MI versus placebo: One study with high risk of bias suggested that MI improves weight, BMI, testosterone, androstenedione, fasting insulin, insulin area under the curve and HOMA-IR with very low certainty of evidence for all outcomes.

MI + folic acid (FA) versus FA: Up to five studies are included in meta-analysis depending on the outcome. Evidence suggests that MI + FA is superior to FA alone for biochemical markers including insulin/HOMA-IR, and total testosterone and androstenedione (very low certainty). However, FA alone was superior for BMI (very low certainty). There was no difference in pregnancy rate and fasting glucose between groups.

MI versus metformin: Evidence is derived from up to six studies for different outcomes. Pooled evidence suggests that MI has fewer gastrointestinal adverse effects than metformin (moderate certainty). Wide confidence intervals for androgens, glucose, lipids and weight, limit the ability to conclude on these outcomes. Metformin was superior to MI for fasting insulin, WHR, WC, and mFG score (low to moderate certainty). MI was superior to metformin in cycle regulation (moderate certainty). A trend to lower BMI and HOMA-IR was observed with metformin in pooled analysis but there were no significant differences between groups. There is low certainty evidence from one trial that adding MI + DCI to metformin is better than metformin alone for cycle regularity and lipids.

DCI versus placebo: Two studies, both with moderate risk of bias, suggest that DCI improves biochemical markers including free and total testosterone, androstenedione, DHEAS and lipids with no data on QoL, HOMA-IR or 2-hr glucose. Placebo is superior to DCI for BMI with low certainty of evidence.

MI versus DCI: One study with unclear risk of bias suggests that MI improves clinical pregnancy rate and total pregnancy rate versus DCI, but there is no difference for biochemical pregnancy and miscarriage rates. Evidence is of low certainty.

MI + DCI versus MI alone: There were no differences between MI + DCI and MI alone for critical outcomes (HOMA-IR, BMI, FG score). There were improvements seen for biochemical markers including free and total testosterone, DHEAS, fasting glucose and AUC glucose. The effects for total testosterone, DHEAS and AUC glucose remained significant at 6 months. All outcomes were ranked as very low certainty of evidence.

MI + metformin versus metformin: One study of unclear risk of bias shows no difference between the groups for BMI, weight and fasting insulin with low certainty of evidence.

MI + DCI + metformin versus metformin: One study suggests there were improvements in menstrual regularity and lipid profile with the inositol containing combination, with no differences for hirsutism, androgens, anthropometry or glucose, with low certainty of evidence.

Recommendations

4.7 #		Inositol	
4.7.1	**EBR**	Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, yet with limited clinical benefits including in ovulation, hirsutism or weight.	❖❖❖ ⊕◯◯◯
4.7.2	**EBR**	Metformin should be considered over inositol for hirsutism and central adiposity, noting that metformin has more gastrointestinal side-effects than inositol.	❖❖❖ ⊕◯◯◯
4.7.3	**PP**	Women taking inositol and other complementary therapies are encouraged to advise their health professional.	
4.7.4	**PP**	Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence.	
4.7.5	**PP**	Shared decision making should include discussion that regulatory status and quality control of inositol in any form (like other nutrient supplements) can differ from those for pharmacological products and doses and qualities may vary.	
4.7.6	**PP**	Policy makers and healthcare professionals have a responsibility to ensure women have access to unconflicted, evidence-based information to inform shared-decision making, whilst also acknowledging and respecting individual values and preferences, including for complementary therapies.	

Justification

Whilst the evidence at this time on the benefit of inositol (in all forms) was inadequate to make an evidence-based recommendation on efficacy for clinical outcomes, there is moderate certainty of evidence for potential benefits of inositol on menstrual cycles and limited data supporting metabolic and hormonal benefits, where certainty of the evidence was very low. Regulation of supplements varies globally, hence quality of products vary and costs are not regulated. As inositol is available over the counter and appears to have limited harm, it may warrant consideration despite limited and very low certainty evidence, considering values and preferences of women. Women should also be advised to inform their healthcare team if using these preparations. These recommendations have evolved since the 2018 Guideline respecting shared-informed decision making for the use of products with potential benefits and without evidence of harm. These recommendations may impact clinical care as they highlight the limited quality evidence, despite wide spread use.

4.8 Mechanical laser and light therapies for hair reduction

Is mechanical laser and light therapy for hair reduction alone, or in combination with other therapies, effective for management of hirsutism in adolescents and adults with PCOS?

Clinical need for the question

Hirsutism, in particular facial hirsutism, is a distressing symptom of hyperandrogenism in women with PCOS at any age. Excessive hair growth can have a negative impact on emotional wellbeing and QoL. Cosmetic treatment and COCP are generally considered first-line treatment for hirsutism in women, including in PCOS. Selective thermolysis has revolutionised mechanical hair removal, with increasing efficacy and safety. Different devices are commercially available: Intense Pulsed Light (IPL) technology, long-pulsed ruby (694 nm), long-pulsed alexandrite (755 nm), diode (800–980 nm), and long-pulsed Nd:YAG (1064 nm). Due to the high priority given to clinical hyperandrogenism outcomes during guideline development and revision, and due to previously limited evidence in 2018, this clinical question was prioritised

Summary of systematic review evidence

Given the detailed and heterogeneous studies identified, further information can be found in the technical report in Section 4.8.

Eight studies were included in the systematic review: four RCTs and four cohort studies. Meta-analysis was not performed due to heterogeneity in mechanical hair removal techniques used, varying outcomes and duration. Five studies had high risk of bias, and three had moderate risk of bias. Laser treatment was effective as a hair reduction technique for facial hirsutism. The combination of laser treatments with pharmacological agents such as metformin or COCP, appeared to improve efficacy compared to laser treatment alone. Similar findings were noted when IPL treatments alone were compared to treatments in combination with metformin. No studies investigated whether the combination of IPL and systemic agents would lead to differing results when compared to the combination of laser and systemic agents, however one study reported laser treatments alone to be superior to IPL treatment alone. Overall, certainty of evidence was low or very low.

Of the four studies that reported on psychological outcomes with patient satisfaction, quality of life, depression and anxiety scores, hair removal technique was found to improve all measures, and more so when combined with pharmacological agents. Adverse effects including redness and pigmentation were noted, emphasising the need for experienced operators.

Recommendations

4.8		Mechanical laser and light therapies for hair reduction	
4.8.1	EBR	Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety and quality of life in women with PCOS.	❖❖❖ ⊕○○○
4.8.2	EBR	A greater number of laser treatment sessions may be required in women with PCOS, compared to women with idiopathic hirsutism, to achieve hair reduction.	❖❖❖ ⊕○○○
4.8.3	CR	Adverse effects appear limited in the hands of experienced and suitably qualified providers, and women should be encouraged to seek hair reduction therapies from such providers.	❖❖❖❖
4.8.4	PP	Where laser hair removal is prescribed, the following need to be considered: • Wavelength and delivery of laser treatment varies by skin and hair colour. • Laser is relatively ineffective in women with blond, grey or white hair. • The addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone. Low and high fluence laser appear to have similar efficacy in reducing facial hair, while low fluence laser has reduced associated pain.	
4.8.5	PP	Mechanical hair removal with Intense Pulse Light (IPL) could be considered, albeit benefits may be less pronounced compared to laser treatment. There is no evidence to support the efficacy of home-based IPL kits.	
4.8.6	PP	Policy makers should consider funding this evidence-based effective therapy for women with PCOS to alleviate distressing symptoms of hirsutism, and related negative impact on quality of life, body image and psychological health.	

Justification

These new recommendations reflect the patients' and health professionals' priorities. Overall, the identified studies reported reduction of facial hirsutism, less time spent on hair removal and improvement of depression, anxiety and QoL, with the use of laser or light devices. We found a high heterogeneity in methods of treatment, treatment schedules and methods for efficacy assessment. Just one study reported data on pain during the procedure, documenting worst pain score in high fluence compared with low fluence laser. However, the undesirable effects, when reported, were mild and on balance evidence was felt to favour laser use in those with distressing hirsutism. Access issues for treatment of a medical manifestation of PCOS was also emphasised and is an important advocacy and funding issue in PCOS. These recommendations are likely to significantly impact clinical practice and come at some cost, however on balance, desirable effects outweigh undesirable effects and the GDG reached consensus on these recommendations.

4.9 Bariatric/metabolic surgery

In adults and adolescents with PCOS, is bariatric/metabolic surgery effective for management of hormonal and clinical PCOS features and weight?

Clinical need for the question

Markedly increased weight is increasing in prevalence throughout the world with up to 50-70% of women with PCOS above healthy weight, adversely affecting fertility and psychological health and increasing metabolic risks including T2D. Weight loss improves outcomes. In higher weight categories (BMI > 35 kg/m²), lifestyle interventions are not durably effective, whereas bariatric/metabolic surgery has been demonstrated to provide substantial durable weight loss with accompanying improvement in health, well-being and longevity,[259] with guidelines recommending surgery to aid weight loss with a BMI > 35 kg/m² and potentially for a BMI between 30- 34.9 kg/m² with associated metabolic co-morbidity.[260] Vertical Sleeve Gastrectomy and Roux-en-Y gastric bypass are the most common weight loss surgeries and are usually minimally invasive with low morbidity and mortality.[260] RCTs in T2D show persistent benefits and superiority of weight loss and improvement or remission of T2D, hypertension and dyslipidaemia in general populations.[260] In PCOS, pregnancy issues are relevant with weight loss appearing top improve ovulation and fertility and reduce pregnancy comorbidities. But bariatric/metabolic surgery can cause nutrient deficiencies important for fetal development and increases perinatal mortality, pre-term birth and small for gestational age babies. Given the significant concerns of women with PCOS about weight, long term health and reproductive and pregnancy outcomes, understanding the risks and benefits of metabolic and bariatric/metabolic surgery is of importance for women and healthcare professionals.

Summary of systematic review evidence

Bariatric/metabolic surgery versus medical therapy: One RCT[261] compared bariatric/metabolic surgery (laparoscopic sleeve gastrectomy) to medical therapy (oral contraceptive pill and metformin) with a high risk of bias as it was non-randomised, and investigators were not blinded. Patients in the medical therapy group were prescribed six months of an oral contraceptive pill (35 mcg ethinyl-oestradiol and 2 mg cyproterone acetate) and twelve months of metformin. It was not possible to perform a meta-analysis, however surgery improved metabolic outcomes with greater improvement in anthropometric measures (weight, BMI, waist circumference, hip circumference, W/H), hormonal measures (total testosterone, FAI), metabolic measures (fasting glucose, fasting insulin, triglycerides, LDL-cholesterol, and haemoglobin A1C, with very low certainty of evidence.

Bariatric/metabolic surgery versus conservative management: One prospective, non-randomised study[262] compared bariatric/metabolic surgery (gastric sleeve resection) to conservative management in women with and without PCOS with a high risk of bias as it was non-randomised, and investigators were not blinded. Bariatric/metabolic surgery compared with conservative management improved ovulation, percentage total weight loss, and intermenstrual length among women with PCOS. These results are of very low certainty.

PCOS versus Non-PCOS: Nine studies compared the effect of bariatric/metabolic surgery in women with and without PCOS with eight cohort studies and one cross-sectional study. Six studies looked at reproductive outcomes and one explored pregnancy outcomes. Others examined ovulation, intermenstrual length, menstrual regularity and AMH levels. These studies are all at high risk of bias as surgical cohorts where investigators were not blinded to the outcomes. Eight studies reported on anthropometric, metabolic, and hormonal outcomes with a high risk of bias and D2M, hypertension, hirsutism, cost-effectiveness, and QoL were not reported. There were improvements in women with and without PCOS across weight loss and metabolic markers and in PCOS there was more improvement post bariatric/metabolic surgery in fasting glucose and BMI. There were no significant differences between women with and without PCOS post bariatric/metabolic surgery in total weight loss, total testosterone, sex hormone binding globulin, AMH, total cholesterol, LDL, triglycerides or HDL with very low certainty of evidence.

Recommendations

4.9 #		Bariatric/metabolic surgery	
4.9.1	CR	Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, ovulation and pregnancy rates in women with PCOS.	❖❖❖
4.9.2	CR	Bariatric/metabolic surgery in women with PCOS should be informed by general population guidelines.	❖❖❖❖
4.9.3	CR	PCOS is a metabolic condition and could be considered an indication at a lower BMI threshold for bariatric/metabolic surgery similarly to other metabolic conditions including diabetes.	❖❖❖
4.9.4	CR	Women should be strongly counseled on the likelihood of rapid return of fertility and the need to commit to effective contraception, ideally prior to surgery. Even when pregnancy is desired, contraception should be continued until a stable weight is achieved, usually after one year, to avoid significantly increased risk of growth restriction, prematurity, small for gestational age, pregnancy complications and prolonged hospitalisation of the infant.	❖❖❖❖

Justification

General population data is clear on the role of bariatric/metabolic surgery. In PCOS evidence is more limited. Whist not captured in the evidence synthesis at the time of the GDG meeting, a recent large single centre prospective cohort study was published in 993 women with PCOS[263] showing dramatic improvement in hirsutism, menstrual irregularity and associated comorbidities [T2D (79.7%), hypertension (78.7%), sleep apnea (98.5%)] and symptoms of PCOS were statistically ($p < 0.0001$) reduced at follow-up. There was a high risk of bias and low certainty or evidence, but it was supported by existing literature in the general population and in PCOS. Hence recommendations were based on consensus largely, informed by population data and recommendations were conditional with further research needed. The evidence and the recommendations are stronger than in the 2018 Guideline, including consideration of evidence from the general population. Hence, recommendations were strengthened here.

4.10 Pregnancy outcomes

Are women with PCOS at increased risk of adverse pregnancy outcomes?

Clinical need for the question

PCOS related comorbidities such as high BMI, metabolic disturbances, hyperandrogenism and infertility would all presume a higher risk of adverse pregnancy outcomes. The first reports on pregnancy complications in women with PCOS emerged in the 1980s. Although publications from both clinical and registry data on pregnancy outcomes have increased significantly since, guidelines are scarce on how to manage PCOS pregnancies and identify possible risk factors. During pregnancy, PCOS symptoms including irregular cycles, hyperandrogenism or polycystic ovarian morphology, are difficult to detect, and the condition is seldom considered in everyday obstetric practice. During antenatal care, delivery and post-partum, there is little attention paid to PCOS by patients and healthcare professionals, often as there is a lack of awareness of the impact of the condition on pregnancy outcomes. There is a lack of quality evidence on pre-pregnancy management of women with PCOS.

Summary of systematic review evidence

Given the extensive studies included and the meta-analyses, please see the technical report for detailed references and study characteristics in Section 4.10.

One hundred and nine studies were identified. Outcomes explored included miscarriage, gestational diabetes, pregnancy-induced/gestational hypertension, pre-eclampsia/eclampsia, preterm birth, low birth weight, small for gestational age, macrosomia, large for gestational age, intrauterine growth restriction, instrumental delivery/ Induction of labour, caesarean section, perinatal depression, gestational weight gain, birthweight and BMI. Sensitivity analyses were performed in those on metformin, post bariatric/metabolic surgery and in BMI and age matched as well as post ART pregnancies.

Miscarriage: Forty-three studies were included in the meta-analysis, 21 were prospective cohort studies and 22 were retrospective cohort studies, with 27 poorly defining miscarriage and eight defining it before 12 weeks. Thirty studies had high risk of bias, seven moderate risk of bias and the remaining six had low risk of bias. Miscarriage OR overall was 1.50 [1.20, 1.87] in PCOS versus non-PCOS pregnancies. Six studies matched women on the basis of BMI and seven matched on the basis of age.

Gestational diabetes: Fifty-seven studies were included in the meta-analysis with 22 prospective cohort studies and 35 retrospective cohort studies. Thirty-four studies had high risk of bias, fifteen had moderate risk of bias and the remaining eight had low risk of bias. The OR ratio for gestational diabetes was 2.35 [1.90, 2.90] in PCOS versus non-PCOS pregnancies. Seven studies matched women for BMI and fourteen for age.

Pregnancy-induced hypertension: Forty studies were included in the meta-analysis with 17 prospective cohort studies and 23 retrospective cohort studies. Twenty-one had high risk of bias, nine had moderate risk of bias and the remaining ten had low risk of bias. The overall OR was 2.20 [1.82, 2.67] in PCOS versus non-PCOS pregnancies. Seven studies were matched women by BMI and twelve by age.

Pre-eclampsia: Thirty-six studies were included in the meta-analysis with 18 prospective and 18 retrospective cohort studies. Nineteen studies had high risk of bias, eleven had moderate and the remaining six had low risk of bias. The overall OR was 2.28 [1.88, 2.77] in PCOS versus non-PCOS pregnancies. Seven studies matched women on the basis of BMI and ten on the basis of age.

Eclampsia: Two studies reported eclampsia in women with and without PCOS. One had no women affected by eclampsia; therefore, one study with a retrospective cohort design was captured here for eclampsia. The study had moderate risk of bias and no differences were noted between groups.

Preterm birth: Fifty-five studies were identified with 54 included in the meta-analysis. Twenty-one studies were prospective cohort studies and thirty-four were retrospective cohort studies. Thirty-six studies had high risk of bias, nine had moderate risk of bias and the remaining had low risk of bias. The overall OR was 1.54 [1.34, 1.76] in PCOS versus non-PCOS pregnancies. Nine studies matched women on the basis of BMI and twelve matched on the basis of age.

Low birth weight: Fifteen studies were included in the meta-analysis with two prospective cohort studies and 13 retrospective cohort studies. Ten had high risk of bias, four moderate and the remaining one had low risk of bias. The overall OR was 1.28 [1.04, 1.59] in PCOS versus non-PCOS pregnancies. There were no studies reporting low birth weight in BMI/age matched women.

Small for gestational age: Twenty-six studies were identified, with 25 were included in the meta-analysis, of which 12 were prospective cohort studies and thirteen retrospective cohort studies. Fifteen studies had high risk of bias, six had moderate risk of bias and the remaining four had low risk of bias. The overall OR was 1.12 [0.89, 1.40], in PCOS versus non-PCOS pregnancies. Six studies matched women on the basis of BMI and six matched on the basis of age,

Macrosomia: Twenty-three studies were included in the meta-analysis with six prospective cohort and seventeen retrospective cohort studies. Sixteen studies had high risk of bias, four had moderate risk of bias and the remaining three had low risk of bias. There was no significant difference between groups. Two studies matched women on the basis of BMI and two matched on the basis of age.

Large for gestational age: Twenty-five studies were identified with 23 included in the meta-analysis, thirteen were prospective and ten were retrospective cohort studies. Fourteen studies had high risk of bias, five had moderate risk of bias and the remaining four had low risk of bias. The OR overall was 1.12 [0.98, 1.28], in PCOS versus non-PCOS pregnancies. Five studies matched women on the basis of BMI and five matched on the basis of age.

Intrauterine growth restriction: Twelve studies were identified with ten included in the meta-analysis. Four studies were prospective cohort studies and six were retrospective cohorts. Five studies had high risk of bias, two had moderate risk of bias and the remaining three had low risk of bias. The OR overall was 1.77 [1.16, 2.69], in PCOS versus non-PCOS pregnancies. Three studies matched women on the basis of BMI and four matched on the basis of age.

Instrumental delivery: Ten studies were included in the meta-analysis, six were prospective cohort studies and four were retrospective cohorts. Five studies had high risk of bias, two had moderate risk of bias and the remaining three had low risk of bias. Overall there was no difference between groups. Four studies matched women on the basis of BMI and four matched on the basis of age.

Induction of labour: Eight studies were included in the meta-analysis, six were prospective cohort studies and two were retrospective cohorts. Five studies had high risk of bias, two had moderate risk of bias and the remaining one had low risk of bias. There were no differences between groups overall. One study matched women on the basis of BMI and one matched on the basis of age.

Caesarean section: Thirty-seven studies were included in the meta-analysis, 16 were prospective cohort studies and 21 were retrospective cohorts. Twenty-three studies had high risk of bias, seven had moderate risk of bias and the remaining seven had low risk of bias. The OR was 1.23 [1.06, 1.43] overall. Six studies matched women on the basis of BMI and nine matched on the basis of age.

Perinatal depression: Only one retrospective cohort study with moderate risk of bias was included and there were no differences between groups.

Gestational weight gain: Sixteen studies were included in the meta-analysis with six prospective and ten retrospective cohort studies. Eight had high risk of bias, five had moderate and the remaining three had low risk of bias. The weighted mean difference was 0.96 kg [0.01, 1.90] in PCOS versus non-PCOS pregnancies. Four studies matched women on the basis of BMI and seven matched on the basis of age.

Birthweight: Forty-five studies were included in the meta-analysis with 18 prospective cohort studies and 27 retrospective cohort studies. Twenty-six studies had high risk of bias, twelve had moderate risk of bias and the remaining seven had low risk of bias. The weighted mean difference was -41.52 [-62.70, -20.34] grams with smaller babies in PCOS. Ten studies matched women on the basis of BMI and thirteen matched on the basis of age.

Body mass index: Sixty-two studies were included in the meta-analysis with 21 prospective cohort studies and forty-one retrospective cohort studies. Thirty-four studies had high risk of bias, eighteen had moderate risk of bias and the remaining ten had low risk of bias. The weighted mean difference was 0.88 kg/m² [1.56, 2.20], in PCOS versus non-PCOS pregnancies. Twelve studies matched women on the basis of BMI and sixteen matched on the basis of age.

Meta-analysis summary: On pooled meta-analyses, women with PCOS had significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, low birth weight, intrauterine growth restriction, and caesarean section versus women without PCOS. Women with PCOS also had significantly higher gestational weight gain, and BMI, but lower birthweight. Eclampsia, small for gestational age, macrosomia, large for gestational age, instrumental delivery and perinatal depression were not different between groups on both pooled and sensitivity meta-analyses.

On sensitivity analyses, in BMI matched studies significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, and caesarean section, and also significantly lower birthweight were retained in women with PCOS. Small for gestational age was higher in PCOS, which was maintained across subgroup analyses. In high quality studies, significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, and caesarean section, and also significantly lower birthweight were retained in women with PCOS.

Studies where women continued to take metformin or that were post bariatric/metabolic surgery were not included in the meta-analyses. Meta-analyses by age, BMI and post ART pregnancies were performed.

Recommendations

4.10		Pregnancy outcomes	
4.10.1	EBR	Women with PCOS have higher risk pregnancies, and healthcare professionals should ensure that PCOS status is identified during antenatal care, and appropriate monitoring and support is provided.	❖❖❖❖ ⊕○○○
4.10.2	EBR	Healthcare professionals should recognise that pregnant women with PCOS have an increased risk of: • higher gestational weight gain • miscarriage • gestational diabetes • hypertension in pregnancy and preeclampsia • intrauterine growth restriction, small for gestational age babies and low birth weight • preterm delivery • caesarean section.	❖❖❖❖ ⊕○○○
4.10.3	EBR	Assisted reproductive technology in women with PCOS should be considered as not conferring additional risk of miscarriage, preterm birth, impaired fetal growth and caesarean section, over that observed in women without PCOS.	❖❖❖ ⊕○○○
4.10.4	EBR	Women with PCOS should be considered as not having an increased risk of large for gestational age babies, macrosomia and instrumental delivery.	❖❖❖ ⊕○○○
4.10.5	PP	Early lifestyle intervention should be offered to pregnant women with PCOS, given the risk of higher baseline weight, excess gestational weight gain and pregnancy complications.	
4.10.6	PP	Blood pressure measurement should be performed when planning pregnancy or seeking fertility treatment, given the high risk of hypertensive disorders in pregnancy and the associated comorbidities in women with PCOS.	
4.10.7	PP	An OGTT should be offered to all women with PCOS when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed in the preconception phase, an OGTT should be offered at the first antenatal visit and repeated at 24-28 weeks gestation.	

