Evidence-based guideline for the assessment and management of polycystic ovary syndrome

Developed 2011
Updated August 2015 - Section 7.4 Aromatase inhibitors
Further update scheduled 2016/2017
Publication approval

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 29 July 2011, (with a subsequent amendment approved on 15 June 2015) under Section 14A of the National Health and Medical Research Council Act 1992. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of 5 years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.
PCOS Australian Alliance: A single voice for polycystic ovary syndrome

In 2008 Jean Hailes for Women’s Health facilitated a national meeting on polycystic ovary syndrome (PCOS), with 25 leaders attending from the research, clinical and community sectors. The outcome of this meeting was the establishment of the independent PCOS Australian Alliance and the mapping of an ambitious plan to improve health outcomes in women with PCOS.

The vision of the PCOS Australian Alliance is to improve the lives of Australian women with PCOS through education, research and evidence-based health care. The Alliance provides leadership and cohesion to promote education, health and research and support consistent, evidence-based, multidisciplinary service provision. This involves cross-sector collaborations, community partnerships and interactions with government and policy makers aimed at prevention and management of PCOS within Australia.

Jean Hailes for Women’s Health, a national not for profit organisation with a track record in clinical research, community and professional education and clinical care for women, facilitates and supports the Alliance. It provides an authoritative national information service to women, their families, health care professionals and policy makers in Australia, funded by the Australian government.

There are currently no international evidence-based guidelines to inform women and health professionals about PCOS. Australia was in a prime position to take a leadership role in the development of clear guidelines, evidence-based research and translation to women with PCOS, the community and health care providers. Our national Alliance provided guidance and expertise including internationally recognised researchers and clinicians and an established consumer advocacy group, the Polycystic Ovary Association of Australia (POSAA). The Alliance was supported by Jean Hailes for Women’s Health, providing management and leadership, infrastructure and translation capability.

The Alliance, representing the key stakeholders in PCOS in Australia, at the inaugural meeting in 2008 identified key clinical priorities for the guideline using the following criteria:

- highest clinical priority
- greatest knowledge gaps
- priorities identified by the commissioning Australian government
- expertise of Alliance members

This guideline reflects the identified key clinical priorities and areas of clinical need, covering assessment of PCOS, assessment of emotional wellbeing, management of lifestyle and management of infertility in women with PCOS.

A list of Alliance members can be found in Appendix I.
Acknowledgments

We gratefully acknowledge the volunteers in the Alliance who were involved in the development of the guideline (see Appendix II for a list of individuals and organisations), the Jean Hailes for Women’s Health team who contributed so much to this project over the past 2 years, the Department of Health and Ageing and Health Minister Roxon for their support and funding of this guideline and the subsequent translation program. Finally we acknowledge the commitment and support of the Centre for Clinical Effectiveness for providing evidence synthesis and guideline development expertise, including guidance from Dr Claire Harris and Dr Tari Turner during the early planning phase, and to the Australasian Cochrane Centre for appraising the guidelines (using AGREE II).

AGREE II appraisal

1st independent rater: 6, 2nd independent rater: 6-7 (1=Lowest possible quality and 7=Highest possible quality) [3]. The full AGREE II appraisal is available upon request, email linda.downes@monash.edu

<table>
<thead>
<tr>
<th>Domain scores (calculated based on two independent raters’ scores)</th>
<th>Obtained score</th>
<th>Maximum score</th>
<th>Minimum score</th>
<th>Scaled domain score (%)</th>
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Disclaimer

This document is a guide to best practice, designed to provide information to assist decision-making. It is based on the best available evidence and clinical judgement at the time of development of this publication and is to be followed subject to the clinician’s judgement and patient’s preference in each individual case.

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ISBN Print: 978-0-646-55470-9

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Suggested citation  Evidence-based guidelines for the assessment and management of polycystic ovary syndrome. Jean Hailes for Women’s Health on behalf of the PCOS Australian Alliance; Melbourne, 2015.
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Preface

This national evidence-based guideline for the assessment and management of polycystic ovary syndrome, designed to provide clear information to assist clinical decision making and support optimal patient care, is the culmination of the work of many individuals including women with PCOS. Most gave of their time and expertise voluntarily and it is important to appreciate the considerable contributions of the guideline development groups and particularly of the guideline development group chairs: Dr Michael Costello, Dr Amanda Deeks, Dr Lisa Moran and Clinical Professor Dr Bronwyn Stuckey. We would like to thank the tireless efforts, commitment, dedication and drive of the Project Director, Professor Helena Teede and Project Manager, Ms Linda Downes, the Senior Evidence Officer and Guideline Writer, Dr Marie Misso and the Guideline Evidence Team: Ms Angela Melder, Ms Marie Garrubba and Mr Henry Ko for their contribution to the body of evidence reviews and guideline. Finally we would like to acknowledge the PCOS Australian Alliance who provided expertise and guidance and Jean Hailes for Women’s Health who auspiced and managed the guideline development process. It is hoped that women with PCOS, their families, health professionals and policy makers find this useful.