Justification

This extensive systematic review and meta-analyses shows that women with PCOS had significantly higher odds of miscarriage, gestational diabetes, gestational hypertension, pre-eclampsia, preterm birth, low birth weight, intrauterine growth restriction, and caesarean section; and women with PCOS had significantly higher gestational weight gain, and body mass index but lower birthweight. These findings were generally retained in subgroup analyses matching for BMI and high-quality studies. Eclampsia, small for gestational age, macrosomia, large for gestational age, instrumental delivery and perinatal depression were not difference between groups on both pooled and sensitivity meta-analyses with generally few studies capturing these outcomes and with very low certainty of evidence. The impact of assisted reproductive technology in pregnancy may play a role in risk evaluation in PCOS-pregnancies. Consideration of preconception BMI, hypertension and diabetes status is recommended in screening. It was deemed vital that PCOS status was captured and recognised in antenatal care and risk assessment. These recommendations are likely to significantly impact clinical practice and come at some cost, but will offer prevention opportunities that are likely to reduce cost and morbidity. Hence, on balance, desirable effects outweigh undesirable effects, underpinning these recommendations with consensus across the GDG.

4.11 Metformin in pregnancy

In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?

Clinical need for the question

Metformin is an oral medication commonly used for seven decades to treat T2D. It is readily available and affordable worldwide. Metformin has glucose lowering properties mediated via reduced hepatic gluconeogenesis, increased insulin sensitivity, and enhanced uptake of peripheral glucose.[264] Metformin is actively transported through cell membranes mainly by organic cation transporters.[265] Metformin use has been promoted in PCOS, given the underlying insulin resistance in the condition. During the last two decades, metformin has been used to facilitate weight management, improve fertility and regulate menstrual cycles in those with PCOS. Use has also been suggested for reducing the risk of early miscarriage and pregnancy complications.

Pregnancy in women with PCOS is associated with a strong early mobilisation of inflammatory and other serum cytokines persisting throughout pregnancy, indicating immune activation. Endometrial dysfunction and subsequent dysregulated placentation, also seems to result into altered placental function. These findings provide new insights into the connection between PCOS and pregnancy complications.

During pregnancy, renal metformin clearance is increased, and serum concentration drops to about 70% compared to non-pregnant state.[266,267] Metformin also crosses the placenta, and consequently, the fetus is exposed to therapeutic concentrations of the medication.[268] Dosages and treatment protocols (immediate versus extended release) are variable with 500-2500 mg daily in use. Common practices also vary regarding the start of the drug therapy (prior to pregnancy or in early pregnancy) and the time of cessation (pregnancy test positive, or during the pregnancy). Side-effects are mostly mild, transient gastrointestinal symptoms and there is potential for a lowering of vitamin B-12 levels. Teratogenicity is not reported,[269] however, some potential concerns have been raised on long-term metabolic effects of metformin on the offspring.[270 271]

Summary of systematic review evidence

Please see the technical report in Section 4.11 for details of study characteristics. Only RCTs (n=7) were included. Risk of bias for the included studies varied. Studies on preterm delivery and gestational age were rated as of low risk of bias. Studies focusing on gestational diabetes (GDM), glucose homeostasis, pre-eclampsia, hypertension, miscarriage, and gestational weight gain were rated as high risk of bias and should be interpreted with caution. The bias was often related to studies being underpowered. Studies on neonatal outcomes were rated as high risk of bias and should be interpreted with caution. The most common reasons for the ratings assigned include: allocation to the intervention group was not blinded (two studies); power calculations were not reported; insufficient number of patients in the trials, and a lack of conflict-of-interest statements. These methodological issues may cause bias and have an impact on the reliability of the results. Studies were conducted at university hospitals, infertility clinics in hospitals and laboratories covering countries across the world.

Recommendations

4.11		Metformin in pregnancy	
4.11.1	EBR	Healthcare professionals should be aware that metformin in pregnant women with PCOS has not been shown to prevent: • gestational diabetes • late miscarriage (12 weeks +1 day to 21 weeks +6 days gestational age) • hypertension in pregnancy • pre-eclampsia • macrosomia or birthweight ≥ 4000 g.	❖❖❖❖ ⊕⊕◯◯
4.11.2	EBR	Metformin could be considered in some circumstances (e.g. risk for preterm birth), to reduce preterm delivery and limit excess gestational weight gain, in pregnant women with PCOS.	❖❖❖ ⊕⊕⊕◯
4.11.3	PP	Women should be counselled that the consequences of metformin exposure on long-term offspring health remain unclear and there is a suggestion of increased childhood weight, although causality is not certain.	
4.11.4	PP	Side-effects of metformin are mostly mild, transient gastrointestinal symptoms and are not worse in pregnancy.	

Justification

These new recommendations reflect patients' and health professionals' priorities. Most outcomes were not improved with metformin therapy. However, preterm birth and gestational age at delivery had high certainty and one outcome (gestational weight gain) had moderate certainty for benefits of metformin in pregnancy in PCOS. The studies did not focus on women with high risk of preterm delivery (previous late miscarriage, preterm delivery, smokers, cervical conisation), who theoretically may benefit more from metformin therapy. In addition, subgroup analysis or categorising according to pre-pregnancy weight may help take into account any potential confounding effect of gestational weight gain. Further there is a need to examine whether metformin may assist in glycaemic control (alongside diet/lifestyle) among women with PCOS and an established GDM diagnosis (i.e. for treatment rather than for prevention). These recommendations are unlikely to change clinical practice, but provide reassurance for shared-informed decision making based on evidence. A conditional recommendation for the option was given for 4.11.3 despite the moderate certainty of evidence, due to uncertainty of prenatal metformin exposure on longer term offspring health effects.

Chapter Five

Assessment and treatment of infertility

		General principles
	PP	All fertility treatment in PCOS should be guided by the fertility management algorithm.
	PP	Those with PCOS should be reassured that pregnancy can often be successfully achieved either naturally or with assistance.
	PP	Prenatal vitamins supplementation should be commenced with ovulation induction therapy aligned to routine preconception care.
	PP	Pregnancy should be excluded prior to ovulation induction therapy.
	PP	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, healthcare professionals need to inform women and discuss the evidence, possible concerns and side-effects.
	PP	There should be ongoing monitoring of patients for adverse effects and infants for congenital anomalies in all studies conducted with ovulation induction agents and these should be reported in any published papers.

5.1 Preconception risk factors

In women with PCOS and infertility, what are the preconception risk factors associated with poor or negative fertility outcomes?

Clinical need for the question

Preconception care is defined as a set of interventions that aim to identify and modify biomedical, behavioural, and social risks to a woman's health or pregnancy outcome through prevention and management, emphasising those factors that must be acted on before conception or early in pregnancy to have maximal impact. As women with PCOS often require infertility treatment, both the requirement for and the opportunity for preconception care is increased. Preconception care should include routine recommendations and PCOS specific considerations.

Modifiable risk factors that may impact fertility include body mass index (BMI), smoking status, alcohol consumption, pre-existing medical conditions such as diabetes and epilepsy, prescribed and recreational drug use, untreated sexually transmitted infections, nutritional status, supplementation requirements with folate, vitamin D, coeliac disease and dental health, which should be optimised as part of routine preconception care.

Pregnancy and fertility complications are features of PCOS including gestational diabetes, preterm birth, pre-eclampsia, miscarriage (see Chapter 4), longer time to conception and increased risk of ovarian hyperstimulation syndrome (OHSS). Anxiety and depression are also features of PCOS, with routine screening recommended. Body image and eating disorders are increased and should be considered and explored (see Chapter 2). All can impact relationship health and sexual intimacy and impact fertility treatment compliance.[272]

Summary of narrative evidence

Details of specific captured and included studies, patient populations and outcomes for this question can be found at technical report in Section 5.1 and are summarised below.

Healthy weight versus BMI > 25 kg/m² in PCOS: Twenty studies reported on preconception BMI and/or weight in relation to fertility outcomes in PCOS ranging from observational to RCTs and across fertility treatments.
Most studies had moderate or low risk of bias and large sample sizes. For the purpose of this analysis, a BMI of 18.5 – 24.9 kg/m² or 'lean or normal weight', were compared to those with a BMI > 25 kg/m², or classified as of higher weight, with no upper limit.

Women with PCOS in the lean/normal weight category had a higher live birth rate across 16 studies (1.39 [1.17, 1.65]), and a biochemical (1.35 [1.11, 1.62]) and clinical (1.54 [1.09, 2.18]) pregnancy rate than those in the higher weight categories. Those in the lean/normal weight category had a higher ovulation rate per patient and per cycle and lower miscarriage rate per patient across 11 studies (0.64 [0.59, 0.71]) compared to the higher BMI category. Evidence certainty was very low to low for most outcomes, due primarily to observational study design, despite appropriate study design for this question.

Older versus younger Age Groups: Six studies examined age in relation to fertility outcomes in PCOS. Variations including analysis methods and age groups limited meta-analysis for most outcomes. Three were in IVF treatment and two (the ones pooled in meta-analysis) were with gonadotrophins. All studies identified were of moderate to low risk of bias and were observational. Meta-analyses from two studies on clinical pregnancy rate and OHSS, showed no significant difference between women aged < 35 years compared to > 35 years. Studies not pooled, also found no differences by age in most outcomes. One study reported a decline in pregnancy rate in women with PCOS undergoing IVF aged between 40 and 45, reducing from 24.4% at age 40 to 13.3% at age 44. Live birth rates decreased from 17.8% at age 40 to 6.7% at age 44. In contrast, miscarriage rates increased from 24.3% at age 40 to 50% at age 44 in the same cohort. Certainty of the evidence was low to very low.

Recommendations

5.1 #		Preconception risk factors	
5.1.1	EBR	Women with PCOS should be counseled on the adverse impact of excess weight on clinical pregnancy, miscarriage and live birth rates, following infertility treatment.	❖❖❖❖ ⊕○○○
5.1.2	CR	Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, diet and nutritional status, folate supplementation (higher dose in those with BMI > 30), exercise, sleep and mental, emotional and sexual health should be considered and optimised to improve reproductive and pregnancy outcomes and overall health.	❖❖❖❖
5.1.3	PP	A reproductive life plan and age appropriate education on optimising reproductive health, is recommended in adolescents and women with PCOS, including healthy lifestyle, prevention of excess weight gain, and optimising preconception risk factors.	
5.1.4	PP	Healthcare professionals are encouraged to seek permission and if given, to assess weight and body mass index and initiate a dialogue on the importance of weight and lifestyle on women's health before pregnancy. This requires caution to avoid weight stigma and needs to consider the cultural, social and environmental determinants of health (see 3.6).	
5.1.5	PP	Chronic conditions such as diabetes, high blood pressure, anxiety, depression and other mental health conditions, should be optimally managed and women should be counseled regarding the risk of adverse pregnancy outcomes.	

Justification

General population recommendations highlight the vital role of healthy lifestyle, optimising weight, smoking cessation, omitting alcohol, exercise and management of mental health issues to optimise reproductive outcomes, especially in high-risk groups, which includes in PCOS. It is recognised that the role and degree of weight loss preconception, remains controversial (see Chapter 3). A strong recommendation was provided for 511 despite the certainty of evidence, as the highest level of study design available for this clinical question is observational studies, which impacts on certainty. Also, recommendations here are expected to improve efficacy and potentially reduce infertility treatment costs and optimise outcomes. Women with infertility and their healthcare professionals are attuned to the need for preconception care 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 preconception intervention studies. These recommendations are also guided by WHO, Federation of Gynaecology and Obstetrics (FIGO) and general population guidance. Additional resources may be required in implementation. These important recommendations are likely to impact policy, funding and clinical practice as they confirm the adverse impact of higher weight on fertility and pregnancy outcomes after fertility treatment.

5.2 Tubal patency testing

Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or intrauterine insemination?

Clinical need for the question

One of the leading causes of female infertility is tubal pathology, potentially affecting around 30% of infertile women. The diagnostic assessment of infertility often includes tubal testing by hysterosalpingography, ultrasound (saline infusion sonohysterography, hysterosalpingo-contrast sonography, hysterosalpingo-foam sonography) or laparoscopy. PCOS is the most frequent cause of anovulation in infertile women and ovulation induction is the most common treatment. More detailed clinical context can be found in the technical report in section 5.2. However, there is inadequate information about the indications and need for tubal patency testing for intrauterine insemination with normal semen analysis in infertile women with PCOS.

Summary of systematic and narrative evidence

Given the extensive studies included and the meta-analyses, please see the technical report for detailed references and study characteristics in Section 5.2.

On systematic review, of the eligible 57 studies (after integrity check) across all relevant infertility studies in PCOS, none met the inclusion criteria for this question on tubal patency testing. Therefore, the available evidence has been reviewed narratively.

There is no evidence to support that tubal disease is more frequent in women with PCOS.[273] In a large study with 1002 women with PCOS, 33 had tubal abnormalities (3%) with 97% having at least one patent fallopian tube or a normal uterine cavity.[274] Other studies similarly show 3-5% tubal abnormality in PCOS.

In terms of methods used to assess tubal patency, a multicentre, prospective, comparative study with a randomised design, showed that hysterosalpingo contrast sonography produces similar tubal pathology findings in a majority of infertile couples and, where they differ, a difference in findings does not lead to substantial difference in pregnancy outcome, while hysterosalpingo contrast sonography is associated with significantly less pain.[275] The authors suggested that Hysterosalpingo-Foam Sonography can be preferred as first-choice tubal patency test during fertility work-up. In case of suspected tubal pathology or inconclusive results, further testing can be done.

Whilst adverse effects from tubal patency testing are not common, inconvenience, cost and discomfort can occur and tubal patency testing may be more appropriate when targeted to those at increased risk of tubal infertility. In this context, consideration of risk factors for infertility associated with tubal pathology in PCOS including those with:

- a history of previous abdominal septic surgery like peritonitis or pelvic surgical procedures
- a history of sexual transmitted infection or pelvic inflammatory disease or a positive serum test for sexually transmitted infection
- concomitant endometriosis.

Recommendations

5.2		Tubal patency testing	
5.2.1	CR	In women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing and techniques of tubal patency testing in relation to the cost and complexity of the treatment, should be considered on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination.	❖❖❖

Justification

Given the low overall prevalence of tubal patency abnormalities in PCOS, it was recommended that if there is a clinical history of factors associated with tubal infertility, tubal patency testing could be considered, consistent with routine assessment of infertility. Methodological considerations included that hysterosalpingography requires dilation of the cervix with some discomfort, false positives are described yet other complications are uncommon, whilst ultrasound methods may cause less discomfort and tubal patency testing can be completed during laparoscopy performed for other indications. A lack of evidence was noted in PCOS in terms of who and how best to assess patency. However, general population risk factors were judged as applicable in the PCOS population and can guide decisions in practice.

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[1]. These agents prevent the aromatase-induced conversion of androgens to estrogens, including in the ovary. While the mechanisms by which letrozole induces ovulation are not fully elucidated, secretion of follicle stimulating hormone is increased, stimulating ovarian follicle development and maturation. The efficacy, adverse effects and overall role of letrozole in oral ovulation induction has become clearer over recent decades and the initial concerns around fetal anomalies have been refuted in a recent meta-analysis and systematic review with comparable rates to natural conception or other treatment agents. More detailed clinical background can be found at in the technical document in section 5.3.
With efficacy established the remaining questions related to relative efficacy compared to other agents.

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.3.

Letrozole versus clomiphene citrate: Eleven RCTs were captured, of which six had a high risk of bias, one had a moderate risk of bias, and four had a low risk of bias. Meta-analysis showed that letrozole was superior for
ovulation rate (per patient and per cycle); pregnancy rate, clinical pregnancy rate and live birth rate per patient. Certainty in the evidence is high for live birth rate, and moderate for pregnancy rate, clinical pregnancy rate and ovulation rate. There were no differences between letrozole and clomiphene citrate for other outcomes including multiple pregnancy rate (per patient or pregnancy); and miscarriage rate (per patient or pregnancy). Certainty in these findings ranged from low to very low except for multiple pregnancy rate per patient which was moderate. There was no statistical heterogeneity or publication bias.

Letrozole + metformin versus clomiphene citrate + metformin: Two studies reported ovulation rate per cycle and pregnancy and miscarriage rate per patient. These were moderate to high risk of bias, Meta-analysis showed ovulation and pregnancy rates per patient were greater with letrozole + metformin compared with clomiphene citrate + metformin with odds ratios of 2.02 and 1.90, respectively. Miscarriage rates per patient did not differ with certainty of the evidence low. One study assessed live birth rate per patient with no difference, whereas the other reported full term pregnancy per patient and found that letrozole + metformin was more effective. Outcomes are of very low certainty.

Letrozole versus Letrozole + metformin: Two studies compared letrozole alone or combined with metformin. Clinical pregnancy rate per patient and live birth rate per patient were reported and both had a high risk of bias. Meta-analysis of clinical pregnancy rate per person, showed no difference between groups with very low certainty. For ovulation rate per cycle and live birth rate and miscarriage rate per patient, only one study was available. Liu et al showed no difference in live birth rate between groups (36.8% versus 33.9%) ovulation rate or miscarriage/abortion rate per patient with results of very low certainty.

Letrozole versus clomiphene citrate + gonadotrophins: One study in India in 1387 women with PCOS failure, undergoing intrauterine insemination (IUI), had a moderate risk of bias. Meta-analysis showed that combined clomiphene citrate and FSH was less effective than letrozole for clinical pregnancy or ovulation per patient, with odds ratios of 0.55 and 0.35, respectively. There were no differences for miscarriage rates per patient with moderate certainty given the narrow confidence intervals and large sample size.

Letrozole + metformin versus clomiphene citrate: One study with a high risk of bias and showed that Letrozole + metformin was more effective for clinical pregnancy rate per patient and ovulation rate per cycle with no differences for the outcomes of live birth or miscarriage rate per patient and very low certainty of evidence.

Letrozole versus clomiphene citrate + metformin: One study compared letrozole with clomiphene citrate + metformin with a high risk of bias with no differences between groups and very low certainty.

A network meta-analysis performed in 2017 and updated in 2022 after retracted (two RCTs with integrity concerns) and ineligible (one study confirmed to be non-randomised) studies were removed, supported letrozole as the first-line treatment for anovulatory infertility in PCOS. This meta-analysis allowed relative comparison on ovulation induction agents in PCOS and informed algorithm II development for infertility treatment use. In this study, no first-line oral therapy was associated with a difference in multiple pregnancy rate.

An updated Cochrane review on AIs was published later in 2022 after the current guideline literature search and was considered in the final recommendations. This also incorporated an integrity check and overall findings were similar to the systematic review and meta-analysis presented here.

Recommendations

5.3		Letrozole	
5.3.1	**EBR**	Letrozole should be the first-line pharmacological treatment for ovulation induction in infertile anovulatory women with PCOS, with no other infertility factors.	❖❖❖❖ ⊕⊕⊕⊕
5.3.2	**PP**	The use of letrozole is still off-label in many countries. Where it is not allowed, clinicians could use other ovulation induction agents.	
5.3.3	**PP**	Letrozole should not be given where there is any possibility of a pre-existing pregnancy, though there is no evidence for increased teratogenicity compared to other ovulation induction agents.	

Justification

This recommendation was based on the totality of evidence from the updated evidence provided in the technical report for the 2023 International Evidence-based guideline on letrozole, metformin, clomiphene citrate, gonadotrophins and laparoscopic ovarian surgery, the updated Cochrane review on Aromatase Inhibitors 2022 and the recent network meta-analysis by Wang et al. There was a consistency about the benefit across all surrogate outcomes including improved ovulation and clinical pregnancy rates as well as the primary clinical outcome of live birth rates per patient. The recent systematic review demonstrating no increase in fetal anomaly rates also informed this recommendation. The lack of approval by regulatory agencies, despite clear evidence of efficacy and no evidence of higher anomaly rates may limit implementation and should be revisited in light of the evidence and recommendations presented here. The certainty of evidence here is stronger, confirming previous recommendations.

5.4 Clomiphene citrate and metformin

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

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

Clinical need for the questions

Clomiphene citrate is a selective estrogen receptor modulator with both estrogenic and anti-estrogenic properties, first approved for use in women with anovulation in 1967. Resistance and failure are well documented with a discrepancy between good ovulation rates and lower pregnancy rates, due to the anti-estrogenic effects of this agent on the endometrium and cervical mucus. Twin pregnancy and triplets with clomiphene citrate are 5–7% and 0.3%, respectively and ovarian hyperstimulation syndrome is less than 1%. The potential for borderline increased risk of ovarian tumours with 12 cycles or more has been noted[1].

Metformin is an insulin sentitising agent used to address the underpinning insulin resistance common in PCOS,[276] that drives ovarian androgen biosynthesis and increased bioavailability of free androgens. Excess local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation, leading to insulin-sensitising drugs use in ovulation induction. Metformin has been most widely studied in PCOS[277] and has the most reassuring safety profile, yet efficacy has been controversial and therapeutic regimens are not well standardised in clinical practice, with variable doses in use.[1]

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.4.

Metformin versus placebo: Seven studies were captured with six having a moderate and one having a low risk. Two were in clomiphene citrate-resistant cases, and three had mixed populations, whilst others did not clarify the population. Most outcomes were amenable to meta-analysis with metformin superior to placebo for improving live birth, clinical pregnancy and overall pregnancy rates, with odds ratios (OR) > 1.8 and moderate certainty, due to risk of bias. No differences for ovulation rate, miscarriage rate or multiple pregnancy rates per patient or pregnancy were noted with low certainty.

Metformin versus clomiphene citrate: Three included studies, two with a BMI < 30-32 kg/m² and one with a mean BMI ≥ 30-32 kg/m² were captured. Risk of bias was low to moderate and populations and sample sizes varied. On meta-analysis, there were no differences for live birth, clinical pregnancy, multiple pregnancy or ovulation rates per patient with highly significant heterogeneity. In one study, ovulation rate per cycle was significantly lower with metformin (OR= 0.43) and miscarriage rate per patient was significantly higher with metformin in meta-analysis of three studies (OR= 2.44). In subgroup analysis by BMI, clomiphene citrate was more effective than metformin for achieving live birth rate and clinical pregnancy rates among women with a BMI ≥ 30-32 kg/m², from a single study, which should be interpreted with caution. Certainty in the evidence was low for live birth, clinical pregnancy, and ovulation rate per cycle while the remaining outcomes were of moderate. Sensitivity analysis restricting meta-analysis to RCTs with low risk of bias explained the heterogeneity and demonstrated a lower live-birth rate and clinical pregnancy rate per patient and lower ovulation rate per cycle with metformin.

Metformin + clomiphene citrate versus metformin: Three studies were captured with low to moderate risk of bias with variable populations and mixed ovulation induction medication use history. On meta-analysis metformin combined with clomiphene citrate had a favourable effect on live birth rate and ovulation rate per patient, with ORs of 2.44 and 3.72, respectively of moderate certainty. Subgroup analysis by BMI showed that the beneficial effect of metformin + clomiphene citrate on live birth rate was most pronounced in women with a BMI
≥ 30-32 kg/m², however only one study was included in this subgroup. Sensitivity analysis restricting meta-analysis to RCTs with low risk of bias explained the heterogeneity and demonstrated a higher live-birth rate and clinical pregnancy rate per patient and higher ovulation rate per cycle with metformin combined with clomiphene citrate.

Metformin + letrozole versus letrozole: Two studies had a high risk of bias. Meta-analysis for clinical pregnancy rate per person, showed no difference between metformin + letrozole versus letrozole. There were no differences in live birth rate, clinical pregnancy rate per patient, ovulation rate per cycle, or miscarriage/abortion rate per patient. These results are of very low certainty.

Metformin + letrozole versus metformin + Clomiphene Citrate: Two studies had high risk of bias and meta-analysis showed clinical pregnancy and ovulation rates were greater with metformin + letrozole compared with metformin + clomiphene citrate with ORs of 1.90 and 2.02, respectively. Miscarriage rates per patient did not differ between groups. Certainty of the evidence for these three outcomes was low.

Metformin versus gonadotrophins: One study compared metformin with human menopausal gonadotrophin with a moderate risk of bias. There were no differences in pregnancy or ovulation rates and certainty was low.

Metformin + gonadotrophins versus gonadotrophins: Three studies had variable populations and moderate to high risk of bias. There were no differences in pregnancy rate, ovulation rate, multiple pregnancy rate or miscarriage rate per patient with a very low certainty for multiple pregnancy rate per patient and for the other outcomes, the evidence was of low certainty.

Clomiphene citrate versus metformin + clomiphene citrate: Eight studies had a low risk of bias in one, three moderate and four high risk with variable populations. Meta-analysis showed clomiphene citrate alone was less effective for clinical pregnancy rates and ovulation rates per patient and per cycle. Subgroup analysis by BMI, combined therapy was more effective for clinical pregnancy rate in the BMI < 30-32 kg/m² subgroup. Ovulation rate per cycle was better with metformin + clomiphene than clomiphene alone across both BMI subgroups. There were no significant differences in live birth rates, multiple pregnancy rates or miscarriage rates per patient or per pregnancy, including after subgrouping by BMI. There is low to moderate certainty in the evidence.

Clomiphene citrate versus letrozole: Eleven studies were included with six having a high risk of bias, one moderate and four low risk of bias. On meta-analysis, letrozole was superior for ovulation rate, pregnancy rate, clinical pregnancy rate and live birth rate per patient. Certainty in the evidence was high for live birth rate, and moderate for other outcomes. There were no differences between clomiphene citrate and letrozole for other outcomes. Certainty ranged from low to very low, except for multiple pregnancy rate per patient which was moderate with no evidence of statistical heterogeneity or publication bias.

Clomiphene citrate versus metformin + letrozole versus clomiphene citrate + metformin: One study had a high risk of bias. Clomiphene citrate alone was less effective than metformin + letrozole for clinical pregnancy rate per patient and ovulation rate per cycle, but no differences for live birth or miscarriage rate per patient with very low certainty, with no differences with clomiphene citrate + metformin.

Clomiphene citrate versus gonadotrophins: Two studies in therapy naïve women had moderate or high risk of bias. No differences in ovulation rate, multiple pregnancy rate or miscarriage rate per patient was noted; however, FSH was superior for live birth rate per patient, clinical pregnancy rate per patient, and ovulation rate per cycle with moderate certainty except for ovulation rate per cycle, which was of very low certainty.

Clomiphene citrate + gonadotrophins versus gonadotrophins: Two studies were captured. One involved 1387 women with PCOS who had previously failed to conceive or ovulate with clomiphene and were undergoing IUI with multiple regimens compared. Both studies were judged as having a moderate risk of bias. On meta-analysis, there were no differences in any outcomes and certainty in the evidence ranged from very low to moderate.

Clomiphene citrate + gonadotrophins versus letrozole: The study noted above compared clomiphene citrate + gonadotrophins (rFSH) versus letrozole with a moderate risk of bias. Combined clomiphene citrate and FSH was less effective than letrozole in achieving clinical pregnancy or ovulation per patient, with odds ratios of 0.55 and 0.35, respectively. There were no differences for miscarriage rates per patient and certainty was moderate.

Clomiphene citrate + metformin versus gonadotrophins: One study in clomiphene citrate-resistant women with PCOS had a high risk of bias and meta-analysis was not possible. Clinical pregnancy rate was higher with FSH compared to clomiphene citrate + metformin, with an OR of 2.81 favouring FSH. Certainty in these results is very low.

Clomiphene citrate versus laparoscopic surgery: One UK study with a moderate risk of bias showed no differences in live birth rate or clinical pregnancy rate per patient or miscarriage rate per pregnancy with low certainty for all outcomes

Recommendations

5.4		**Clomiphene citrate and metformin**	
5.4.1		**Metformin versus placebo**	
5.4.1.1	**EBR**	Metformin could be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, whilst informing women that there are more effective ovulation agents.	❖❖❖ ⊕⊕◯◯
5.4.1.2	**PP**	Women should be counseled as to potential mild gastrointestinal side-effects with metformin.	
5.4.1.3	**PP**	Healthcare and resource burden including monitoring, travel and costs are lower with metformin.	
5.4.1.4	**PP**	Consideration of age and screening for other fertility factors needs to be discussed before prescribing metformin.	
5.4.2		**Clomiphene citrate versus metformin**	
5.4.2.1	**EBR**	Clomiphene citrate could be used in preference to metformin in women with PCOS with anovulatory infertility and no other infertility factors, to improve ovulation, clinical pregnancy and live birth rates.	❖❖❖ ⊕⊕◯◯
5.4.2.2	**PP**	The risk of multiple pregnancy is increased with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene cycles may require ultrasound monitoring.	

5.4.3		**Clomiphene citrate and metformin versus clomiphene citrate alone**	
5.4.3.1	**EBR**	Clomiphene citrate combined with metformin could be used rather than clomiphene citrate alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and clinical pregnancy rates.	❖❖❖ ⊕⊕◯◯
5.4.4		**Clomiphene citrate and metformin versus metformin alone**	
5.4.4.1	**EBR**	Clomiphene citrate combined with metformin could be used rather than metformin alone in women with PCOS with anovulatory infertility and no other infertility factors to improve live birth rates.	❖❖❖ ⊕⊕◯◯
5.4.4.2	**PP**	Monitoring of combined cycles will need to be equivalent to clomiphene citrate alone.	
5.4.5		**Clomiphene citrate versus Letrozole**	
5.4.5.1	**EBR**	Letrozole should be used rather than clomiphene citrate in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy, and live birth rates.	❖❖❖❖ ⊕◯◯◯
5.4.5.2	**PP**	Current evidence demonstrates no difference in fetal abnormality rates between letrozole or clomiphene citrate ovulation induction or natural conception.	

Justification

This extensive evidence review informed overall recommendations for infertility treatment in PCOS including the infertility algorithm, noting letrozole as first-line treatment. The overall strength of this recommendation is strong based on overarching evidence in 5.3.1, whilst acknowledging that the certainty of evidence is very low in 5.4.5.1. Comparing clomiphene citrate therapy and metformin, clomiphene has greater efficacy but requires specialist care, monitoring, and costs to the patient which may present barriers. Metformin is low cost, accessible, has mild gastrointestinal side-effects and has lower efficacy. It can be used alone and/or in combination with clomiphene. Patient explanation and consent including an explanation of efficacy, benefits and risks is important including noting that metformin use is evidence-based but for infertility use off-label. After the integrity check process, these recommendations were similar to the 2018 Guideline, reassuring health professionals.

5.5 Gonadotrophins

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

Clinical need for the question

Gonadotrophin therapy is used clinically in those with 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 luteinising hormone or an anti-estrogenic endometrial effects).[1] To prevent overstimulation and multiple pregnancy, the traditional standard step-up regimens were replaced by either low-dose step-up regimens or step-down regimens with gonadotrophins used alone and different gonadotrophin preparations appearing to work equally well. It can be difficult to predict stimulation responses in PCOS and to achieve a single dominant follicle to reduce multiple pregnancy and ovarian hyperstimulation and careful monitoring of follicular development by ultrasound is required with triggers only used with two or less follicles over 14 mm. The efficacy, safety and role of gonadotrophins compared to other agents including single or combined oral ovulation induction agents or laparoscopic diathermy/drilling is unclear.

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.5.

Gonadotrophins versus clomiphene citrate: Two studies had moderate to high risk of bias and were in therapy naïve populations. Meta-analysis demonstrated no differences in ovulation rate, multiple pregnancy rate or miscarriage rate per patient; however, gonadotrophins were superior for live birth rate OR 1.74 [95% CI 1.10, 2.74], clinical pregnancy rate per patient OR 1.84 [95% 1.18, 2.87] and ovulation rate per cycle OR 3.11 [95% CI 0.76, 12.79]. Evidence for these outcomes was moderate certainty, except for ovulation rate per patient and per cycle which was very low. There was no difference in risk of multiple pregnancy or miscarriage.

Gonadotrophins + clomiphene citrate versus gonadotrophins: Two studies and a meta-analysis showed no differences in any outcomes with very low to moderate certainty.

Gonadotrophins versus laparoscopic ovarian surgery: Three studies in clomiphene citrate resistance were integrated into meta-analysis showing that gonadotrophins were superior to LOS for live birth rates OR 2.21 [95% CI 1.32, 3.71] (moderate certainty) but a much higher rate of multiple pregnancy OR 5.10 [95% CI 1.39, 18.68], with no difference in the other outcomes.

Gonadotrophins versus clomiphene citrate + metformin: One study in clomiphene citrate-resistant women with PCOS showed clinical pregnancy rate was higher with gonadotrophins (OR 2.81 [95% CI 1.05, 7.52]) with very low certainty.

Gonadotrophins versus metformin: One study compared human menopausal gonadotrophin with metformin in clomiphene citrate-resistant women with no difference in pregnancy or ovulation rates with low certainty.

Recommendations

5.5		Gonadotrophins	
5.5.1	EBR	Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naïve women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates (refer to PP 5.5.6).	❖❖❖ ⊕⊕○○
5.5.2	EBR	Gonadotrophins alone could be used over gonadotrophins combined with clomiphene citrate in women with PCOS who are anovulatory and infertile with clomiphene citrate resistance or failure, and no other infertility factors.	❖❖❖ ⊕⊕○○
5.5.3	EBR	Gonadotrophins could be considered rather than the combination of clomiphene citrate and metformin in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance and no other infertility factors.	❖❖❖ ⊕○○○
5.5.4	EBR	Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS who are anovulatory and infertile, with clomiphene citrate-resistance and no other infertility factors, following counselling on higher live birth rate and higher multiple pregnancy rates with gonadotrophins.	❖❖ ⊕⊕○○
5.5.5	EBR	Gonadotrophins could be second-line pharmacological therapy for women with PCOS who are anovulatory and infertile, with no other infertility factors and who have failed first-line oral ovulation induction.	❖❖❖ ⊕⊕○○
5.5.6	PP	Where gonadotrophins are to be prescribed, the following should be considered: • Cost of the intervention for ovulation induction. • Expertise required for the use of the intervention for ovulation induction. • The degree of intensive ultrasound monitoring that is required. • A low dose step-up gonadotrophin protocol should be used to optimise the chance of monofollicular development. • Implications of potential multiple pregnancy.	
5.5.7	PP	There appears to be no difference in the clinical efficacy of the available gonadotrophin preparations.	
5.5.8	PP	When using gonadotrophins, best clinical practice is to avoid multiple pregnancy. Considerations here include cancelling cycles when there is more than a total of two follicles greater than 14 mm in diameter and advising avoidance of unprotected intercourse.	
5.5.9	PP	Live birth rate, clinical pregnancy rate per patient and ovulation rate per cycle are higher with gonadotrophins than with clomiphene citrate.	
5.5.10	PP	A low dose gonadotrophin protocol should be used to optimise the chance of monofollicular growth and minimise multiple pregnancy.	
5.5.11	PP	Cycle monitoring and drug costs coupled with multiple injection will influence choice in gonadotrophin use.	

Justification

Gonadotrophin therapy is an effective treatment for women with PCOS, anovulation and no other fertility factors. However, it requires adequate resource (trained medical/nursing personnel and ultrasound machinery), specialist access and monitoring. All gonadotrophin preparations are significantly more expensive than oral agents and require parenteral administration and close monitoring with regular ultrasound, with a higher risk of multiple pregnancy compared with oral agents or surgery. These factors contributed to algorithm II with gonadotrophins generally second-line therapy in PCOS. Some changes to recommendations are made compared with the 2018 guideline, reflected in the infertility algorithm guiding overall choice of therapy. These recommendations are based on robust evidence after the integrity check.

5.6 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. Observational data looked promising, but surgery was surpassed by ovulation induction agents, until less invasive laparoscopic surgery emerged. Minor methodological variations are reported (electrocautery, laser vaporisation, multiple ovarian biopsies and others), all with apparent endocrine effects. For the purpose of this review, laparoscopic ovarian drilling (LOD), sometimes also referred to as laparoscopic ovarian diathermy or laparoscopic ovarian surgery (LOS), is a keyhole surgical procedure in which a diathermy instrument (usually a monopolar needle) is used to puncture the ovarian cortex, followed by the delivery of an electrical current to the ovarian stroma. With these procedures, ovarian hyperstimulation syndrome and multiple pregnancy risks appear 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 women with PCOS and infertility.

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.6.

LOD versus gonadotrophins: Three studies compared LOD with FSH, in the Netherlands, New Zealand and India. All were in women with clomiphene citrate resistance and all had a high risk of bias. FSH was superior to LOD for live birth rates; however, FSH had a higher rate of multiple pregnancies per patient, with an OR of 0.20 favouring LOD. Certainty of evidence for live birth rates per patient was moderate and for all other outcomes was low or very low.

LOD versus clomiphene citrate: One UK study examined a clomiphene citrate-resistant population then offered LOD, with a moderate risk of bias. There were no differences in live birth rate or clinical pregnancy rate per patient or miscarriage rate per pregnancy. There was low certainty for all outcomes.

Unilateral LOD versus bilateral LOD: Two studies in India examined unilateral versus bilateral LOD in women with PCOS and clomiphene citrate resistance, both with high risk of bias. There were no differences between bilateral versus unilateral LOD for any assessed outcomes, including live birth rate, pregnancy rate, ovulation rate and multiple pregnancy rate per patient or miscarriage rate per patient or per pregnancy. Certainty in the evidence was low for live birth rate, and very low for the remaining outcomes.

Other comparisons are covered under letrozole, metformin and other relevant sections of Chapter 5.

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%.[278] This was considered along with RCT data.

Recommendations

5.6		Laparoscopic ovarian surgery	
5.6.1	**EBR**	Laparoscopic ovarian surgery could be second-line therapy for women with PCOS who are anovulatory and infertile, with clomiphene citrate resistance and no other infertility factors.	❖❖❖ ⊕⊕◯◯
5.6.2	**PP**	When using laparoscopic ovarian surgery, the following should be considered: • Comparative cost of the intervention for ovulation induction. • Expertise required for the safe use of the intervention for ovulation induction. • Both intraoperative and postoperative risks, which are higher in women who are above healthy weight.	

Justification

The justification for these recommendations considered all relevant comparisons, relative efficacy, single procedure, no monitoring, costs, side-effects and potential long-term considerations. FSH was superior to LOD for live birth rates, yet higher rate of multiple pregnancies per patient were significant. Informed shared decision making can allow choice of second-line therapy based on patient preferences and priorities.

5.7 In vitro fertilisation and in vitro maturation

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 costs, risks and limitations, yet also offers the opportunity for pregnancy and live birth. Challenges exist across the diversity of protocols available and concerns in PCOS include ovarian hyperstimulation syndrome, high oestradiol levels, accelerated endometrial maturation and optimally the use of 'freeze all' interventions. An alternative to full IVF is in vitro maturation (IVM) of oocytes followed by IVF, using intracytoplasmic sperm injection (ICSI). The IVM protocol, particularly in the circumstances where no gonadotrophins are used, eliminates the risk of ovarian hyperstimulation syndrome, reduces patient burden and offers a potential treatment alternative prior to stimulated IVF/ICSI[279]. Clinical practice questions here include indications, timing (where ART fits in the treatment options) and comparative efficacy with other treatments and if unstimulated IVM with ICSI outcomes are comparable to stimulated IVF/ICSI.

Summary of systematic review evidence

Please see the technical report for detailed references and study characteristics in Section 5.7.

In total, 102 unique studies met inclusion criteria across all non-IVF, IVF and IVF questions, of which 57 were included in the guideline update following the integrity check. Of these eligible 102 studies, 1 study met the inclusion criteria on stimulated IVF/ICSI. With no RCTs comparing stimulated IVF/ICSI therapy with alternative therapies including aromatase inhibitors, metformin, clomiphene citrate, gonadotrophins, ovarian surgery, IUI or no intervention, in women with PCOS the literature has been reviewed narratively.

One study comparing live birth rates after unstimulated IVM with ICSI treatments compared to stimulated IVF/ICSI treatments after freeze all and embryo transfers in frozen cycles was from China and was in infertile women aged 20–38 years with PCOS and infertility scheduled for their first IVF treatment. Relevant outcomes included live birth rate per patient and per pregnancy, clinical pregnancy rate per patient, and miscarriage rate per pregnancy. This study had a low risk of bias, with high-quality methodology. Meta-analysis was not possible with only one study, however, comparing groups, IVF resulted in higher rates of live births per patient and clinical pregnancy rates per patient compared with IVM. There were no differences in live birth rates or miscarriage rates per pregnancy. Certainty in the evidence is moderate.

Summary of narrative review evidence

The role of IVF in PCOS was explored by the guideline development group. 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 with outcomes including time to conception, cost of therapy, QoL, ovarian hyperstimulation syndrome, multiple pregnancy, miscarriage and livebirth rates should be investigated.

Recommendations

5.7		In vitro fertilisation and in vitro maturation	
5.7.0.1	**CR**	In the absence of an absolute indication for in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI), IVF could be offered in women with PCOS and anovulatory infertility, if first- or second-line ovulation induction therapies have failed.	❖❖❖
5.7.0.2	**PP**	In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimised.	
5.7.0.3	**PP**	Women with PCOS undergoing IVF/ICSI treatment should be counselled prior to starting treatment about the increased risk of ovarian hyperstimulation syndrome and options to reduce the risk should be offered.	

Justification

The GDG deemed IVF should be considered after failed ovulation induction treatment with high pregnancy rates per cycle, especially in younger women. Access, risks and high costs can be prohibitive for many patients, hence IVF should be considered after other ovulation induction therapies. However, conception and delivery are highly valued by healthcare professionals and women with PCOS and even when cost and risks are increased, some may elect to undertake IVF. Healthcare professionals must present benefits and risks to enable an informed decision.

5.7.1 Gonadotrophin releasing hormone protocol

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

Clinical need for the question

Women with PCOS are at high risk of ovarian hyperstimulation syndrome with IVF ± ICSI treatment, prompting caution and leading to exploration of different protocols including with gonadotrophin releasing hormone and other options including in vitro maturation. One of the proposed methods to reduce the risk of this is to use a GnRH antagonist (as opposed to a GnRH agonist) protocol. This question was addressed in the context of acknowledged complexity in interpreting outcomes from IVF treatments in PCOS, with variable protocols and endpoint reporting, requiring close evaluation of the literature.

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.7.1.

Gonadotrophin-releasing hormone (GnRH) antagonist protocol versus GnRH agonist long protocol: Seven studies were captured with five with moderate risk of bias and two with high risk and one with low risk of bias. Meta-analysis showed no differences in any of the measured outcomes (including clinical pregnancy rate, number of eggs collected, amount of gonadotrophins used, serum estradiol on day of trigger, ovarian hyperstimulation syndrome rate, multiple pregnancy rate, miscarriage rate and cycle cancellation rate), between the GnRH antagonist protocol compared with the GnRH agonist long protocol, with the exception of days of ovarian stimulation, which were lower with the GnRH antagonist protocol (mean difference -3.07 days). Certainty for most outcomes was low to moderate, and certainty was very low for days of ovarian stimulation.

Recommendations

5.7.1		Gonadotrophin releasing hormone protocol
5.7.1.1	**PP**	Gonadotrophin releasing hormone protocol (GnRH) antagonist protocol cannot be recommended over GnRH agonist long protocol for women with PCOS undergoing IVF/ICSI to improve clinical pregnancy or live birth rate.
5.7.1.2	**PP**	The use of a GnRH antagonist protocol for women with PCOS undergoing IVF/ICSI is recommended as it enables the use of an agonist trigger, with the freezing of all embryos generated if required, without compromising the cumulative live birth rate, to reduce the risk of significant ovarian hyperstimulation syndrome.

Justification

The duration of stimulation with a GnRH antagonist approach is around three days 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. These recommendations differ to the 2018 guideline after the integrity check process, here with less available evidence no evidence-based recommendation could be made.

5.7.2 Trigger type

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

Clinical need for the question

One of the prominent causes of ovarian hyperstimulation syndrome is the occurrence in women with PCOS undergoing ovarian hyperstimulation for IVF, particularly where hCG is used to trigger ovulation. GnRH-agonist use emerged as an alternative for IVF to induce a surge of endogenous FSH and LH for final oocyte maturation and fertilisation. Ovarian hyperstimulation syndrome 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 pregnancy rate is dependent of endometrial quality. An alternative option therefore in women with PCOS at high risk, is to freeze oocytes or embryos after GnRH agonist triggering and to 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 and narrative review evidence

Of the eligible 57 studies (after integrity check) across all non-IVF, IVF and IVM, none met the inclusion criteria for this particular question and evidence has been reviewed narratively. Details of narrative review for this question can be found in the technical report in Section 5.7.2.

In the general population, this question was addressed in a Cochrane review in 2014 with 17 RCTs with a lower live birth rate and a lower incidence of mild, moderate or severe ovarian hyperstimulation in fresh embryo transfer cycles. In women at high risk of ovarian hyperstimulation syndrome or in frozen cycles, GnRH is increasingly used.[280]

Recommendations

5.7.2		Trigger type	
5.7.2.1	CR	Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos is recommended, in an IVF/ICSI cycle with a GnRH antagonist protocol, where a fresh embryo transfer is not intended or where there is an increased risk of ovarian hyperstimulation syndrome.	❖❖❖❖

Justification

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

5.7.3 Choice of follicle stimulating hormone

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 and narrative review evidence

Of the eligible 57 studies (after integrity check) across all non-IVF, IVF and IVM, none met the inclusion criteria for this question, hence available evidence has been reviewed narratively. Details of narrative review for this question can be found in the technical report in Section 5.7.3.

Given the limited evidence in PCOS, additional information was sought from the general population. Consistent with the previous guideline, we sourced a Cochrane systematic review and meta-analysis, of 42 trials with a total of 9606 couples compared rFSH against three different uFSH preparations.[281] rFSH irrespective of the down-regulation protocol, did not result in a statistically significant different live birth rate or ovarian hyperstimulation syndrome rate, concluding that clinical choice of gonadotrophin should depend on availability, convenience and costs and that further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.

Recommendations

5.7.3		Choice of follicle stimulating hormone	
5.7.3.1	CR	Either urinary or recombinant follicle stimulating hormone (FSH) could be used in women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, with insufficient evidence to recommend a particular type of FSH preparation.	❖❖

Justification

Systematic review and meta-analysis in the general IVF population, where extensive research has been concluded, has shown no significant difference in birth rate or ovarian hyperstimulation syndrome and no further research in the general population was recommended. Hence clinical choice of gonadotrophin should depend on availability, convenience and costs.

5.7.4 Exogenous luteinising hormone

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

Clinical need for the question

Options have been explored to reduce ovarian hyperstimulation syndrome 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 luteinise. 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. The lack of clarity around the role of exogenous LH in the setting of IVF/ICSI prompted this clinical question.

Summary of systematic and narrative review evidence

Of the eligible 57 studies (after integrity check) across all non-IVF, IVF and IVM, none met the inclusion criteria for this question (Q 5.7.2) on hCG or GnRH trigger, hence the available evidence has been reviewed narratively. Details of narrative review for this question can be found in the technical report in Section 5.7.4.

Consistent with the previous guideline, systematic reviews and meta-analysis in the general infertility population have demonstrated that there is no significant difference between different ovarian stimulation protocols (hMG, purified FSH, recombinant FSH) regarding fertility outcomes. Therefore, clinical gonadotrophin choice depends on availability, convenience, and cost. In standard IVF/ICSI protocols, and the types of controlled ovarian stimulation (FSH alone or addition of LH as a supplement) have little impact on the fertility outcomes.[281,282] Endogenous LH levels may fall too low in women > 35yrs), during ovarian stimulation, especially with GnRH-antagonist use. LH supplementation has been proposed, however a multicenter RCT of exogenous LH during the follicular phase, showed no fertility benefits outcomes in women over 35.[283]

Recommendation

5.7.4		Exogenous luteinising hormone	
5.7.4.1	CR	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

Aligned to the prior guideline and general infertility population evidence, there is no anticipated effect or benefit to add exogenous LH supplement in women with PCOS undergoing ovarian stimulation for IVF ± ICSI. There is insufficient evidence to determine the benefits of using or not using exogenous LH.

5.7.5 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

Metformin has been shown to restore ovulation and enhance pregnancy rates in PCOS with mechanisms that provide a physiological rationale for management of insulin resistance in IVF and 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 ovarian hyperstimulation syndrome. 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 ovarian hyperstimulation in IVF in PCOS.

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.7.5.

Adjunct metformin versus placebo or no treatment: Eight studies were identified all comparing adjunct metformin to placebo or no treatment in women with PCOS undergoing IVF/ICSI using either a GnRH agonist or a GnRH antagonist protocol. One study compared adjuvant metformin with no treatment, while the remaining seven were placebo-controlled. Two studies had a low risk of bias, two were moderate and the rest had a high risk of bias.
On meta-analysis, no differences in any of the measured outcomes were noted, except for side-effects which were higher with adjuvant metformin compared with placebo. For ovarian hyperstimulation syndrome the risk with adjunct metformin was 0.56 [0.30, 1.06], although this did not reach significance. Certainty of the evidence was moderate to low for most outcomes. Only multiple pregnancy rate had a high certainty of evidence.

For subgroup analysis by GnRH agonist protocol, adjunct metformin reduced the ovarian hyperstimulation rate per patient (0.45, [0.24, 0.83]) and the miscarriage rate per pregnancy (0.3, [0.18, 0.84]), but also increased the incidence of gastrointestinal side-effects.

Recommendations

5.7.5		Adjunct metformin	
5.7.5.1	EBR	Adjunct metformin therapy could be used before and/or during FSH ovarian stimulation in women with PCOS undergoing IVF/ICSI treatment with GnRH agonist long protocol, to reduce the risk of developing ovarian hyperstimulation syndrome and miscarriage.	❖❖❖ ⊕⊕◯◯
5.7.5.2	PP	Good practice in PCOS and IVF is the use of a GnRH antagonist protocol as it gives the flexibility of using a GnRH agonist trigger, freeze all strategy to reduce the risk of ovarian hyperstimulation syndrome. However, if using a GnRH agonist long protocol then metformin could be considered. If using metformin, the following could be considered: • Commence metformin at the start of GnRH agonist treatment. • Gradually titrate metformin up to a dose of between 1000 mg to 2500 mg daily in order to minimise side-effects. • Stopping metformin therapy at the time of the pregnancy test or period, unless the metformin therapy is otherwise indicated.	

Justification

Women and healthcare professionals would generally value reduced miscarriage rate and reduced ovarian hyperstimulation (with its associated morbidity and rarely mortality). Gastrointestinal side-effects were recognised, but noted as mild and self-limiting and potentially 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 in this setting with explanation required for use.

5.7.6 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, ovarian hyperstimulation risks are increased with gonadotrophin stimulation. IVM of oocytes limits or omits ovarian stimulation prior to oocyte retrieval, the maturation of oocytes occurring post retrieval, thus avoiding the ovarian hyperstimulation risk. The definition of an IVM cycle requires harmonisation, as cycles employing an hCG trigger injection are generally associated with asynchronous oocyte maturation rates, poor embryo implantation rates and lower pregnancy rates. Given that IVM is used in practice and has theoretical benefits, this question was prioritised.

Summary of systematic and narrative review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.7.6.

IVM versus IVF. One study with a low risk of bias and high-quality methodology, compared IVM with standard IVF in infertile women aged 20–38 years with PCOS and infertility scheduled for their first IVF attempt.[279] IVM patients had a lower rate of live births and clinical pregnancies per patient compared with IVF (22.3% versus 50.6%, p < 0.001), with no differences in live birth rates or miscarriage rates per pregnancy. Moderate to severe ovarian hyperstimulation syndrome did not occur in the IVM group, with 11 women having moderate to severe cases with IVF. Certainty in the evidence is moderate for all outcomes.

Narrative review captured a further RCT comparing IVM versus conventional IVF/ICSI for women with a high antral follicle count, in which > 70% have PCOS.[284] No significant difference in live birth rate per single transfer (35.2% versus 43.2%, RR 0.81 [0.66 – 1]) or live birth rate after first transfer (35.7% versus 41.1%; P=0.27) was noted. Cumulative ongoing pregnancy rates at 12 months were 44.0% with IVM and 62.6% with IVF/ICSI. Ovarian hyperstimulation syndrome did not occur with IVM, versus two cases in the IVF/ICSI group. Also, an RCT compared fresh embryo transfer versus freeze-only after IVM in women with high antral follicle count, in which the majority of patients had PCOS. The live birth rate was significantly higher in the freeze-only group (60% versus 20%; p = 0.02), suggesting effectiveness of IVM can be improved via a freeze-only strategy, with frozen embryo transfer in subsequent cycles.[285]

Recommendations

5.7.6		In vitro maturation	
5.7.6.1	**EBR**	The use of in vitro maturation (IVM) and ICSI could be considered in women with PCOS, as an alternative to a stimulated IVF/ICSI cycle, where an embryo is frozen and replaced in a subsequent embryo transfer cycle, acknowledging there is no risk of ovarian hyperstimulation syndrome, but a lower cumulative live birth rate.	❖❖❖ ⊕⊕◯◯
5.7.6.2	**CR**	The use of IVM and ICSI could be considered prior to stimulated IVF/ICSI cycles acknowledging both benefits and limitations.	❖❖
5.7.6.3	**PP**	IVM should only be considered in services with sufficient expertise, and advocacy is needed for regional or national centres of expertise.	
5.7.6.4	**PP**	IVM could be offered as an option in women with prior severe ovarian hyperstimulation syndrome and where the risk of severe ovarian hyperstimulation syndrome is deemed unacceptably high, provided that expertise in IVM techniques exists.	
5.7.6.5	**PP**	Evidence suggests that IVM/ICSI is less effective than standard IVF/ICSI in terms of clinical pregnancy per patient and live birth rate per patient.	

Justification

The GDG deemed that key elements to consider included that IVM when compared with stimulated IVF in PCOS, results in a significantly lower cumulative live birth rate per cycle and IVM completely avoids ovarian hyperstimulation syndrome. A clear definition of the term IVM, use in clinical units with sufficient expertise were considered. These recommendations are extended here, based on additional evidence. A conditional recommendation is made for either using or not using the interventions considering in 5.7.6.

5.8 Inositol

In adolescents and adults with PCOS, is inositol alone or in combination, effective for management of reproductive outcomes?

Clinical need for the question

Inositol is a nutrient supplement that acts as a second messenger in insulin and FSH signalling and has nine stereo-isomers.[286] Myo-inositol promotes glucose uptake and is also involved in FSH mediated pathways which regulate the proliferation and maturation of granulosa cells. It has been hypothesised that overproduction of insulin in PCOS enhances myoinositol to dichiroinositol conversion altering the ratios.[286].

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be found in the technical report in Section 5.8 and GDG 4.

See section 4.7 for the summary of systematic review and meta-analyses including the limited evidence for reproductive outcomes.

Recommendations

5.8 #		Inositol	
5.8.1	EBR	Inositol in any form alone, or in combination with other therapies, should be considered experimental therapy in women with PCOS with infertility, with benefits and risks currently too uncertain to recommend the use of these agents as fertility therapies.	❖❖❖ ⊕◯◯◯
5.8.2	PP	There is limited evidence with uncertain results, on the effect of inositol on ovulation, clinical pregnancy and live birth rates.	
5.8.3	PP	Side-effects and safety are not known for inositol.	
5.8.4	PP	Women need to be aware that these agents can have limited regulation with variable dose, quality, consistency and combination with other agents.	
5.8.5	PP	Women's personal goals and preferences should be considered when discussing complimentary therapies.	

Justifications

There was a strong consumer voice on the need to inform women on the limited efficacy, poor quality evidence and concerns were raised around misinformation surrounding these products which was supported by GDG members, as well as consideration of costs. Conflicts of interest were also raised in this field of research, alongside the need for high quality research in this area. These recommendations are similar to the overall recommendations of inositol in the 2018 guideline.

5.9 Anti-obesity agents

Are anti-obesity pharmacological agents alone or in combination, effective for management of reproductive outcomes in adolescents and adults with PCOS?

Clinical need for the question

Excess weight is a major concern for many women with PCOS. Whilst lifestyle change has a key role in the management of obesity, efficacy and sustainability of lifestyle induced weight loss in those with significant obesity is limited and the role of anti-obesity pharmacological agents in achieving weight loss and potential associated health benefits is well recognised in the general population in systematic reviews and guidelines. Semaglutide, liraglutide, phentermine/topiramate, naltrexone/bupropion and orlistat are approved anti-obesity medications in adults, each of which has been compared to placebo in RCTs. These medications are increasingly being used in adults for assistance with weight loss. However, there is limited available data in women with PCOS and in reproductive aged women.

Summary of systematic review evidence

Details of specific captured and included studies and patient populations and outcomes for this question can be foundin the technical report in Section 5.9 and in GDG 4.

See section 4.5 for the summary of systematic review and meta-analyses including the lack of evidence for reproductive outcomes, hence despite being prioritised, only a research recommendation can be made.

Recommendations

5.9 #		Anti-obesity pharmacological agents	
5.9.1	**CR**	We recommend using anti-obesity agents in PCOS for reproductive outcomes only in research settings to establish the efficacy and safety.	❖

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 and according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[16] These methods were aligned with European Society of Human Reproduction and Embryology (ESHRE) guideline development methods.

The work builds on the original Australian guideline in PCOS, the update in 2014, the World Health Organisation (WHO) guideline evidence synthesis in infertility management, and the International guideline in the assessment and management of PCOS.[1]

The International evidence–based guideline for the assessment and management of PCOS underpins an international initiative to engage women affected by PCOS and their healthcare professionals to improve health outcomes. The Centre for Research Excellence in PCOS (CRE PCOS) and the CRE in Women's Health in Reproductive Life (CRE WHiRL), funded by the NHMRC and led by Monash University, partnered with the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology. Extensive international health professional and consumer engagement informed the gaps, needs, priorities and core clinical outcomes for the guideline, through the CRE, partners and the 40 organisations engaged in formal collaboration.

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, psychologists, dietitians, exercise physiologists, public health experts, researchers and other co-opted experts including in sleep and bariatric/metabolic surgery. Other experts were engaged outside GDG meetings where specific individual questions required including dermatology and psychiatry. They were supported by an experienced project management, evidence synthesis team and international early career network and the 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 panel from across the continents, a management committee, five GDGs, a paediatric advisory panel, and a translation and consumer committees (See Figure 1). CRE PCOS and CRE WHIRL, funded by NHMRC and led by Monash University, partnered with the American Society for Reproductive Medicine, the Endocrine Society, the European Society of Endocrinology and the European Society of Human Reproduction and Embryology and collaborated with a further 36 organisations. The majority of the funding was provided by the Australian government, with contributions from partner organisations. Advisory, management committee, guideline development group, translation and consumer committee meetings occurred online and face to face over 9 months across Europe, USA and Australia and enabled guideline training, development and translation. Feedback from the partner and collaborating societies and their convened special interest groups of experts and consumers, as well as public consultation, will inform the final guideline.

Multidisciplinary international guideline development groups

GDGs were convened to address each of the five key clinical areas. Expertise was sought through partner and collaborator organisations aiming for multidisciplinary, consumer and geographical 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 in the mental health GDG), consumer representatives, evidence officers and representative to consider cultural aspects. See Appendix III. Co-opted experts were also included as needed and additional experts including in dermatology were consulted.

Consumer participation, Indigenous and Culturally and Linguistically Diverse (CALD) populations

Consumer/patient partnership

In the development of this guideline, we have sought not only to inform or consult with those affected by PCOS, but to partner with and empower them as the ultimate beneficiaries of this work. We have engaged with international consumer bodies in PCOS including the Polycystic Ovary Syndrome Association Australia (POSAA) (Australia), Verity (United Kingdom), PCOS Challenge: The National Polycystic Ovary Syndrome Association (United States), and PCOS Vitality (Ireland), all of whom were actively partnered in the guideline process. Other groups including PCOS consumer groups in India, were actively involved.

Consumer/patient representation partnered in the development of the Australian NHMRC Centre for Research Excellence funding submission, which supported this work, Consumers/patients also had input into all stages from planning through delivery and will take a key role in translation. An international survey was completed by 750 women worldwide and focus groups were held with those with PCOS to inform priorities for the guideline update. We also built here on the 2018 guideline process of priority setting and prioritised outcomes for each intervention with input from 3500 people with PCOS and the diverse healthcare professional who partner with women with PCOS in their care. This work also informed guideline translation, education and support needs and preferred methods of delivery in the dissemination and implementation plan.

All levels of governance involved consumers/patients. The International advisory panel, the management committee, the consumer committee, all guideline development groups and the translation committee all included consumers. This was supplemented by our input from our Indigenous cultural advisor. Consumers have been involved in every stage, including development of the guideline scope, developing and refining the clinical questions, interpreting the evidence and making the recommendations through the GRADE framework. Consumer representatives are also extensively engaged and are partnering in the guideline translation activities.

Indigenous and CALD engagement

This is an international guideline that aimed to be relevant to all those with PCOS. As such ethnicity and culture were considered at all stages from seeking priority questions, partnering with societies, exploring evidence and making all recommendations. For CALD representation, stakeholders from five continents were included in the consumer input into the guideline. GDGs included multi-disciplinary professionals from seven continents and comprised many clinicians with experience working with CALD communities. Through the PICOs, evidence synthesis and GRADE recommendation process, ethnicity and culture were considered in all recommendations. The translation of the guideline allows for adaptions on cultural and ethnicity grounds, with the current translation of the guideline into 12 languages, expected to be updated and expanded here.

As a mandatory requirement for all Australian Government funded and NHMRC approved guidelines and in recognition of the increased prevalence and severity of PCOS in this population, Australian Indigenous engagement included a workshop before the guideline to establish priorities, the appointment of an Indigenous cultural advisor who was engaged across the guideline update process, the inclusion of Aboriginal and Torres Strait Islander peoples as a subgroup in all PICOs and literature searches, representation in the guideline governance. In the dissemination plan, cultural safety will be at the forefront and national adaptation and translation will include strong engagement with all relevant cultural groups.

Gender inclusiveness

Since the publication of the 2018 PCOS Guideline, a rich discourse on gender inclusive language has taken place. The authors of this guideline recognise that healthcare and medical research must be responsive to external context, and that language is a powerful determinant of inclusion/exclusion, empowerment, and equity.

In response and from a position of ally ship, we aim to use language that is gender inclusive,[287-289] medically accurate, concise, and sensitive to the needs of those with lived experience of PCOS. We acknowledge that use of binary or one-size-fits-all anatomical language may not be appropriate for all, and therefore, within a patient-centered care framework, we use an expanded range of terms that seek to contribute to a culture of safety for all genders, and aims to improve healthcare outcomes across all patient populations.

We also understand that inclusive language is evolving, and that disagreement and lack of consensus around various terms co-exists alongside a momentum for change. The sensitivity in some groups to the perceived erasure of 'women' which many identify with, is pertinent here. Therefore, we have developed an approach aiming to acknowledge the need for respectful inclusive language, whilst also retaining the use of terms 'woman/women', during language evolution. To this end, we have applied the following approaches throughout the guideline:

1. Increasing the use of gender-neutral terminology (e.g. adolescents, adults, individuals and those with PCOS), when gender is not central to the subject matter
2. Using accessible language that is inclusive of persons with lower levels of health and/or PCOS literacy;
3. Increasing use of the term female, where biological sex is most relevant
4. Retaining use of the term 'woman/women' which where used, intends to encompass all genders affected by PCOS irrespective of how they choose to identify.

Weight stigma

We recognise that PCOS is associated with excess weight and that this both increases the prevalence of PCOS and the severity of the features of the condition. We also recognise that key drivers of lifestyle and higher weight are environmental, and sociocultural with some contribution from genetics. These often sit outside the realm of control of any given individual. Healthy lifestyle brings broader benefits and can prevent weight gain or induce some weight loss, but for those with significantly higher weight, healthier lifestyle alone to induce weight loss are usually unsuccessful in the longer term. In this context, we acknowledge that stigma around weight in the general population and in PCOS. is rife and adversely impacts on care and patient experience in many ways. We have a dedicated question on weight stigma and strategies to limit this in PCOS, including recognising that the terms 'overweight' and 'obese/obesity' can be stigmatising with suggested alternatives including 'higher weight'. We have undertaken to reduce stigmatising language and judgement in the guideline. We advise awareness, support and education for women and healthcare professionals alike to limit weight stigma and the adverse related impacts this has. However, we also share the evidence on the significant adverse health impacts of higher weight in PCOS, and hence emphasise that supported healthy lifestyle is key for prevention of excess weight in this condition.

Declarations and conflicts of interest and confidentiality

Conflict of interest has been proactively managed throughout the guideline development process as outlined in NHMRC Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. All members of the GDGs and all committee, project and board members have provided signed declarations of interest and a confidentiality agreement. These disclosures of interest are publicly available. Additionally, declarations of interest were a standing agenda item at each meeting and at the GDG meeting where recommendations were endorsed and GRADE templates completed, all declarations of interest were presented, discussed and recognised when discussing the GRADE recommendation process. More details on the process for managing conflicts of interest and confidentiality and recorded declarations can be provided on request (cre-whirl@monash.edu).

Training of GDGs in evidence review and guideline development methods

All GDG members attended training sessions on both guideline development and on research integrity, where the methods of reviewing evidence and guideline development were described in detail. The purpose of these sessions 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
- the new research integrity check process (Appendix V)
- grading the strength of evidence and its suitability to support evidence-based recommendations
- when to facilitate discussion and clinical judgement to formulate 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 in 2018 and informed work here, supplemented by extensive consultation with the development of the core outcome set in PCOS in 2020. For 2023, a prioritisation exercise was conducted to determine new questions. This targeted those with PCOS and attracted 750 responses. Partner and collaborating organisations provided input and the expert GDGs and consumer advisory group had input into which clinical questions were to be addressed by a systematic review or by narrative review.

Systematic reviews were performed for all questions where systematic evidence appraisal was suited. Narrative evidence reviews were completed where questions were less well suited to a PICO systematic review format.

Of the 55 questions, 52 were addressed by guideline systematic reviews, and three by narrative reviews of isolated PCOS studies supported by systematic reviews/guidelines in the general population. Of the 52 systematic reviews, some searches identified no evidence addressing the specific question and/or PICO (i.e. no eligible studies), in which case results were described narratively, drawing on clinical expertise and evidence from the general population.

The clinical questions addressed by each GDG are as follows:

GDG 1 – Screening, diagnostic and risk assessment and life stage

- In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction?
- In women with suspected PCOS, what is the most effective measure to diagnose PCOS related biochemical hyperandrogenism.
- In women with suspected PCOS, what is the most effective measure to clinically diagnose PCOS related hyperandrogenism?
- What are the most effective ultrasound criteria to diagnose PCOS?
- Is anti-mullerian hormone (AMH) effective for diagnosis of PCOS?
- Is AMH effective for diagnosis of PCOM?
- In women with suspected PCOS, is there evidence of ethnic and geographic variations in prevalence and presentation?
- What is the post-menopausal phenotype of PCOS and how elevated should androgens be to indicate PCOS?
- Are women with PCOS at increased risk for cardiovascular disease (CVD)?
- Are women with PCOS at increased risk for impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2D)?
- In women with PCOS, what is the most effective tool/method to assess risk of T2D?
- Are women with PCOS at increased risk for sleep apnea?
- Are women with PCOS at increased risk of endometrial cancer?
- What is the risk of PCOS and cardiometabolic outcomes (CVD, T2D) in relatives of women with PCOS?

GDG 2 - Prevalence, screening and management of psychological features and models of care

- In women with PCOS, what is the prevalence and severity of reduced quality of life (QoL)?
- In women with PCOS, what is the prevalence and severity of depression and anxiety?
- In women with PCOS, what is the prevalence and severity of psychosexual dysfunction?
- In women with PCOS, what is the prevalence and severity of body image distress?
- In women with PCOS, what is the prevalence and severity of disordered eating?
- What are the information, resource and education needs of women, adolescents, CALD groups and healthcare providers regarding PCOS?
- What are the characteristics of available models of care implemented in PCOS clinics or services?
- How can we best support women to navigate the impact of PCOS on family and interpersonal relationships?
- What are the key challenges for those with PCOS when interacting with healthcare professionals about polycystic ovary syndrome and related features?
- 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?
- Are antidepressants and anxiolytics effective for management and support of depression and/or anxiety or disordered eating in women with PCOS?

GDG 3 – Lifestyle management

- In women with PCOS, are lifestyle interventions (compared to minimal or nothing) effective for improving anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes?
- In women with PCOS, are behavioural interventions in addition to diet and/or exercise (compared to diet and/or exercise alone) effective for improving 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?
- Why are women with PCOS at increased risk of weight gain (intrinsic and extrinsic factors)?
- What is the burden of weight stigma in women with PCOS?

GDG 4 – Management of non-fertility features

- Is the combined oral contraceptive pill (COCP) effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
- Is metformin effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?
- Is metformin versus the COCP with or without other agents effective for management of features of PCOS 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?
- In adolescents and adults with PCOS, is inositol alone or in combination with other therapies, effective for management of hormonal and clinical PCOS features, weight and reproductive outcomes?
- Is mechanical laser and light therapy for hair reduction alone, or in combination with other therapies, effective for management of hirsutism in adolescents and adults with PCOS?
- In adults and adolescents with PCOS, is bariatric/metabolic surgery effective for management of hormonal and clinical PCOS features and weight?
- Are women with PCOS at increased risk of adverse pregnancy outcomes?
- In women with PCOS in pregnancy, is metformin compared to placebo/standard care effective in reducing pregnancy complications and adverse neonatal outcomes?

GDG 5 – Screening, diagnostic assessment and management of infertility

- In women with PCOS and infertility, what are the preconception risk factors associated with poor or negative fertility outcomes?
- Should women with PCOS and infertility due to anovulation alone with normal semen analysis undergo tubal patency testing prior to starting ovulation induction with timed intercourse or intrauterine insemination?
- In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes?
- 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, are gonadotrophins effective for improving fertility outcomes?
- In women with PCOS, is ovarian surgery effective for improving fertility outcomes?
- In women with PCOS, is stimulated In vitro fertilisation/intracytoplasmic sperm injection effective for improving fertility outcomes?
- In women with PCOS undergoing IVF/ICSI treatment, is the gonadotrophin releasing hormone antagonist protocol or gonadotrophin releasing hormone agonist long protocol the most effective for improving fertility outcomes?
- In women with PCOS undergoing GnRH antagonist IVF/ICSI treatment, is the use of hCG trigger or GnRH agonist trigger the most effective for improving fertility outcomes?
- In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, does the choice of FSH effect fertility outcomes?
- In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF/ICSI, is exogenous lutinising hormone (LH) treatment during IVF ± ICSI effective for improving fertility outcome?
- In women with PCOS undergoing (controlled) ovarian (hyper) stimulation for IVF ± ICSI, is adjunct metformin effective for improving fertility outcomes?
- In women with PCOS, is in vitro maturation (IVM) effective for improving fertility outcomes?
- In adolescents and adults with PCOS, is inositol alone or in combination, effective for management of reproductive outcomes?
- Are anti-obesity pharmacological agents alone or in combination, effective for management of reproductive outcomes in adolescents and adults with PCOS?

* 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 healthcare 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, healthcare professionals or policy-makers. Table 4 outlines the considerations when deciding importance of outcomes.[16] GDG members, including consumers also participated in this exercise.

Table 4: 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. Additionally, the collective experience of the GDG members, including consumers, will be used using transparent methods for documenting and considering them.

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

Rating scale:

1	2	3	4	5	6	7	8	9
of **least** importance								of **most** importance
Of limited importance for deciding (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 (Patient/Population, Intervention, Comparison, Outcome) of interest should be sought for adaptation before starting a new one. Apart from the International evidence-based guideline for the assessment and management of PCOS, completed by this group in 2018, no other international guideline covering all health aspects related to the syndrome was available. 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, all partnering and collaborating organisations have agreed to adopt and if required adapt these guidelines and we have updated and expanded the scope and evidence from the 2018 guidelines. This process involved new questions and updated evidence review for all existing questions from 2018. It also included a new research integrity process aligned to the tools applied by Cochrane (Appendix V)

Evidence reviews to answer the clinical questions

Evidence reviews were conducted for each clinical question and from the evidence reviews, the GDGs developed 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.

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 highest quality systematic reviews that met our benchmark criteria (see Table 5) and met the selection criteria, was used as a starting point for the updated search and systematic review. Additional randomised controlled trials (RCTs) that were not included in the previous systematic reviews, but met the current selection criteria were also used, with meta-analyses updated as needed. Where applicable, risk of bias appraisals from previous systematic reviews were adopted.

Table 5. Benchmark criteria for a systematic review to be used as a starting point

1	Must have met the PICO and completed a search in at least Medline and another relevant database
2	Must have listed key search terms
3	Must have listed selection criteria
4	Must have used an appropriate framework to assess risk of bias/quality appraisal
5	Where the evidence is sought for an intervention question and a systematic review has included non-RCTs, the analysis must be sub-grouped 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 were identified by the search. Furthermore, whilst a systematic review of health economic analyses was performed in this guideline, very limited evidence curtailed consideration of costs. Costs were considered based on GDG expertise 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.

The following electronic databases were employed to identify relevant literature:

- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- Medline (OVID)
- Medline in-process and other non-indexed citations (OVID)
- PsycINFO (OVID)
- EMBASE
- All EBM (Evidence-Based Medicine) Reviews (OVID), which includes:
  - 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)

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, one to two reviewers scanned the titles, abstracts and keywords of every record retrieved by the search strategy. This process was supervised by the expert evidence team and GDG key contacts who also engaged in decisions on included studies. Full articles were retrieved for further assessment if the information given suggested that the study met the selection criteria. Studies were selected by one to two reviewers 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). 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 6). Quality appraisal tables for each evidence review can be found in the supporting document titled Technical report. This follows the NHMRC approved 2018 evidence synthesis process.

Table 6. Risk of bias ratings[290]

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 developed by the 2023 Evidence Synthesis Team]. 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/outcomes (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; and where possible 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 were 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. Meta-analyses were performed using Review Manager 5.3. or 5.4. or STATA software. 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, duration of treatment or study quality. These can be found in the supporting Technical report.

Research Integrity Assessment

Findings from systematic reviews are underpinned by the assumption that the included studies follow good clinical research practice to produce trustworthy results. However, the last decade has seen a rapid rise in the frequency of 'problematic studies', the most visible of which are retracted studies,[291,292] suggesting that these studies are increasing in number and/or that there is increased awareness around integrity issues among the scientific community. While there is no universally accepted definition of a 'problematic study', the term generally refers to a study with questionable data or findings, irrespective of its retraction status. This could be a result of scientific misconduct, poor research practices, or naïve but honest error(s). Regardless of the cause, the resultant findings may be erroneous and could have significant and far-reaching consequences, jeopardising the validity of systematic reviews and undermining patient and public trust in scientific research. In response to this increasingly recognised issue, tools and policies have been introduced by several groups, including the Cochrane collaboration,[293] the Committee on Publication Ethics (COPE) and others (e.g. RIA;[294] TRACT)[295] to incorporate research integrity assessments, alongside quality appraisal as routine steps in systematic reviews processes. As yet, however, no process has been established to ensure the authenticity and accuracy of evidence in the context of guideline development. This is of critical importance, as the evidence included in guidelines is used to formulate recommendations, which directly influence patient care, often on a global scale.

Here, we have developed the *Research Integrity for Guideline Development (RIGID)* framework - a transparent, unbiased, and rigorous process to identify and manage problematic studies encountered during the guideline development process. The RIGID framework, outlined in Appendix V, is a complementary but critical process to be integrated alongside risk of bias and GRADE assessments to ensure that recommendations are based on high-quality, authentic and accurate evidence. The framework was piloted across all clinical questions in GDG 5 on infertility, with details provided in the supplementary Technical report and published tools.[295]

Briefly, the RIGID framework starts with the search and screening of studies for inclusion as per usual systematic review methodology. Once full text screening is complete and the final list of included studies is determined, the following integrity assessment steps are applied:

1. Review team identifies and excludes studies on the Retraction Watch database (tabulated with reasons)
2. Independent reviewer(s) assess(es) the remaining included studies using a research integrity tool/checklist (e.g. Cochrane, RIA, TRACT, etc.), clearly documenting areas of concern
3. An integrity committee made up of six guideline leads and guideline integrity experts independently review the manuscripts, and the checklist scores/results. Each member votes on classification as low, moderate or high risk. Votes are tallied to reach a final classification and, if required, a meeting is convened to reach consensus.
4. Studies considered *low risk* are included as part of the guideline evidence (and meta-analyses where applicable)
5. Studies considered *moderate or high risk* are categorised as 'awaiting classification', and authors are contacted by email. If authors respond and wish to engage in addressing or clarifying issues raised on the integrity checklist, the study is reclassified as awaiting classification. If issues can be resolved promptly, the manuscript is moved to low risk and included as per step 4. If the authors provide an intention to submit (response indicating intention to supply the required information/data within a specified timeframe) however this
   will extend beyond the guideline timeframe ore resources (such as individual patient data sharing and re analysis), the study is noted as awaiting classification but is not considered in evidence synthesis or meta-analyses. If no response is provided, the moderate or high risk is moved to the not included category
6. All moderate and high risk studies that are in the awaiting classification or not included categories, are tabulated with integrity scores in the technical document for transparency.

* Classification as moderate or high risk does not imply fraudulent data or research misconduct. These classifications reflect a medium to high score on the integrity checklist, suggesting that issues were identified that require clarification (and may be subsequently adequately addressed), before guideline development groups can be confident in using these studies to inform recommendations with direct impact on patient care.

Quality (certainty) of evidence; GRADE evidence profiles

As per the 2018 guideline, a GRADE evidence profile was prepared for each comparison within each clinical question that was addressed by a systematic review. For each prioritised outcome, a certainty rating was documented with consideration of the following:

- information about the number and design of studies addressing the outcome
- judgments about the quality of the studies and/or synthesised evidence, such as risk of bias, inconsistency, indirectness, imprecision and any other considerations that may influence the quality of the evidence.

The definitions of these factors are described below:

- overall quality of evidence rating using the judgments made above (see ratings in Table 7);
- key statistical data
- classification of the importance of the outcome.

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

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

Table 7. Quality of evidence

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 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 notes that the quality of evidence is a continuum; any discrete categorisation involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations.[16] Evidence profiles can be found in the Technical report.

Aligned to Cochrane methods, certainty of evidence varies significantly across outcomes for each clinical question. In this guideline, the recorded evidence certainty reflects the lowest certainty for the top three critical outcomes for each question. Here, evidence was often stronger for the most critical outcome and often high quality RCT's had addressed an individual question, but consideration of multiple outcomes and inclusion of additional low-quality studies may have resulted in low certainty evidence overall. These nuances in the evidence were considered by the GDG for every clinical question and are outlined in the technical report and GRADE tables. Hence, an apparent discrepancy may be observed between the strength of the recommendation and the certainty of the evidence. Where this occurs, a justification is added to the guideline under the relevant clinical question.

Formulation of recommendations using the GRADE Evidence to Decision framework

As per the 2018 NHMRC approved guideline, the Evidence to Decision framework was used to transparently 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 capturing the strength of the recommendation and capturing 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
- research priorities.

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

After reviewing the evidence, and considering all aspects of the GRADE framework, the GDG then discussed at length until a consensus was reached. Wherever a recommendation was controversial or conditional and where dissenting views were noted in discussion, a vote was held. Only one recommendation had a non-consensus vote and after further discussion this was resolved achieving consensus across all recommendations.

The strength of the recommendations can be identified throughout the guideline by the following (adapted from ESHRE manual for guideline development and the GRADE approach.[16] Recommendations categories are outlined in Table 1 and include EBR: Evidence-based recommendations: Evidence sufficient to inform a recommendation made by the guideline development group, CR: Consensus recommendations: In the absence of adequately strong evidence, a consensus recommendation has been made by the guideline development group, also informed by evidence from the general population and PP: 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 consensus recommendations. Table 8 outlines the approach to the strength of the recommendations.

Table 8: Strength of recommendations

Target group	Strong recommendations*	Conditional (weak) recommendations for the option (test or treatment)	Conditional (weak) recommendations for either the option or the comparison	Research only recommendations	Practice points (PP)**
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 with appropriate approvals and safety precautions have been established.	Clinicians, patients and policy makers are informed on the clinical implications relevant to implementation of recommendations.
Healthcare 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 may not apply to all patients in all conditions; no recommendation can consider all of the often-compelling unique features of individual patients and clinical circumstances.

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

The 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. Conditional recommendations are reflected using the terms 'could' or 'should/could consider' which are 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.

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 they have attempted to reflect this in the strength of the grading given to recommendations on interventions that are not directly supported by evidence in women with PCOS. 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.

Public consultation

Public and targeted consultation was conducted for a period of thirty days commencing 28th of February to 30th of March 2023 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 Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines. The public consultation strategy included an online portal requesting detailed feedback including evidence where recommendation changes were requested. Details of the process are available upon request, email cre-whirl@monash.edu and contributions made during consultation and GDG responses will be posted online. This includes all partner, collaborator health professional groups and consumer groups working with the guideline team across the world.

External review

This guideline has been reviewed by all GDG members, the international advisory panel, and independently by collaborating and partnering professional colleges and societies, by consumer groups and by NHMRC recommended government agencies as well as through public consultation. The purpose of the review was to engage broadly and nuance regional issues including feasibility and applicability. Reviewers' submissions have been incorporated into a table, deidentified and are posted online. Following review, all GDGs reconvened online to consider each individual comment and where agreed, GRADE processes were revised and amendments were made to recommendations with consensus.

Scheduled review and update of the guideline

This is a living guideline, hence the relevant GDG will be reconvened, evidence updated and the GRADE process repeated with NHMRC engaged around process and recommendations and translation tools, 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 efficacy or safety of the recommendations in this guideline – all guideline experts will be surveyed annually for awareness of advances in evidence as those leading the file dinternationally. Evidence synthesis will occur annually for all recommendations most likely to change over the next five years (see Table 3#). If new significant evidence is identified, the GDG panel will be reconvened online and the same GRADE methodlogy applied. Funding and resources are available to complete this work.

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

PCOS guideline generated research priorities

GDG 1	**Screening, diagnostic assessment, risk assessment and life stage**
Question #	**Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:**
1.1. Irregular cycles and ovulatory dysfunction	• Longitudinal studies to identify early predictors and natural history of PCOS in adolescents from different ethnic backgrounds, targeted to allow for timely and accurate diagnosis. • Quality and current normative data across ethnicities and BMI assessing pubertal development with and without PCOS.
1.2. Biochemical hyperandrogenism	• Large-scale quality studies comparing testosterone, DHEAS and androstenedione measured by reference standard tandem mass spectrometry, including predefined cut-off thresholds, prospectively tested and validated in independent cohorts of women with well characterised PCOS and women without PCOS. • Evaluate the diagnostic value of the active 11-oxygenated androgens in detecting biochemical hyperandrogenism in PCOS, comparing it to the diagnostic performance of recommended androgens. • Characterising a large cohort of women with PCOS from different ethnic backgrounds to comprehensively identify biochemically defined clusters of women and relationships to clinical features of PCOS.
1.3. Clinical hyperandrogenism	• In an unselected population of adolescents and adults, determine the predictive value biochemical hyperandrogenism and/or PCOS status across acne alone, female pattern hair loss alone, hirsutism alone. • Determine the naturally occurring 'abnormal' cut-off value of the mFG score for defining hirsutism by ethnicity, and BMI, in large unselected populations. • Explore simpler methods of assessing hirsutism (including validity of self-reported hirsutism).

1.4. Ultrasound and polycystic ovarian morphology	• Study natural history of ovarian morphology in community-based populations across the lifespan and across the globe. • Examine the relationship of polycystic ovary morphology with PCOS-related health outcomes over the lifespan. • Establish rigor and reproducibility in measuring and reporting of ovarian ultrasonographic markers in a clinical workflow. • Study the impact of COCP on polycystic ovary morphology.
1.5. Anti-mullerian hormone	• Normative data assessing AMH levels in adolescents and in different age groups. • Longitudinal studies to assess AMH levels in women with PCOS compared to controls. • Cost effectiveness studies comparing pelvic US and AMH assessments. • Study the impact of COCP on serum AMH levels. • Study the relationship between BMI, ethnicity and serum androgen levels and AMH.
1.1-1.5	• Explore cluster analyses integrating all core diagnostic features for more accurate diagnosis across ethnic groups.
1.6. Ethnic variation	• Assess PCOS prevalence in diverse populations, including the African and South American continents. • Study ethnic variation, including prevalence, and characteristics in adolescents and adults. • Study migrant populations assessing the impact of migration and environment.
1.7. Menopause life stage	• Study features of PCOS in the postmenopause, including variation by ethnicity and BMI. • Long-term cohort studies post menopause to assess health outcomes including androgen levels, clinical hyperandrogenism, cardiometabolic disease, bone health, psychosexual function (accounting for impacts of treatment).
1.8. Cardiovascular disease	• Long-term, large, longitudinal studies for assessment of CVD events. • Cardiovascular risk prediction models to be developed and validated in PCOS, considering ethnic variation. • Cost effectiveness in screening and prevention programs for CVD in PCOS.
1.9.1 Impaired glucose tolerance and type 2 diabetes	• Evaluation of relative risk of diabetes across ethnicities and age ranges, including postmenopausal. • Exploring risk of T2D in different subgroups including ethnic variation and by degree of hyperandrogenicity. • The rate of progression of prediabetes into diabetes in women with and without PCOS.
1.9.2. Glycaemia monitoring	• Compare accuracy of different diagnostic tests against the OGTT including a combination of diagnostic strategies for glucose testing incorporating a combination of parameters to simplify glycaemic evaluation in settings where OGTT may not be practical.

1.10 Obstructive sleep apnea	• Validate existing screening tools for OSA in PCOS. • Explore mechanisms of OSA in PCOS and relationships with metabolic and psychological features. • Study adherence and effectiveness of treatment for OSA in PCOS.
1.11. Endometrial hyperplasia and cancer	• Mechanisms including the impact of insulin and androgen excess on endometrial cancer development. • Long-term natural history of endometrial hyperplasia and incidence of endometrial cancer across ethnicities. • The impact of COCP treatment.
1.12. Risks in relatives	• Studies in families of women with PCOS including male and female relatives, including exploration of mechanisms. • Studies including daughters of women with PCOS who are at least 8 years post menarche are a key gap.
GDG 2	**Psychological features and models of care**
Question #	**Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:**
2.1. Quality of life	• Studies in adolescents/adults to develop a PCOS specific QoL tool to overcome current limitations.
2.2. Depression and anxiety	• Explore aetiology and pathophysiology of mental health disorders in PCOS, which may inform more targeted therapy. • Where regions, ethnic, population subgroups and life stages (including perinatal period) have not been adequately included, prevalence studies could be justified. Otherwise, further prevalence studies are not warranted. • Longitudinal follow-up to determine frequency of screening for depressive and anxiety symptoms. • Effectiveness of treatment for depression or anxiety in PCOS, including impact on PCOS treatment and outcomes.
2.3. Psychosexual function	• Psychosexual function in combination with sexual distress (psychosexual dysfunction) to be assessed across cultures. • Effect of lifestyle or pharmacological intervention on psychosexual dysfunction by treatment type. • Interventional studies in PCOS to include psychosexual dysfunction as an outcome, where appropriate.
2.4. Body image	• Study body image in adolescents. • Validate existing body image measurement tools. • Determine clinically meaningful differences in body image scores. • Assess preferences of women with PCOS on treatment of body image issues, considering diversity. • Examine impact of PCOS treatment on body image.

2.5. Eating disorders and disordered eating	• Prevalence of eating disorder/disordered eating in PCOS, including subgroups (e.g. adolescents, ethnicities), using a structured clinical interview and considering all types of eating disorders. • Adapt and validate existing screening and assessment tools in PCOS, including diverse groups. • Examine impact of treating eating disorders/disordered eating on outcomes and on effectiveness of PCOS treatment.
2.6.1. Information needs	• Exploration of optimal delivery methods of health information for end users. • Exploration of needs, satisfaction and impact of education strategies on practice and health outcomes. • Identify avenues of integration into models of care.
2.6.2. Models of care	• Develop benchmarking and performance indicators that address all aspects of multidisciplinary service. • Develop and implement a best practice framework outlining critical and aspirational elements of a PCOS model of care.
2.6.3 Support to manage PCOS	• Understand impact of PCOS on wider family and interpersonal relationships. • Explore role of family, social and peer support in providing psychological support. • Investigate stigma and explore strategies to reduce stigma, considering cultural contexts.
2.6.4. Patient care	• How to implement well-established and effective frameworks for sharing news and shared decision making in PCOS. • Evaluate effectiveness of these frameworks for outcomes that matter to patients (e.g. decision quality, causal understanding, agency, good health). • Explore how biases manifesting in interactions around sharing news and shared decision making can be addressed.
2.7. Psychological therapy	• Examine role and efficacy of psychological intervention for depression and/or anxiety, disordered eating, body image distress, self-esteem, gender identity or psychosexual dysfunction in adults and adolescents with PCOS. • Examine stepped care models incorporating evidence-based interventions and delivery modes (e.g. telehealth, apps).
2.8. Antidepressants and anxiolytics	• Understand aetiology and pathophysiology of mental health disorders in PCOS, which may inform targeted therapy. • Explore role and efficacy of various therapies in mental health disorders in PCOS in adults and adolescents. • Examine impact of PCOS treatment on depression or anxiety.

GDG 3	Lifestyle Management
Question #	**Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:**
3.1. Effectiveness of lifestyle interventions	• Large, high quality RCTs and pragmatic implementation lifestyle trials, specifically: • Codesigned interventions and delivery methods (app based for example) with longer term sustainability and outcomes. • Improved outcome capture including reproductive (menstrual cycle, ovulation, pregnancy, live births) and psychological. • Study across ethnicities in low resource environments and across life stages. • Role and benefits in non-overweight populations. • Effects of lifestyle in the preconception period in women, reporting on live birth and obstetric outcomes.
3.2. Behavioural interventions	• Clear, consistent definition of behavioural lifestyle interventions and outcomes. • Evaluate outcomes, alongside feasibility including cost-effectiveness. • Efficacy of behavioural interventions to optimise health behaviours and/or weight with lifestyle on anthropometric, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes.
3.3. Dietary interventions	• High-quality research to determine the impact of different dietary interventions on a range of outcomes across the BMI range. • Investigate impact of range of diet interventions on anthropometric, metabolic, hormonal, reproductive, psychological outcomes in PCOS. • Monitoring safety and harm of specific dietary interventions (including disordered eating) and long-term follow-up.
3.4. Exercise interventions	• Explore exercise types, intensity, duration and duration of effect to optimise efficacy and efficiency. • Strategies to increase engagement and address barriers, cultural factors, acceptability, feasibility and sustainability. • Medium to longer term exercise studies (6-12 months or greater). • Impact of improvements in cardiorespiratory fitness and/or strength on PCOS features. • Assess the impact of reducing sedentary behaviour on clinical outcomes.

3.5. Weight gain extrinsic	• Examine more precise quantification of diet, physical activity, appetite hormone regulation, appetite, insulin and energy expenditure in women with and without PCOS and examine relationships with weight/weight change across BMI range.
	• Primary longitudinal studies assessing:
	  • Physiological, behavioural and psychosocial predictors of weight gain in PCOS, across age and BMI ranges
	  • Mechanisms including food or nutrient intake on adipokines, gastrointestinal appetite hormones, functional MRI, meal induced thermogenesis, metabolic flexibility and neuropeptide responses, linked to energy homeostasis
	  • Total energy expenditure in PCOS using doubly labelled water, diet intake measures and physical activity measures by accelerometry.

3.6. Weight stigma	• Extent of weight-stigma in PCOS (across weight spectrum) by health professionals, family, workplace and community. • Health professionals' awareness of their own weight-stigmatising beliefs and behaviours and implementation of weight-neutral/weight-inclusive care in PCOS. • Impacts of weight-neutral/weight-inclusive care on the biopsychosocial wellbeing of women with PCOS. • Consideration of other sources of stigma in PCOS (e.g. infertility, acanthosis nigricans, hirsutism, alopecia etc).
GDG 4	**Management of non-fertility features**
Question #	**Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:**
4.2. & 4.3. COCP and metformin	• Large scale population-based studies to capture side-effects and risks in individuals with PCOS. • Large scale comparative studies in adolescents to determine optimal COCP preparation including progestins and doses. • Efficacy of COCP on acne, hair loss, hirsutism and psychological outcomes • Adverse events including weight, metabolic effects and psychological outcomes • Efficacy of progestin only preparations (including intrauterine system, implant, progesterone only pills etc).
4.4. Metformin	• Explore metformin adherence and adverse effects in adults/adolescents by dose, preparation type and longer duration. • Explore across the BMI range to understand potential differential effect of metformin associated with BMI. • Study efficacy of combination therapy including metformin in addressing PCOS clinical features. • Assess Vitamin B12 levels in women on metformin to inform frequency of monitoring.
4.5. Anti-obesity pharmacological agents	• Compare efficacy of anti-obesity medications versus placebo in adolescents and adults with PCOS. • Assess impacts on metabolic, reproductive, psychological and pregnancy outcomes and adverse effects. • Explore role and adverse effects of long-term therapy.
4.6. Anti-androgen pharmacological agents	• Determine optimal AA preparation and schedules including benefits and harms. • Determine optimal combination therapies by BMI groups.
4.7. Inositol	• Optimal formulations, dose and adverse effects. • Critical clinical outcomes including ovulation, clinical pregnancy and live birth as well as QoL, metabolic, reproductive, psychological and pregnancy outcomes and adverse effects. • High priority for independent funding as a consumer priority.

4.8. Hair reduction	• COCP alone or COCP + antiandrogens vs laser. • Feasibility and efficacy of laser treatment of hirsutism in different age subgroups and breastfeeding women. • More clarity on best laser treatment by skin type (given the heterogeneity of skin types in the studies). • Evaluation of laser efficacy in general body areas other than face. • Adverse events and side-effects and cost effectiveness of laser treatment.
4.9. Bariatric/metabolic surgery	• Evaluate bariatric surgery impacts including comparison to anti-obesity therapy and by ethnicity. • Compare different types of bariatric/metabolic surgical procedures by outcomes. • Pre-conception and pregnancy requirements post bariatric/metabolic surgery. • Cost effectiveness studies. • Individual and patient cohorts long-term is critical, including psychological, pregnancy and child outcomes.
4.10. Pregnancy outcomes	• Identify PCOS-status in antenatal care and follow-up PCOS vs non-PCOS, registering predefined outcomes. • Explore how phenotype, age and preconception BMI and ART affect adverse outcomes in addition to PCOS-status on individual patient data meta-analysis across international cohorts.
4.11. Metformin in pregnancy	• Understand mechanisms of metformin action in pregnancy. • Timing, dosing, duration and subgroups that benefits most in pregnancy. • Explore potential long-term health effects in the next generation of metformin-exposure in utero.
GDG 5	**Assessment and treatment of infertility**
Question #	**Priority for high quality multisite adequately powered and robustly designed studies in partnership with consumers on:**
5.1. Preconception risk factors	• Individual patient data meta-analysis of preconception risk factors in PCOS and impact on fertility outcomes. • Explore ethnic and geographical variation in PCOS reproductive outcomes and fertility treatment responses. • Impact of age on fertility and fertility treatment outcomes in PCOS. • Cumulative weight gain over the reproductive life course and the impact on fertility and pregnancy outcomes. • Impact of underweight on fertility outcomes in PCOS.
5.2. Tubal patency testing	• Explore if tubal patency tests should be done during infertility work-up to identify the optimal timing and method of assessing tubal patency in PCOS and infertility due to anovulation alone with normal semen analysis, considering cost effectiveness and QoL

5.3. Letrozole	• Establish ideal number of cycles of ovulation induction with letrozole before other treatments. • Validation of prediction models for first-line ovulation induction agents and dose. • Study combination therapies of aromatase inhibitors with other inexpensive and widely available medications with different mechanisms of action such as metformin, inositol and clomiphene citrate. • Best therapies for drug naïve vs drug resistant/drug failure patients.
5.4. Clomiphene citrate and metformin	• Exploring side-effects and mitigation. • Best time for cessation of metformin in pregnancy. • A definitive trial to assess magnitude of efficacy on critically important outcome of live birth by BMI and metformin status.
5.5. Gonadotrophins	• Compare letrozole versus gonadotrophins in women with anovulatory PCOS who are therapy naïve for clinical and cost effectiveness and quality of life.
5.6. Laparascopic ovarian surgery	• Understand how LOS restores ovulatory function. • Compare LOS with other ovulation induction agents in PCOS. • Explore profiles in PCOS who may respond to LOS. • Determine minimal effective intervention of LOS (i.e. number of drillings, energy level, modality and unilateral/bilateral).
5.7. IVF and IVM	• Explore benefits of stimulated IUI vs IVF in PCOS. • Comparing IVM-ICSI to Stimulated-ICSI only.
5.7.1. GnRH protocol	• Compare effectiveness of GnRH antagonist protocol versus GnRH long protocol to improve reproductive outcomes.
5.7.2. Trigger type	• Ascertain whether combination of GnRHa trigger and intensive luteal steroid support in the OHSS high-risk patient is associated with better clinical outcomes than GnRHa trigger and subsequent frozen embryo transfer.
5.7.3. Choice of FSH	• Compare different types of FSH in PCOS in controlled ovarian (hyper) stimulation for IVF/ICSI using GnRH antagonist or agonist long protocol on live birth rate per cycle, cumulative live birth rate from one egg retrieval, OHSS, cost effectiveness.
5.7.4. Exogenous LH	• Investigate dose of exogenous LH in addition to FSH appropriate for follicular development on live birth rate and OHSS. • Explore groups that will benefit from exogenous LH addition to FSH in IVF +/- ICSI.
5.7.5. Adjunct metformin	• RCTs of adjunct metformin before and/or during IVF/ICSI with GnRH antagonist protocol assessing benefits and harms, optimal start and finish times for metformin for pregnancy rate, live birth rate and infant outcomes.
5.7.6. In vitro maturation	• Optimal IVM protocol for PCOS. • Long term health of offspring with IVM.
5.8/5.9 Inositol, anti-obesity pharmacological agents	See 4.5 and 4.7

Dissemination and implementation plan

Within the guideline we use best practice principles of research translation, dissemination, and implementation that optimise the process of turning research findings into tangible outcomes and actions. Effective communication plays a crucial role, ensuring that research results are conveyed in a clear, concise, and accessible manner to various stakeholders, including policymakers, practitioners, and the general public. In addition, collaboration and engagement with end-users and key stakeholders throughout the research process foster a sense of ownership, relevance, and applicability.

This involvement allows for a better understanding of the target audience's needs, preferences, and constraints, ultimately increasing the likelihood of successful implementation. Additionally, establishing partnerships between researchers and knowledge users facilitates the co-creation of knowledge, enabling research to be directly embedded into policy and practice. Furthermore, the use of rigorous evaluation methods and continuous monitoring allows for the assessment of impact, effectiveness, and scalability of research translation efforts, providing valuable feedback to refine and improve future implementation strategies. Ultimately, embracing a culture of learning, adaptability, and responsiveness to feedback is essential for effective research translation, dissemination, and implementation, ensuring that evidence-based interventions and practices are integrated into real-world settings to achieve meaningful and sustainable outcomes.

In this context, a comprehensive implementation, translation, and dissemination program has been developed to amplify the impact of the 2023 International Evidence-based guideline for the assessment and management of polycystic ovary syndrome (PCOS), building on the extensive plan from 2018.

The program is grounded in three guiding principles:

- All components of the plan are informed by the needs and preferences of end-users.
- All materials co-created with, and assessible to, end-users.
- Implementation and dissemination strategies will be evidence-based, multi-faceted, multi-modal, and co-delivered by to end-users.

The aims of this extensive, international translation program are:

- Guide the implementation of the recommendations.
- Equitable distribution of resources to diverse groups.
- Build the capability of health professionals in high-quality, evidence-based, assessment and management
- Augment the health literacy to enhance self-directed care by those with PCOS.
- Promote evidence-based, best practice PCOS models of care.
- Orientate international health policy towards an evidence-based, best practice approach.

Key outcomes:

- Prevention of overdiagnosis.
- Avoidance of missed diagnosis.
- Avoidance of expensive, excessive, ineffective, and inaccessible diagnostic testing.
- Increased awareness of lifestyle and emotional wellbeing as first-line treatment options
- Increased use of cheaper and safer fertility management.
- Embed evidence-based models of care that promotes self-directed care.

Barriers and facilitators to dissemination and implementation

These have been considered in each question and recommendation in the GRADE template of the technical report. Overall, these were considered in constructing the dissemination and implementation plan and were informed by the last guideline. Issues such as the need for awareness and education, targeting all stakeholders including those affected, their support networks diverse healthcare providers and policy makers, are targeted. Issues such as language, accessibility, reach, cross discipline and setting approaches and consumer empowerment were all considered and integrated here.

Equity focus

A key priority of this plan is to work in partnership and codevelopment to meet the needs of culturally and linguistically diverse groups internationally. Given Australian government funding and priority populations including Indigenous and Torres Strait Islander groups, the Australian adaptation and translation resources, we will work with a range of Indigenous and Torres Strait Islander groups using an approach aligned to the National Aboriginal and Torres Strait Islander Health Plan.

The successful dissemination of this guideline is heavily reliant on the active involvement of the 4 partners, 36 collaborating societies, health professional peak bodies, and consumer organisations (see guideline Appendix III). The guideline recommendations provide practical guidance for clinical implementation, including information on dosage, frequency, monitoring criteria, and more. In addition, the guideline provides links to a variety of implementation tools such as the AskPCOS app, Primary Care Tool (a practical resource to guide clinicians in the implementation of evidence-based practice), algorithms (brief summaries of the recommendations designed for use within a clinical setting), the Berlin Sleep Apnea Tool, emotional well-being tools, and the Ferriman Gallwey hirsutism tool.

A substantial increase in funding has been granted in 2023 by the Australian Government through the Medical Research Future Fund to support the development of the resources and tools including the AskPCOS app. This funding will facilitate advanced efforts aimed at enhancing personalisation, interactivity, self-management, and analysis of individual data to aid in shared decisions making and improved information and models of care and support. A virtual clinical interface will be established, enabling health professionals and individuals with PCOS to connect and utilise personalise data to inform clinical care. To our understanding, this will be the first evidence-based, cost-free healthcare support application in PCOS to achieve such outcomes, making a significant contribution towards enhancing PCOS literacy, self-management, and clinical outcomes.

In the Australian context, we commit to working within the National Policy Guidance Frameworks including, A Guide to applying The AIATSIS Code of Ethics for Aboriginal and Torres Strait Islander Research, the Uluru Statement from the Heart, the National Agreement on Closing the Gap and the Monash Aboriginal and Torres Strait Islander Framework: 2019–2030. In partnership we will work within The Cultural Safety Framework and the enabling principles of:

- Aboriginal Self Determination
- Social and Restorative Justice
- Equity
- Negotiated Partnership
- Transparency
- Reciprocity
- Accountability
- Sustainability
- Political Bipartisanship
- Cultural Contextuality

Thus, ensuring effective and sustainable transformational change within the health system whereby cultural safety strategies are embedded within the processes and policies to increase health outcomes for Aboriginal and Torres Strait Islander peoples.

The guideline implementation, translation, and dissemination plan directly address implementation barriers identified during the evidence synthesis process, including clinician knowledge gaps and condition-specific health literacy among women with PCOS. Resource implications were extensively considered during the development process of the guideline and are expected to result in a reduction in the use of resources due to less use of diagnostic ultrasound, less expensive treatment options such as metformin, simpler diagnostic criteria, less intensive metabolic screening, and a reduction in expensive IVF treatments.

Recommendations that are most likely to lead to improvements in health outcomes will be highlighted for consideration in implementation. This plan addresses the full spectrum of evidence-based, end-user interventions including; information and education, strategies to build capacity to actively engage in treatment, management and self-directed care, effective behaviour change support, skill development to optimise self-management, and self-care, strategies to involve consumers in decision making about healthcare, and a voice to inform policy and shape healthcare systems.

This plan is supported by a robust evaluation plan, which includes big data capture and analysis from the Australian Longitudinal Study on Women's Health, Pharmaceutical Benefits Scheme, Medicare Benefits Schedule, analysing appropriate diagnosis, care, testing, and medications. Also, benchmarking and feedback will guide further alignment with evidence-based care, with government and NHMRC funding this initiative. In addition, altimetrics will monitor downloads of the guideline and guideline resources. Finally, focus groups and surveys will measure knowledge and awareness in consumers and health professionals, with results compared to large-scale data collected prior to guideline release.

Table 9: Dissemination and implementation stakeholders and strategies

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation measures
Aim	**Promote self-directed care for those with PCOS**					
Consumers	**Free accessible tools:** Enhance the highly successful PCOS app (AskPCOS) currently used by 35,000 users across 184 countries and available in 4 languages (English, Spanish, Arabic, and Simplified Chinese). This will be upgraded to 11 languages including the plain English summary and resources. The app will be extended to support shared decision making and optimise interaction with health professionals.	PCOS app (AskPCOS)	• Monash University • PCOS-CRE • MCHRI • PCOS consumers • International consumer groups including PCOS Vitality, PCOS Challenge: The National Polycystic Ovary Syndrome Association, Verity (PCOS UK), VARTA, POSSA. And a range of other consumer groups	• Apple iTunes • Android play store • MCHRI website • Partner websites • Consumer groups • Social media	• Enhance evaluation metrics (Hotjar) • Increase language groups from 5 to 10 • Embed consumer version of the 2023 PCOS guideline using an engaging and interactive interface	• Evaluation metrics (Alimetrics) • Consumer feedback (Integrated into the app for continuous improvement) • Uptake • Knowledge gain • Integration into care

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation measures
Aim	**Promote self-directed care for those with PCOS**					
Consumers	**Indigenous Australian translation stream:** Working in partnership and codevelopment to meet the needs of Aboriginal and Torres Strait Islander groups.	• A range of codeveloped resources to meet the needs of Aboriginal and Torres Strait Islander groups	• National, state and local Aboriginal and Torres Strait Islander bodies and groups	• Aboriginal and Torres Strait Islander groups communication channels	• Accessible PCOS resources for Aboriginal and Torres Strait Islander groups	• Evaluation data captured with outcomes agreed in partnership with Aboriginal and Torres Strait Islander groups
	CALD groups: Working in partnership and codevelopment to meet the needs of culturally and linguistically diverse groups.	• A range of codeveloped resources to meet the needs of CaLD groups	• A range of partners for CALD groups	• CALD groups communication channels, translated into 14 languages	• Accessible PCOS resources for CALD groups.	• Evaluation data captured in partnership with CALD groups
	Reducing access barriers: Address barriers to accessibility for diverse users in the AskPCOS app.	• An accessible app for diverse groups	• Aboriginal and Torres Strait Islander groups • CALD groups	• Apple iTunes • Android play store • MCHRI website • Partner websites	• Co-designed content developed with Aboriginal and Torres Strait Islander groups an CALD groups • Dissemination methods to reach diverse audiences	• Google Analytics • Reach, maintenance • Sub-group data capture • In app surveys and feedback

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation measures
Aim	**Promote self-directed care for those with PCOS**					
Consumers	**Multilingual and culturally appropriate resources;** Provision of translated, e-health, evidence-informed PCOS information, informed by consumer needs and preferences.	• e-health PCOS information accessible to consumers	• Jean Hailes for Women's Health • Verity • PCOS Challenge • Victorian Assisted Reproductive Treatment Authority (VARTA) • Women's Health Victoria • Polycystic Ovary Syndrome Association of Australia (POSSA)	• PCOS Centre for Research Excellence website • Jean Hailes for Women's Health website • VARTA website • Women's Health Victoria website	• Accessible, translated PCOS e-health information informed by the highest quality evidence and consumer needs and preferences	• Breadth of resources (app, online education programs, resources etc) • Dissemination into different languages • Professional Society and consumer engagement endorsement and dissemination • Google analytics, reach • Uptake of consumer and health professional online education programs
	Lifestyle Education Program codeveloped and delivered for women with PCOS	• PCOS Lifestyle Education Program	• Monash Health • Victorian Government	• Monash Health PCOS clinic	• Provision of an evidence-based, tailored lifestyle education program	• Uptake of programs • App based resources, enable feedback
	Education courses: Codevelop and deliver an accessible, interactive, and internationally available online PCOS course for consumers.	• Consumer learning module • Health professional learning module	• Monash University • PCOS-CRE • MCHRI	• Monash University	• Accessible, online, interactive, internationally available PCOS courses	• Uptake of course • Level of engagement • Evaluation feedback

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation measures
Aim	**Promote self-directed care for those with PCOS**					
Consumers	**PCOS Model of Care** codeveloped and underpinned by a sustainable, psychosocial multidisciplinary approach and incorporating a comprehensive PCOS dissemination platform.	• PCOS Clinical Model of Care	• Monash Health • Victorian Government	• Monash Health PCOS clinic	• A sustainable, evidence-based, psychosocial-multidisciplinary PCOS clinic and comprehensive PCOS dissemination platform	• Uptake of model of care • Evaluation of outcomes with audit and feedback tools
	Written and online free materials: Range of translated accessible PCOS written materials tailored to the needs of consumers.	• A range of PCOS written materials: fact sheets, booklets for different consumer groups, language translated health materials, summary of guideline recommendations	• Jean Hailes for Women's Health • Victorian Assisted Reproductive Treatment Authority (VARTA) • Women's Health Victoria • Polycystic Ovary Syndrome Association of Australia (POSSA) • CALD and Aboriginal and Torres Strait Islander organisations	• Monash PCOS clinic • Jean Hailes for Women's Health • Victorian Assisted Reproductive Treatment Authority (VARTA)	• A range of translated, accessible PCOS written materials tailored to the needs of consumers • Online fact sheets, booklets for different consumer groups, language translated health materials	• Breadth of resources (app, online education programs, resources etc) • Dissemination into 14 different languages • Professional Society and consumer group engagement, endorsement and dissemination • Website: Altmetrics for guideline and resources • Uptake of consumer and health professional online education programs

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation measures
Aim	**Promote self-directed care for those with PCOS**					
Consumers	**Consumer led interactive, learning opportunities.**	• Consumer led seminars	• Polycystic Ovary Syndrome Association of Australia (POSSA) • Verity • PCOS Challenge	• Polycystic Ovary Syndrome Association of Australia (POSSA) • Verity • PCOS Challenge	• Consumer led seminars delivered within Australia and internationally	• Consumer group engagement, endorsement and dissemination • Uptake of consumer programs • Feedback

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation
Aim	**Increase the uptake of PCOS evidence-based practice among health professionals internationally.**					
Health Professionals	**Virtual clinical interface** to be used in collaboration with those with PCOS. Integrated into AskPCOS app.	• Virtual clinic interface	• Android play store • GPs • RACGP • Health professionals	• Apple iTunes • Android play store • MCHRI website • Partner websites	• An interactive, virtual, app-based, clinical interface used in collaboration with those with PCOS	• End-user testing of each iteration during the development phase • Evaluation measures built into the app • Uptake/feedback

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation
Aim	**Increase the uptake of PCOS evidence-based practice among health professionals internationally.**					
Health Professionals	**PCOS evidence-based guideline**	• Disseminate the PCOS Guideline	• Collaborating societies and international PCOS network	• Collaborating societies and international PCOS network	• International dissemination of the PCOS evidence-based guideline.	**1** Guideline and resource reach – Breadth of resources (app, resources) • Different languages • Professional Society and consumer group engagement, endorsement and dissemination • Website Altimetrics • Publication citations • International and national presentations **2** Survey follow-up nationally/ internationally on change in knowledge and practice (compared to > 3500 surveyed pre-guideline) **3** App/resource download, use, feedback **4** Access and evaluation of EB models of care **5** Uptake of consumer and health professional online education programs

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation
Aim	**Increase the uptake of PCOS evidence-based practice among health professionals internationally.**					
Health Professionals	**Extensive publication plan** targeting international journals, discipline specific publications and in the general medical media domain.	• Minimum of 20 publications published in high impact journals and discipline specific publications	• Experts from the 40 international collaborating organisations of the PCOS guideline	• High impact international journals • Discipline specific publications • General medical media	• Minimum of 20 publications published in high impact journals and discipline specific publications	• Number of journal publications • Altimetrics • A range of general media outputs such as interviews, and publications in high quality publications for a general audience.
	Coordinated, international expert speaker program at international conferences, annual meetings and invited speaker events in the US, Aust, Africa, India and Europe, covering of the topics of; fertility, reproduction, chronic disease prevention and lifestyle.	• Up to 35 workshops, symposiums, key note speaker and panel speaker events delivered internationally	• Experts from the international collaborating organisations of the PCOS guideline	• Multiple conferences, annual meeting and events across US, Australia, Africa, India and Europe	35 workshops, symposiums, key note speaker and panel speaker events delivered internationally	• Uptake of workshops and symposiums • End-user feedback
	Range of PCOS health professional educational resources with high utility with health professionals.	• Webinars • Face-to-face events • Flexible learning opportunities	• Jean Hailes for Women's Health • RACGP • Peak bodies	• Peak body learning portals • Jean Hailes for Women's Health CPD program	• A range of PCOS educational resources with high utility with health professionals	• Uptake of educational resources • End-user feedback

	Implementation strategy	Deliverable/s	Collaborator/s	Dissemination	Outcomes	Evaluation
Aim	**Increase the uptake of PCOS evidence-based practice among health professionals internationally.**					
Health Professionals	**Health Professional course in PCOS:** Accessible, interactive, accredited, internationally available online PCOS course for health professionals.	• PCOS accredited CPD for-fee online course	• Monash University • PCOS-CRE • MCHRI	• Monash University • Futurelearn FOOC (For-fee online course)	• Accessible, accredited, online, interactive, for-fee, internationally available PCOS course for health professionals	• Uptake of course • End-user engagement and feedback
	Health Professional education: Cocreate and deliver a range of health professional continuous learning development (CPD) opportunities	• CHECK program for GPs • Accredited CPD modules – nurses, Drs, allied health professionals. • Expert interactive webinars	• Jean Hailes for Women's Health • Monash University • Futurelearn UK • Peak medical bodies • Healthinfonet	• Jean Hailes for Women's Health • Monash University • Futurelearn UK • Peak medical bodies • Healthinfonet	• A range of accredited and non-accredited continuous learning opportunities for health professionals	• Uptake of CPD opportunities • End-user engagement and feedback. Change in practice by monitoring MBS and PBS uptake of recommendations through an established partnership with linked data and the Aust longitudinal women's health study and other international data repositories.
Government	**International/national health policy influence,** leveraging high level health professional expertise and informed by the highest quality evidence and consumer needs and preferences.	• Create PCOS policy position statement	• International and national Governments, health organisations • Health professional experts • PCOS health consumers	• Multi-faceted dissemination strategy	• PCOS position statement disseminated via health departments and policy channels.	• Engagement opportunities with policy makers • Policy outcomes.

An additional Australian government grant for $3 million AUD has been acquired to significantly escalate the implementation plan with details to be co-designed with partners and end-users. Given this funding has only just been awarded, the codesign process will enable codevelopment of more specific outcomes and avaulation strategies as part of the guideline implementation and dissemination. This will include a strong focus on Australian adaptation. International adaptation will focus on translation resources only and will follow ADAPTE processes.

Appendix I:
Management committee

Role	Name	Discipline	Organisational Affiliation/Region
Chair Project owner and director Senior supplier Senior user Endocrinology representative	Professor Helena Teede	Endocrinologist	Centre for Research Excellence in Women's Health in Reproductive Life, Australia
Consumer representative Senior user	Ms Lorna Berry	Consumer lead	Polycystic Ovary Syndrome Association of Australia
Guideline development group chair (GDG 1) Senior user Senior supplier Gynaecology representative Endocrine Society representative European Society of Human Reproduction and Embryology representative	Professor Joop Laven	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Erasmus MC Rotterdam, Netherlands
Guideline development group chair (GDG 2) Senior supplier Senior user Reproductive endocrinology representative American Society for Reproductive Medicine representative	Professor Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania, USA

Role	Name	Discipline	Organisational Affiliation/Region
Guideline development group chair (GDG 3) Senior user Senior supplier Allied Health representative	Associate Professor Lisa Moran	Dietitian	Centre for Research Excellence in Women's Health in Reproductive Life, Australia
Guideline development group chair (GDG 4) Senior user Senior supplier Reproductive endocrinology representative European Society of Endocrinology representative European Society of Human Reproduction and Embryology representative	Professor Terhi Piltonen	Obstetrician-Gynaecologist Reproductive Endocrinologist	Oulu University Hospital, University of Oulu, Finland
Guideline development group chair (GDG 5) Senior user Senior supplier Gynaecology representative	Doctor Michael Costello	Obstetrician-Gynaecologist;	University of NSW, Australia
Senior user Academic general practitioner discipline representative	Doctor Carolyn Ee	General Practitioner	Western Sydney University, Australia
Senior user Senior supplier Aboriginal cultural advisor General practitioner discipline representative	Doctor Marlene Kong	General Practitioner	Whitsunday Doctors' Service, Australia
Senior user Senior supplier CRE WHiRL early career network chair Endocrinology discipline representative	Doctor Chau (Jillian) Tay	Endocrinologist	Centre for Research Excellence in Women's Health in Reproductive Life, Australia
Senior supplier Translation and implementation advisor	Doctor Rhonda Garad	Translation and implementation advisor	Centre for Research Excellence in Women's Health in Reproductive Life, Australia

Appendix II:
International advisory panel

Role	Title	Name	Discipline	Organisation	Country
Chair	Professor	Helena Teede	Endocrinologist	Centre for Research Excellence in Women's Health in Reproductive Life, Monash University	Australia
Member	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	University of Adelaide	Australia
Member	Professor	Cindy Farquhar	Obstetrician-Gynaecologist; Chairman of the NZ Guidelines Group	University of Auckland	New Zealand
Member	Professor	Heather Huddelston	Obstetrician-Gynaecologist	University of California San Francisco	USA
Member Endocrine Society representative	Professor	Sabrina Gill	Endocrinologist	University of British Columbia	Canada

Role	Title	Name	Discipline	Organisation	Country
Member Endocrine Society representative	Associate Professor	Kristen Gill Hairston	Endocrinologist	Wake Forest University	USA
Member European Society of Endocrinology representative	Professor	Djuro Macut	Endocrinologist	University of Belgrade	Serbia
Member European Society of Human Reproduction and Embryology representative	Professor	Ying Cheong	Fertility Physician	University of South Hampton	UK
Member Patient representative	Ms	Rachel Morman	Chair of Verity	Verity – PCOS Charity	UK

Appendix III:
Guideline development groups

Terms of reference for each committee can be provided upon request (cre-whirl@monash.edu).

GDG 1: Topic area – Screening, diagnostic and 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	Doctor	Anju Joham	Endocrinologist	Monash University	Australia
Member	Professor	Wiebke Arlt	Endocrinologist	University of Birmingham	UK
Member	Professor	Ricardo Azziz	Reproductive Endocrinologist	University of Alabama at Birmingham	USA
Member	Ms	Lorna Berry	Consumer Representative	Polycystic Ovary Syndrome Association Australia	Australia
Member	Doctor	Carolyn Ee	General Practitioner	Western Sydney University	Australia
Member	Assoc/Professor	Marla Lujan	Reproductive Sciences; Nutrition	Cornell University	USA
Member	Doctor	Chau (Jillian) Tay	Endocrinologist	Monash University	Australia

GDG Role	Title	Name	Discipline	Organisation	Country
Member	Professor	Ronald Ma	Endocrinologist	Chinese University of Hong Kong	Hong Kong/ China
Member	Doctor	Malika Patel	Obstetrician-Gynaecologist; Reproductive Medicine	University of Cape Town; Groote Schuur Hospital	South Africa
Member	Assoc Prof	Alexia Pena	Paediatric Endocrinologist	The Robinson Institute at the University of Adelaide	Australia
Member	Professor	Sharon Oberfield	Paediatric Endocrinologist	Columbia University Medical Center	USA
Member	Professor	Duru Shah	Obstetrician-Gynaecologist; Fertility Specialist	The PCOS Society of India; Gynaecworld: The Centre for Women's Health and Fertility	India
Member	Professor	Fahimeh Ramezani Tehrani	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Shahid Beheshti University of Medical Sciences, Tehran	Iran
Co-opted	Assoc Professor	Darren Mansfield	Sleep Expert	Epworth Health Monash University	Australia

GDG 2: Topic area – Prevalence, screening and management of psychological issues and models of care

GDG Role	Title	Name	Discipline	Organisation	Country
Chair	Professor	Anuja Dokras	Reproductive Endocrinologist and infertility	University of Pennsylvania	USA
Deputy Chair	Professor	Jacky Boivin	Psychologist	Cardiff University	UK
Member	Associate Professor	Leah Brennan	Psychologist	La Trobe University	Australia
Member	Associate Professor	Tania Burgert	Paediatric Endocrinologist	University Missouri – Kansas School of Medicine	USA
Member	Mrs	Maureen Busby	Consumer Representative	PCOS Vitality	Ireland
Member	Doctor	Rhonda Garad	Registered Nurse	Monash University	Australia
Member	Doctor	Melanie Gibson	Women's Public Health Researcher	Te Tātai Hauora o Hine --National Centre for Women's Health Research Aotearoa, Victoria University of Wellington; Monash University	New Zealand Australia
Member	Doctor	Chau (Jillian) Tay	Endocrinologist	Monash Health	Australia
Member	Doctor	Mala Thondan	General Practitioner	Harp Family Medical	Australia
Member	Professor	Elisabet Stener-Victorin	Researcher in Reproductive Endocrinology and Metabolism	Karolinska Institutet	Sweden

GDG3: Topic area – Lifestyle management

GDG Role	Title	Name	Discipline	Organisation	Country
Chair	Associate Professor	Lisa Moran	Dietitian, Research Fellow	Monash University	Australia
Deputy Chair	Professor	Leanne Redman	Obesity; Lifestyle Interventions	Pennington Biomedical Research Centre	USA
Member	Ms	Lorna Berry	Consumer Representative	Polycystic Ovary Syndrome Australia	Australia
Member	Associate Professor	Leah Brennan	Psychologist	La Trobe University	Australia
Member	Doctor	Cheryce Harrison	Exercise Physiologist; Health Coach	Monash University	Australia
Member	Professor	Kathleen Hoeger	Reproductive Endocrinologist	University of Rochester	USA
Member	Professor	Angelica Lindén Hirschberg	Obstetrician-Gynaecologist	Karolinska Institutet and Karolinska University Hospital	Sweden
Member	Doctor	Kate Marsh	Dietitian; Diabetes Educator	Private Practice	Australia
Member	Doctor	Mala Thondan	General Practitioner	Harp Family Medical	Australia
Member	Professor	Chandrika Wijeyaratne	Endocrinologist	University of Colombo	Sri Lanka

GDG 4: Topic area – Management of non-fertility features

GDG Role	Title	Name	Discipline	Organisation	Country
Chair	Professor	Terhi Piltonen	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Oulu University Hospital, University of Oulu	Finland
Deputy Chair	Assoc Professor	Jacqueline Boyle	Obstetrician-Gynaecologist	Monash University	Australia
Member	Doctor	Carolyn Ee	General Practitioner	Western Sydney University	Australia
Member	Professor	Rong Li	Obstetrician-Gynaecologist	Reproductive Medical Centre, Peking University Third Hospital	China
Member	Ms	Rachel Morman	Chair of Verity/Patient Representative	Verity – PCOS Charity	UK
Member	Assoc Prof	Alexia Pena	Paediatric Endocrinologist	The Robinson Institute at the University of Adelaide	Australia
Member	Doctor	Daniela Romauldi	Obstetrician-Gynaecologist	Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome	Italy
Member	Professor	Poli Mara Spritzer	Endocrinologist	Universidade Federal do Rio Grande do Sul	Brazil
Member	Professor	Eszter Vanky	Obstetrician-Gynaecologist	Dept. of Clinical and Molecular Medicine, Norwegian University of Science and Technology; Dept. Obstetrics/Gynaecology, St.Olavs Hospital, University Hosp Trondheim	Norway
Member	Professor	Selma Witchel	Paediatric Endocrinologist	Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh	USA
Member	Doctor	Aya Mousa	Academic epidemiology	Monash University	Australia
Member	Professor	Bulent Yildiz	Endocrinologist	Hacettepe University Turkey	Turkey
Co-opted Member	Professor	Wendy Brown	Bariatric/metabolic Surgeon	Department of Surgery, Central Clinical School, Monash University; Alfred Health	Australia

GDG 5: Topic area – Screening, diagnostic assessment and management of infertility

GDG Role	Title	Name	Discipline	Organisation	Country
Chair	Doctor	Michael Costello	Obstetrician-Gynaecologist; Reproductive Endocrinologist	University of NSW	Australia
Deputy Chair	Professor	Robert Norman	Obstetrician-Gynaecologist; Reproductive Endocrinologist; Chemical pathologist	University of Adelaide	Australia
Member	Professor	Adam Balen	Reproductive Medicine	Leeds Teaching Hospitals; British Fertility Society	UK
Member	Doctor	Lisa Bedson	General Practitioner; Fertility Clinician	Repromed	Australia
Member	Professor	Roger Hart	Obstetrician-Gynaecologist; Reproductive Endocrinologist	The University of Western Australia; City Fertility Clinics Australia	Australia
Member	Doctor	Tuong Ho	Fertility Specialist	HOPE Research Centre, My Duc Hospital	Vietnam
Member	Doctor	Kim Hopkins	Member, PCOS Challenge Patient Advisory Board	PCOS Challenge: The National Polycystic Ovary Syndrome Association	USA
Member	Ms	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	Luk Rombauts	Obstetrician-Gynaecologist; Infertility Specialist	Monash University	Australia
Member	Professor	Shakila Thangaratinam	Obstetrician-Gynaecologist; Clinical Academic	University of Birmingham, NIHR Biomedical Research Centre, Birmingham	UK
Member	Professor	Dongzi Yang	Obstetrician-Gynaecologist; Reproductive Endocrinologist	Reproductive Medical Centre, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University	China

Paediatric expert panel

Role	Title	Name	Discipline	Organisation	Country
Member	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

Consumer/patient expert team

Role	Title	Name	Discipline	Organisation	Country
Member	Professor	Helena Teede	Endocrinologist	Monash Centre for Health Research and Implementation	Australia
Member	Doctor	Kim Hopkins	Consumer	PCOS Challenge	USA
Member	Ms	Rachel Mormon	Consumer	Verity	UK
Member	Ms	Maureen Busby	Consumer	Daisy PCOS	Ireland
Member	Ms	Lorna Berry	Consumer	POSSA	USA

Appendix IV:
Guideline development technical team

- Professor Helena Teede, Project Director, Monash Centre for Health Research and Implementation, Monash University
- Doctor Chau (Jillian) Tay, Evidence synthesis co-lead and lead on the early career PCOS Network
- Doctor Aya Mousa, Meta-analyses and evidence synthesis lead
- Linda Downes, Project Manager – Monash University and CRE WHIRL
- Doctor Rhonda Garad, Senior Project Officer, Knowledge Translation in PCOS, Monash University
- Doctor Marie Misso, Evidence Synthesis expert advisor
- Loyal Pattuwage, Evidence synthesis coordinator
- Sanjeeva Ranasinha, Statistician

International early/mid-career evidence network

Role definitions:

Lead: intellectual involvement and searching, screening, data extraction, and or quality appraisal alongside evidence interpretation, trained and or supervised by the guideline evidence team, and included as an author on the guideline

Member: involved in searching, screening, data extraction and or quality appraisal trained and or supervised by the guideline evidence team with two reviewers for each step, acknowledged as a contributor on the guideline

Role	Title	Name	Organisation	Country
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Lead	Doctor	Jodie Avery	Robinson Research Institute, University of Adelaide	Australia
Lead	Doctor	Mahnaz Bahri	Monash University	Australia
Lead	Doctor	Jamie Benham	University of Calgary	Canada
Lead	Mr	Hugh Bidstrup	Australian Catholic University	Australia
Lead	Doctor	Su Jen Chua	Monash University	Australia
Lead	Doctor	Laura Cooney	University of Wisconsin	USA
Lead	Miss	Thisara Coster	Monash University	Australia
Lead	Associate Professor	Carolyn Ee	Western Sydney University	Australia
Lead	Doctor	Victoria Fitz	Massachusetts General Hospital; Harvard University	USA
Lead	Doctor	Maria Forslund	Sahlgrenska Academy, University of Gothenburg	Sweden
Lead	Doctor	Geranne Jiskoot	Erasmus MC	Netherlands
Lead	Doctor	Maryam Kazemi	Icahn School of Medicine at Mount Sinai	USA
Lead	Doctor	Punith Kempegowda	University of Birmingham	UK

Role	Title	Name	Organisation	Country
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Lead	Professor	Marla Lujan	Cornell University	USA
Lead	Doctor	Johanna Melin	University of Helsinki	Finland
Lead	Doctor	Eka Melson	University of Leicester	UK
Lead	Mr	Yitayeh Belsti Mengistu	Monash University	Australia
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Lead	Doctor	Angelo Sabag	Western Sydney University	Australia
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Lead	Doctor	Katrina Tan	Monash Health	Australia
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Member	Doctor	Kathryn Corbett	University of Calgary	Canada
Member	Doctor	Stephanie Cowan	Monash University	Australia
Member	Doctor	Meri Davitadze	Clinic NeoLab	Georgia
Member	Ms	Shrinkhala Dawadi	Monash University	Australia
Member	Ms	Kiran Ganga	Cornell University	USA
Member	Mr	Sandro Graca	Northern College of Acupuncture	UK
Member	Doctor	Alyse Goldberg	University of Toronto	Canada
Member	Doctor	Kaley Gyorfi	University of Wisconsin	USA
Member	Mr	Demelash Handiso	Monash University	Australia
Member	Ms	Somayeh Hashemi	Brock University	Canada
Member	Mr	James Hawley	Manchester University NHS Foundation Trust	UK
Member	Doctor	Dawn Kimberly Hopkins	Henry M. Jackson Foundation	USA
Member	Ms	Yanan Hu	Monash University	Australia
Member	Ms	Halimah Khalil	University of Birmingham	UK
Member	Ms	Joy Kim	Cornell University	USA
Member	Doctor	Lily Lai	University of Southampton	UK
Member	Doctor	Siang Ing Lee	University of Birmingham	UK
Member	Doctor	Pauline Shun Lin	Monash Health	Australia
Member	Doctor	Shruthi Mahalingaiah	Harvard TH Chan School of Public Health	USA

Role	Title	Name	Organisation	Country
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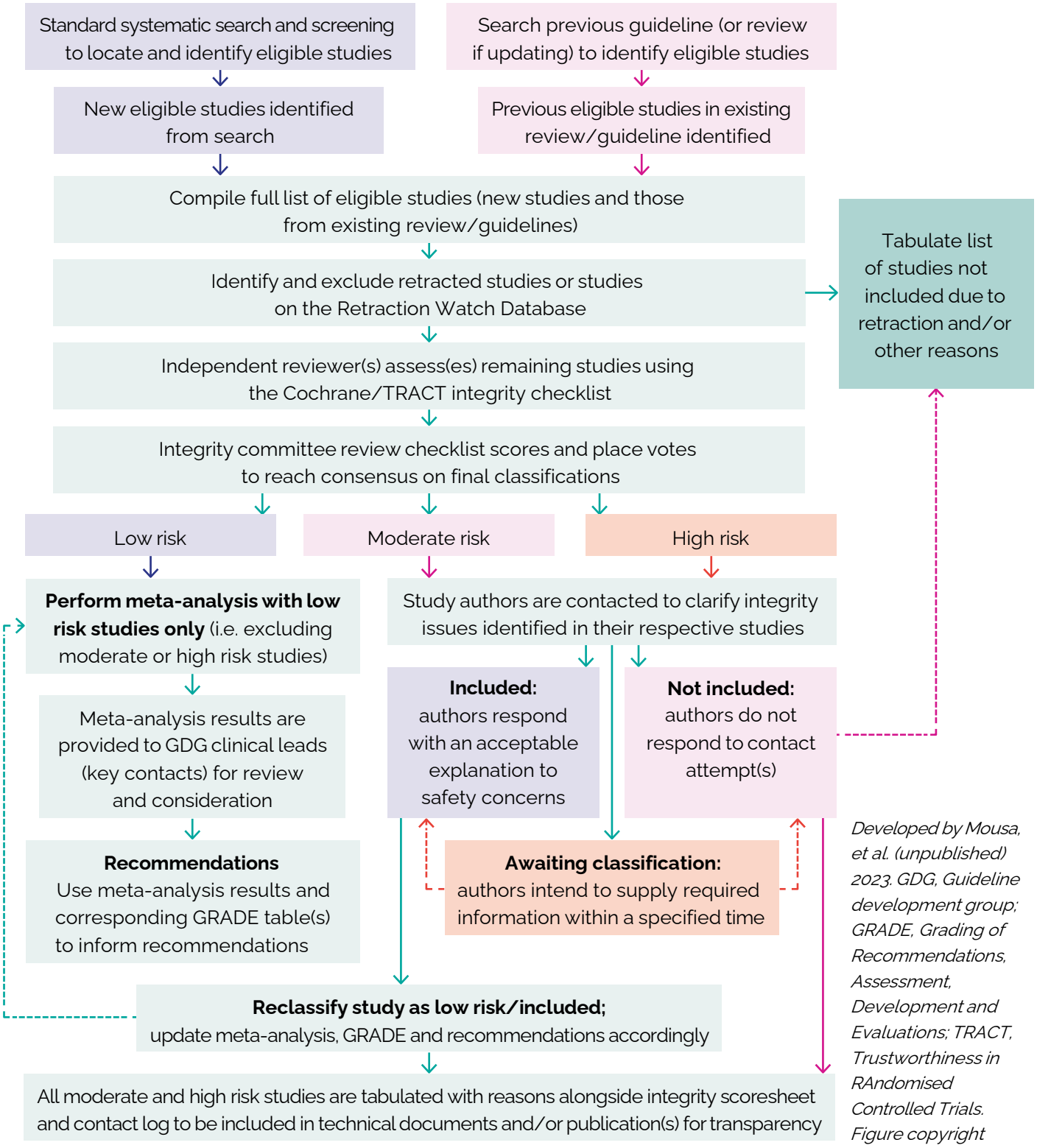
Member	Ms	Alison Maunder	Western Sydney University	Australia
Member	Ms	Margaret McGowan	Monash University	Australia
Member	Ms	Tusyita Menon	Monash University	Australia
Member	Ms	Julia Michalak	Cornell University	USA
Member	Ms	Dhevaksha Naidoo	Western Sydney University	Australia
Member	Ms	Tahani Said Nassar	Monash University	Australia
Member	Doctor	Noel Ng	Chinese University of Hong Kong	Hong Kong
Member	Doctor	Kay Nguo	Monash University	Australia
Member	Doctor	Alexis Oldfield	Cornell University	USA
Member	Doctor	Rhiannon Patten	Victoria University	Australia
Member	Mr	Jeff Pea	Cornell University	USA
Member	Doctor	Stephanie Pirotta	Monash University	Australia
Member	Mr	Darren Rajit	Monash University	Australia
Member	Ms	Vibhuti Rao	Western Sydney University	Australia
Member	Doctor	Awa Sanneh	University of Wisconsin	USA
Member	Doctor	Soulmaz Shorakae	Monash Health	Australia
Member	Doctor	Thais Rasia Silva	Universidade Federal do Rio Grande do Sul	Brazil
Member	Doctor	Uday Pratap Singh	Medeva	India
Member	Ms	Laura Smith	Western Sydney University	Australia
Member	Doctor	Loriana Soma	Ohio State University Wexner Medical Centre	USA
Member	Doctor	Jennifer Tamblyn	Leeds Teaching Hospital Trust	UK
Member	Doctor	Reinier Timman	Retired	Netherlands

Role	Title	Name	Organisation	Country
Member	Ms	Vaishnavi Vaddiparti	Western Sydney University	Australia
Member	Ms	Kim van der Ham	Erasmus MC	Netherlands
Member	Doctor	Anne-Lotte van der Kooi	Erasmus MC	Netherlands
Member	Doctor	Michelle Vu	University of Rochester	USA
Member	Miss	Aadhya Vyas	Monash University	Australia
Member	Ms	Cynthia Wan	Cornell University	USA
Member	Miss	Xin Yi Wu	Melbourne University	Australia
Member	Ms	Isabella Xavier	Cornell University	USA
Member	Ms	Julia Xiong	Cornell University	USA
Member	Doctor	Jennifer Yamamoto	University of Manitoba	Canada
Member	Doctor	Guoyan (Emily) Yang	Western Sydney University	Australia
Member	Doctor	Ladan Yeganeh	Monash University	Australia

Appendix V:
Research integrity process

Figure 3: Research Integrity in Guideline Development (RIGID) Framework



Developed by Mousa, et al. (unpublished) 2023. GDG, Guideline development group; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; TRACT, Trustworthiness in RAndomised Controlled Trials. Figure copyright Monash University.

Evidence integrity committee

Role: The Evidence Integrity Committee is responsible for investigating and managing integrity issues in the identified literature, to ensure recommendations are based on sound evidence (Figure 3). Specifically, the Committee has developed and implemented the RIGID framework (Research Integrity in Guideline Development) to independently review and categorise all relevant studies and to contact authors, before evidence can be used to inform recommendations.

Title	Name	Organisation	Country
Professor	Ben Mol	Monash University	Australia
Doctor	Madeline Flanagen	Monash University	Australia
Doctor	Aya Mousa	Monash University	Australia
Doctor	Michael Costello	University of NSW	Australia
Professor	Robert Norman	University of Adelaide	Australia
Doctor	Chau (Jillian) Tay	Monash University	Australia
Professor	Helena Teede	Monash University	Australia

Appendix VI:
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-CR**	Non-clomiphene citrate resistant
CVD	Cardiovascular disease	**COCP**	Combined oral contraceptive pill
CR	Clomiphene citrate resistant	**OGTT**	Oral glucose tolerance test
Dietitian	ACR edited Practicing Dietitian	**OHSS**	Ovarian hyperstimulation syndrome
T2D	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	**PCO**	Polycystic ovary
ICSI	Intracytoplasmic sperm injection	**PCOS**	Polycystic ovary syndrome
IGT	Impaired glucose tolerance	**PICO**	Patient/Population, Intervention, Comparison, Outcome
HbA1c	Glycated haemoglobin	**POSAA**	Polycystic Ovary Syndrome Association Australia
HDL-C	High density lipoprotein cholesterol	**QoL**	Quality of life
HOMA-IR	Homeostasis model of assessment -insulin resistance	**RCT**	Randomised controlled trial
IR	Insulin resistance	**RR**	Relative risk
IVM	In vitro maturation	**SHBG**	Sex hormone-binding globulin
IVF	In vitro fertilisation	**TGA**	Therapeutic Goods Administration (Australian Government)
LDL-C	Low density lipoprotein cholesterol	**P-value**	Measure of statistical precision
LH	Luteinising hormone		
MPCOSQ	Modified PCOS quality of life questionnaire		

Appendix VII:
Glossary

Sources for this glossary include: The Cochrane Resources Glossary (www.cochrane.org/glossary/5), Jean Hailes for Women's Health (www.jeanhailes.org.au), Diabetes Australia (www.diabetesaustralia.com.au), Better Health Channel (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 (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	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.
Female pattern hair loss	**The presence of shortened anagen phase and miniaturization of hair follicles in the scalp of women, typically exhibiting one of two patterns of hair loss: centrifugal expansion in mid scalp with preservation of the frontal hair line (Ludwig pattern) or a frontal accentuation or Chrstmas tree pattern (Olsen pattern).**

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 female pattern hair loss. 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 ≤ 25 kg/m²
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.
Very high BMI	BMI ≥ 35 kg/m²
Non-clomiphene citrate resistant	Those who are either clomiphene citrate sensitive or who have unknown clomiphene citrate sensitivity.
Excess weight	BMI ≥ 25 kg/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 diarrhea, lower abdominal pain and shortness of breath.

Overweight	BMI ≥ 25.1-30 kg/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.
Public health actors	**Those who influence or determine health policy and practice. Examples may include but are not limited to policy makers (including politicians, health professional/medical societies, non-government organisations who are in a position to influence policy and health system design.**
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 (T2D)	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, higher weight, insufficient physical activity, poor diet and the classic 'apple shape' body where extra weight is carried around the waist.

Appendix VIII:
Algorithms

Algorithm 1: **Screening, diagnostic assessment, risk assessment and life stage: Updates***

Algorithm 2: **Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing**

Algorithm 3: **Lifestyle**

Algorithm 4: **Pharmacological treatment for non-fertility indications**

Algorithm 5: **Management of infertility in polycystic ovary syndrome**

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 or AMH is not indicated = consider at risk of PCOS and reassess later
Adults: Ultrasound for PCOM* OR Anti-Mullerian Hormone (AMH) level, if positive (exclude other causes)* = diagnosis

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***Exclusion of other causes =s TSH, prolactin, 17-OH progesterone, FSH or if clinically indicated exclude other causes** (e.g. Cushing's syndrome, adrenal tumours etc) Hypogonadotrophic hypogonadism, usually due to low body fat or intensive exercise, should also be excluded clinically and with LH and FSH levels

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 occur with regular cycles. If anovulation suspected, check progesterone levels.

Biochemical hyperandrogenism

Use total testosterone and free testosterone for diagnosis. If not elevated, then androstenedione and dehydroepiandrosterone sulfate could be measured, but are less specific with a limited role in PCOS diagnosis.

Highly accurate tandem mass spectrometry (LC-MS/MS) assays recommended. Direct free testosterone assays not preferred. Use lab reference ranges.

Reliable assessment of biochemical hyperandrogenism not possible on hormonal contraception.
Consider withdrawal for ≥ 3 months with alternative contraception

Biochemical hyperandrogenism role is 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 key in assessing for neoplasia, however, some androgen-secreting neoplasms may only induce mild to moderate increases in hyperandrogenism.

Clinical hyperandrogenism

Comprehensive history and physical examination needed. Adults: acne, female pattern hair loss and hirsutism. Adolescents: severe acne and hirsutism.

Note negative psychosocial impact of clinical hyperandrogenism. Patient perception is important, regardless of apparent clinical severity.

Standardised visual scales are preferred including modified Ferriman Gallway score (mFG), a score of ≥ 4-6 = hirsutism, noting self-treatment impacts assessment.

Ludwig visual score preferred for assessing female pattern hair loss.

Ultrasound and polycystic ovary morphology

With irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not necessary for diagnosis.

In diagnosis, follicle number per ovary is most effective, followed by follicle number per cross-section and ovarian volume as ultrasound markers in adults.

Ultrasound should not be used for PCOS diagnosis in adolescents, due to the high incidence of multi-follicular ovaries in this life stage.

Transvaginal ultrasound approach is preferred in diagnosis of PCOS, if sexually active or if acceptable to the individual

Using ultrasound transducers with a frequency bandwidth including 8 MHz, the PCOM threshold is a follicle number per ovary of ≥ 20 and/or an ovarian volume ≥ 10 ml on either ovary, avoiding corpora lutea, cysts or dominant follicles

Serum AMH could be used for defining PCOM in adults as an alternative to pelvic ultrasound. Either serum AMH OR ultrasound may be used but not both to avoid overdiagnosis*

Anti-mullerian hormone (AMH) *

Serum AMH could be used for defining PCOM in adults as an alternative to pelvic ultrasound. Either serum AMH OR ultrasound may be used but not both to avoid overdiagnosis*

Ethnic variation and prevalence

PCOS prevalence appears similar across ethnicities and is 10-13% globally by International guideline/Rotterdam criteria*

Menopause life stage

A diagnosis of PCOS is considered enduring. Postmenopausal women presenting with new-onset, severe or worsening hyperandrogenism including hirsutism, require further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.

Cardiovascular disease risk*

Women with PCOS have an increased risk of cardiovascular disease and potentially of cardiovascular mortality, but overall risk premenopause is low.*

All with PCOS should be assessed for individual cardiovascular risk factors and global CVD risk.

All women with PCOS, regardless of age and BMI, 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 and when planning pregnancy or fertility treatment.

Impaired glucose tolerance and type 2 diabetes

Regardless of age and BMI, impaired glucose tolerance and type 2 diabetes are increased in PCOS, with risk independent of, yet exacerbated by BMI 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 (including a BMI > 25 kg/m² or in Asians > 23 kg/m², history of abnormal glucose tolerance or family history of diabetes, hypertension or high-risk ethnicity.

In high risk women an oral glucose tolerance test (OGTT is the most accurate test for dysglycaemia with fasting glucose or HbA1c second-line due to lower accuracyOGTT 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 the first prenatal visit, and all women with PCOS should be offered the test at 24-28 weeks gestation.

Obstructive sleep apnea

Women with PCOS have a significantly higher prevalence of obstructive sleep apnea.*

If symptoms of PCOS are present, then screen with validated tools or refer for assessment and goals of treatment should target related symptom burden.

Endometrial cancer

Health professionals and women with PCOS should be aware of a two to six fold increased risk of endometrial cancer in premenopausal women with PCOS; however absolute risk remains 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.

Long-standing untreated amenorrhea, higher weight and persistent thickened endometrium are additional to PCOS, are risk factors for endometrial hyperplasia and endometrial cancer. 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.

Risk of PCOS and cardiometabolic risk in first-degree relatives*

Fathers and brothers of women with PCOS may have an increased prevalence of metabolic syndrome, type 2 diabetes, and hypertension, with inadequate data in female relatives.*

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 PCOS.	Capture and consider women's perceptions of their symptoms, impact on their QoL, key concerns and priorities for management. 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 depressive symptoms 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 and use regionally validated tools • 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 initial screening is positive:** Assess risk factors and symptoms using age, culturally and regionally appropriate tools 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. **Psychological therapy:** Women diagnosed with a mental health disorder should be offered psychological therapy as first-line management, guided by regional guidelines and the preference of the woman with PCOS. **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.

Psychological domains	Screening protocol/tools	Intervention
Psychosexual dysfunction	Multiple factors that may contribute to psychosexual dysfunction in PCOS (such as higher weight, hirsutism, mood disorders, infertility and PCOS medications). Psychosexual dysfunction requires not only low psychosexual function, but also related distress.	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.	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	Eating disorders and disordered eating need to be considered, regardless of weight, especially in the context of weight management and lifestyle interventions.	If concerns are identified: • Assess risk factors and symptoms using age, culturally and regionally appropriate tools. • Refer to an appropriate health professional for further mental health assessment. If this is not the patient's usual healthcare provider, inform.
Information needs and patient care	Information, education and resources are a high priority for women with PCOS.	Information, education and resources should be provided in a respectful and empathic manner. Health professionals should employ shared decision making and support patient agency.

Algorithm 3: Lifestyle

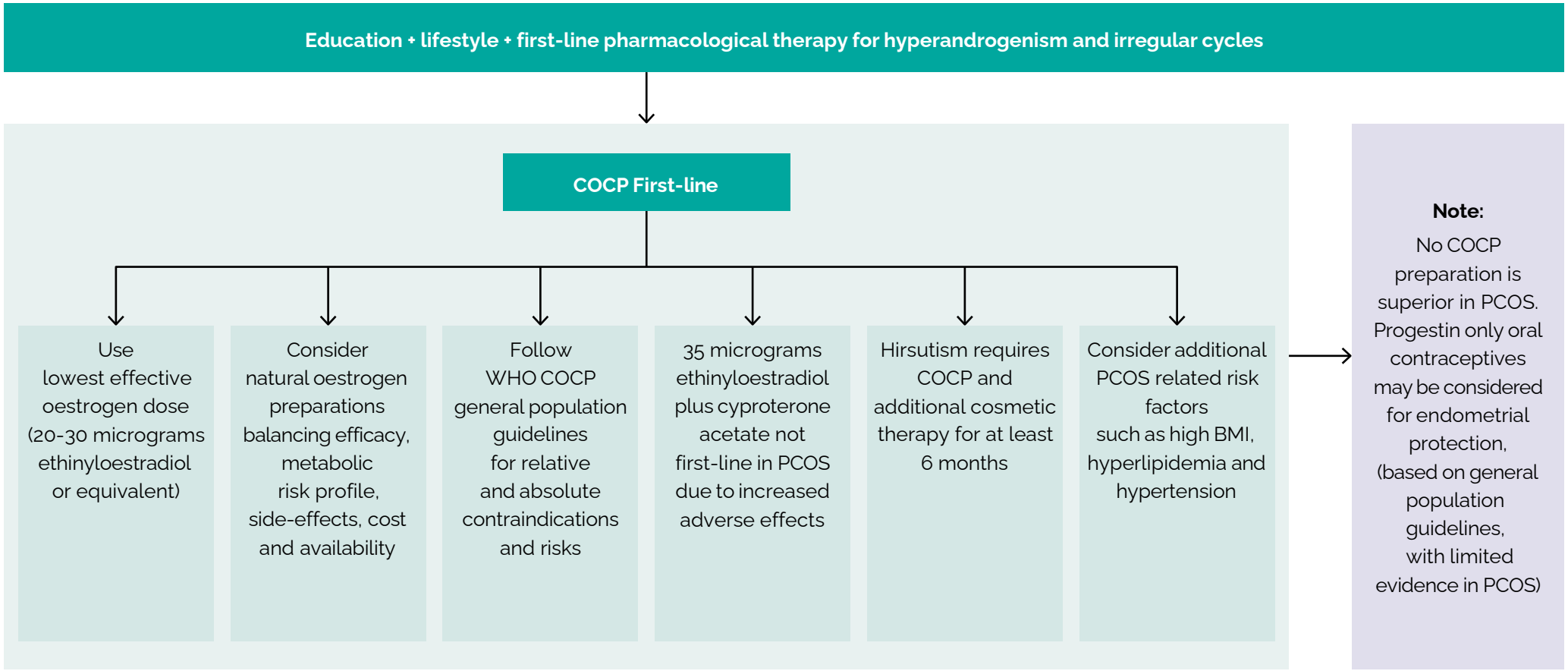
Weight stigma
Healthcare professionals should recognise that many women with PCOS experience weight stigma in healthcare and other settings and that this has negative biopsychosocial impacts.
Factors affecting weight gain in PCOS
Whilst the specific mechanisms are unclear, it is recognised that many women with PCOS will have underlying mechanisms that drive greater longitudinal weight gain
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, marginalization and potential weight-related stigma.
Prevention of weight gain and encouraging evidence-based and socio-culturally appropriate healthy lifestyle is important in PCOS from adolescence.
Effectiveness of lifestyle interventions
Healthy lifestyle behaviours (healthy eating and regular physical activity) should be recommended in all women with PCOS, to achieve and/or maintain healthy weight and to optimise general and metabolic health, and quality of life across the life course. Ethnic groups at high cardiometabolic risk require more consideration.
Lifestyle management goals and priorities should be co-developed in partnership with women with PCOS, and value women's individualised preferences.
Awareness of weight stigma is important when discussing lifestyle management with women with PCOS. 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 could include behavioural strategies such as goal-setting, self-monitoring, problem solving, assertiveness training, 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 evidence to support any one type of diet composition over another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes. .
Barriers and facilitators to optimise engagement and adherence to dietary change should be discussed, including psychological factors, physical limitations, socioeconomic and sociocultural factors, as well as personal motivators for change.
Referral to suitably trained allied healthcare professionals needs to be considered when women with PCOS need support with optimising their diet.
Exercise intervention
There is a lack of evidence supporting any one type and intensity of exercise being better than another for anthropometric, metabolic, hormonal, reproductive or psychological outcomes.
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 to 300 min/week moderate-intensity physical activity or 75 to 150 min/week vigorous-intensity or equivalent combination of both over the week • in adolescents, > 60 minutes moderate to vigorous-intensity physical activity/day including those that strengthen muscle and bone at least 3 times weekly. • activity best performed in bouts of > 10 minutes duration, aiming to achieve at least 30 minutes daily on most days.

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)



Second-line Pharmacological Therapies

COCP + Lifestyle + Metformin

The combination of COCP and metformin appears to offer little additional benefit over COCP or metformin alone, in adults with PCOS with a BMI ≤ 30 kg/m².COCP – first-line for management of hirsutism and irregular menstrual cycles

Metformin – metabolic

Most beneficial in high metabolic risk groups including those with diabetes risk factors, impaired glucose tolerance or high-risk ethnic groups.

COCP + Anti-Androgens

Anti-androgens could be considered to treat hirsutism in women with PCOS, if there is a suboptimal response after a minimum of six months of COCP and/or cosmetic therapy.

Whenever pregnancy is possible, women must be used strongly counselled regarding the use of concurrent effective contraception to prevent male fetal virilisation.

Combination therapy can be tried in 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 ≥ 25 kg/m² and in high risk ethnic groups. Side-effects, including GI effects, are dose related and self-limiting. Consider starting low dose, with 500 mg increments 1-2 weekly. Suggested maximum daily dose: 2.5 g in adults, 2 g in adolescents.

Metformin appears safe long-term. Ongoing monitoring required and has been associated with low vitamin B12.

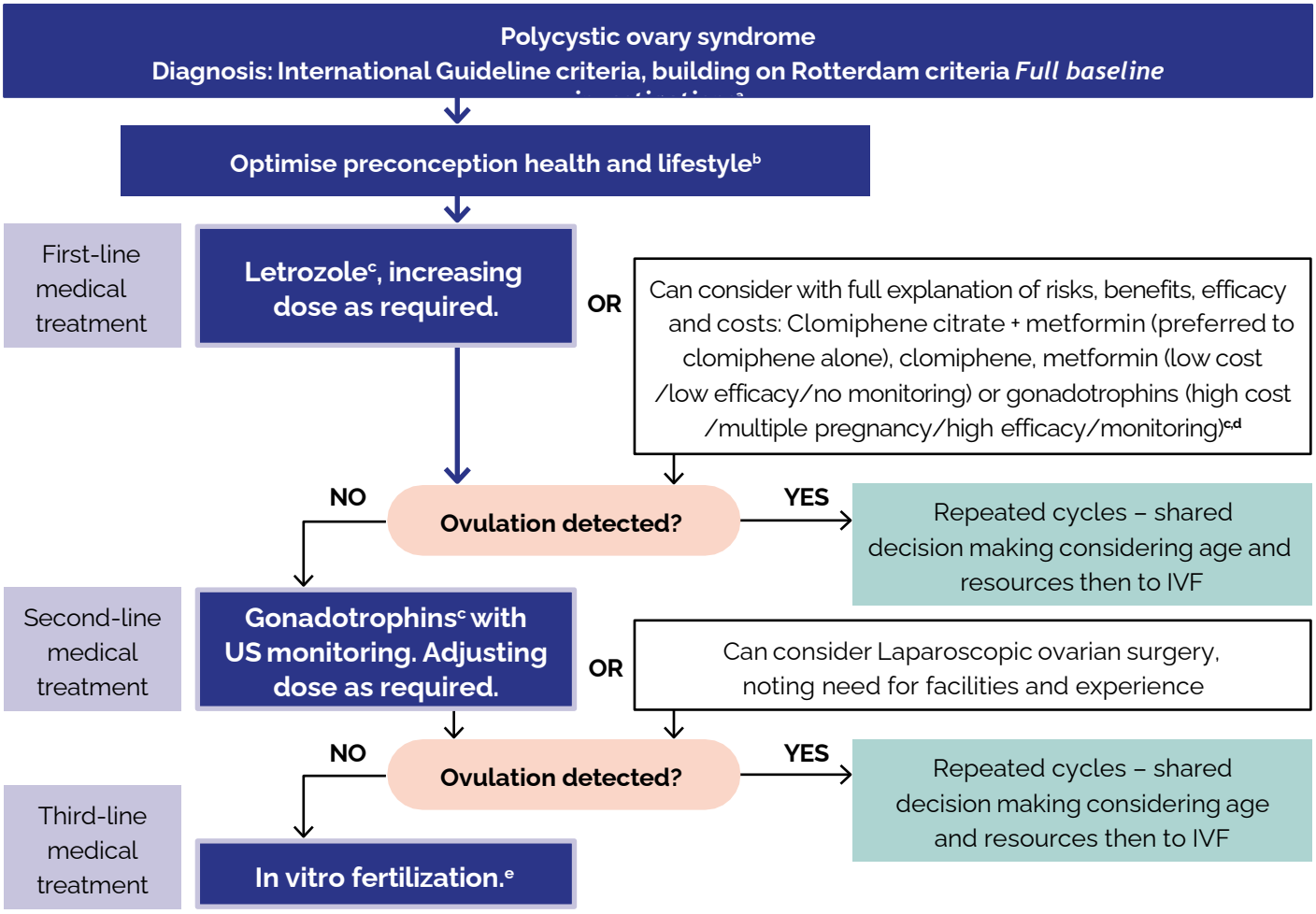
Anti-obesity medications could be considered, in addition to active lifestyle intervention, for the management of higher weight in adult women with PCOS, considering cost, contraindications, side-effects, availability and regulatory status and avoiding pregnancy when on therapy.

Inositol (in any form) may be considered in women with PCOS based on individual preferences and values, given limited harm, potential for reduced biochemical hyperandrogenism and metabolic measures, with limited clinical benefits for ovulation, hirsutism or weight.

Mechanical laser and light therapies should be considered for reducing facial hirsutism. Wavelength and delivery of laser treatment should be recommended taking into account skin colour. Laser is relatively ineffective in women with blond, grey or white hair. The addition of COCP, with or without anti-androgens, to laser treatment may provide greater hair reduction and maintenance compared to laser alone.

Algorithm 5: Management of infertility in polycystic ovary syndrome

Central Blue Pathway follows best practice evidence and is preferred



a. Baseline investigations (see narrative):

- **i.** Diagnosis of PCOS - Endocrine profile and pelvic ultrasound scan
- **ii.** Assessment of BMI, BP & glycemic status (OGTT/HbA1c)
- **iii.** Routine preconception assessments (Rubella immunity, infection screen etc.), advice and supplementation.
- **iv.** Additional investigations: semen analysis and consider tubal patency assessment

b. Healthy lifestyle encompassing healthy eating and regular physical activity should be recommended in all those with PCOS to limit adverse impacts on fertility and fertility treatment outcomes and to optimise health during pregnancy

c. Off-label prescribing: Letrozole, metformin and other pharmacological treatments are generally off-label in PCOS, as pharmaceutical companies have not applied for approval in this condition. However, recommended off-label use is evidence-based and allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side-effects of treatment.

d. Compared to letrozole, metformin has lower efficacy, cost and multiple pregnancy rate and gonadotrophins have higher efficacy, cost and multiple pregnancy rate. Both may be an alternative first-line choice for informed women.

e. In vitro fertilization (IVF) - Third-line unless other infertility factors (e.g. male, tubal). PCOS specific protocols to minimise risk of ovarian hyperstimulation syndrome, consider in vitro maturation if available.

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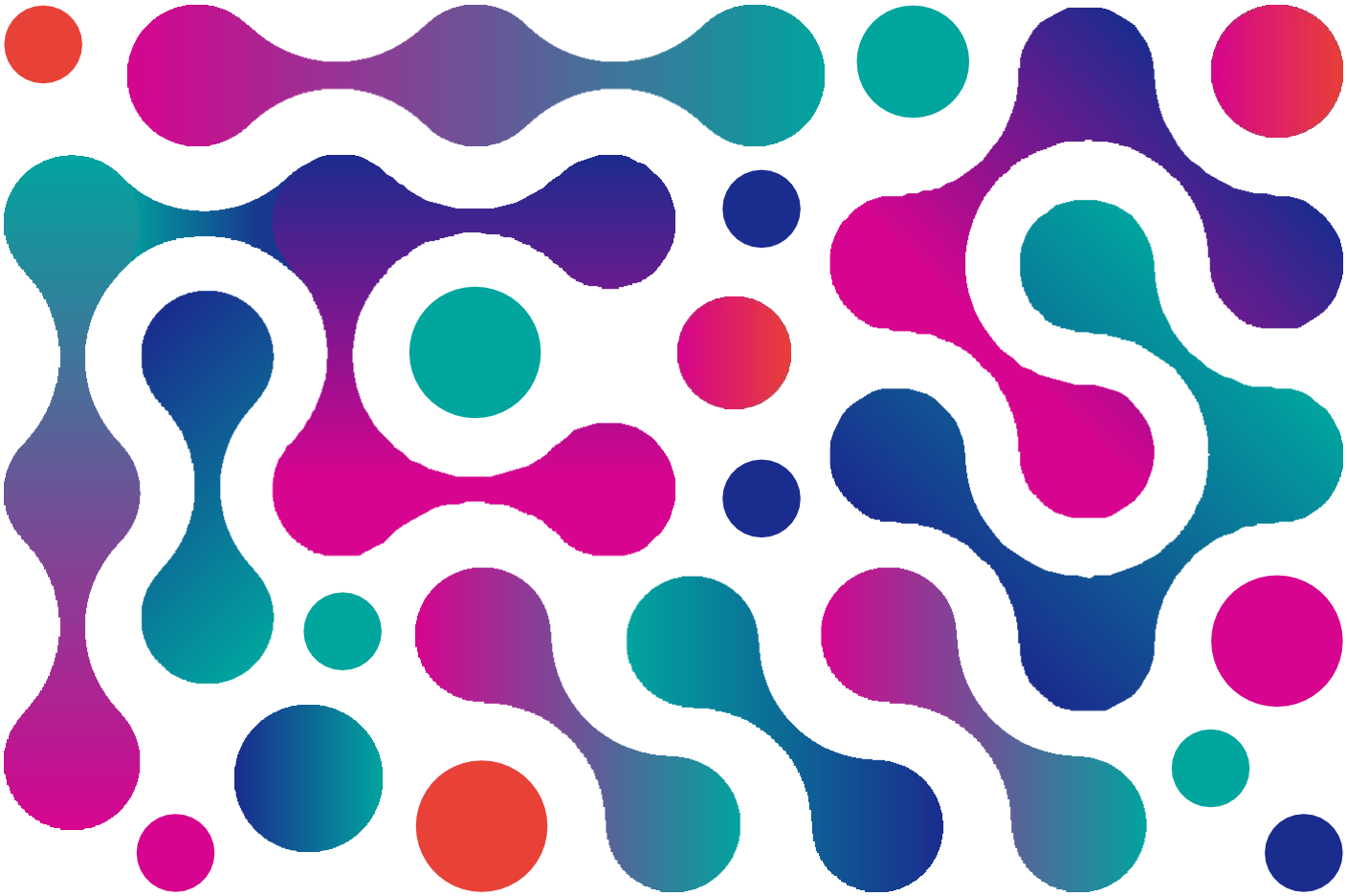
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