The guideline is based on the best evidence available up to November 2010. Where appropriate, the evidence has been interpreted with regard to the Australian context in which the guideline will be implemented. It is intended that the guideline be considered according to the limitations outlined herein and used in conjunction with clinical judgement and patient preference. The guideline contains the following information:

- Recommendations
- Algorithms
- Introduction including a discussion about the clinical need for the guideline, scope of the guideline and a list of clinical questions
- Discussion chapters covering the clinical need for each question, the evidence to answer each question that underpins each recommendation and the clinical impact of the recommendation;
- Composition of the multidisciplinary guideline development groups
- Methods used to develop the guideline
- Additional tools and resources

Useful references and supporting information are provided throughout the guideline in clinical practice points.
Executive summary

This guideline integrates the best available evidence with clinical expertise and consumer preferences to provide health professionals, consumers and policy makers with guidance for timely diagnosis, accurate assessment and optimal management of women with PCOS and promotes consistency of care and prevention of complications.

Polycystic ovary syndrome (PCOS) affects a striking 12-21% of Australian reproductive-aged women, depending on the population studied and the diagnostic criteria used and is a major public health concern [4-6]. The clinical implications of PCOS are broad and vary across the lifespan [7]. Whilst reproductive features are prominent, PCOS has potential for major metabolic consequences including obesity and related type 2 diabetes (DM2) and cardiovascular disease (CVD), all currently national health priority areas [8, 9]. It also has significant mental health and psychological impact, impairing quality of life (QoL) [10, 11]. Overall PCOS has significant health and economic costs. With increasing obesity exacerbating incidence, prevalence and severity of PCOS and weight loss, improving reproductive, metabolic and psychological features and lifestyle change should be first-line PCOS therapy. Currently 70% of Australian women with PCOS remain undiagnosed [5], clinical practice is inconsistent [12], psychological issues are neglected [11] and there is little focus on lifestyle and prevention with most services targeting infertility and costly assisted reproductive technology.

Given the clear gaps in care, PCOS is recognised by government and prioritised in funding for this evidence-based guideline. Jean Hailes for Women’s Health’s efforts in PCOS have been noted in the 2010 national women’s health policy and priority areas including prevention of chronic disease, mental health, sexual and reproductive health [13]. The PCOS Australian Alliance and this evidence-based guideline have prioritised the development and evaluation of interdisciplinary models of care integrated with lifestyle intervention for women with PCOS, with no such services currently available. Interdisciplinary care involves a collaboration between a woman and her care team with shared goals for total wellbeing. This encompasses a multidisciplinary team, an agreed care plan, a care coordinator and clear and regular communication.

Implementation of the PCOS evidence-based guideline through development and evaluation of effective, sustainable community-based interdisciplinary models of care, integrated with lifestyle interventions, addressing psychological, metabolic and reproductive features of PCOS is now vital.

This guideline provides recommendations on assessment and management in women and adolescents with PCOS in the reproductive age groups. The guideline begins by providing guidance around assessment challenges in diagnosing PCOS followed by methods for assessing emotional wellbeing and risk of cardiometabolic complications. The lifestyle options considered in this guideline include diet, exercise and behavioural interventions; pharmaceutical options include clomiphene citrate, metformin, gonadotrophins and aromatase inhibitors; and surgical options include laparoscopic ovarian surgery and bariatric surgery.

Diagnostic criteria were adapted based on current international criteria and were not evaluated in this guideline. IVF therapy and other areas were beyond the scope of the guideline but may be included in subsequent updates.
This guideline was developed using internationally agreed methods for the development of evidence-based guidelines. Multidisciplinary committees included a Project Board, PCOS Australian Alliance Strategic Advisory Group and four guideline development groups, comprising experts in PCOS and multiple consumer representatives appointed by the project board and mostly drawn from Alliance members and the consumer advocacy group Polycystic Ovary Association of Australia (POSAA). These groups determined the clinical questions that make up the structure of the guideline; the search for existing evidence-based guidelines; and the development of clinical practice and research recommendations.

This guideline contains 39 recommendations, each of which is assigned a grade. In developing the guideline recommendations, the guideline development groups placed emphasis on the accurate assessment as well as the management of PCOS. The recommendations in this guideline are strengthened by the use of rigorous methodology for evidence review and guideline development including use of: study designs least susceptible to bias; \textit{a priori} criteria for inclusion and appraisal of studies, extraction of study data; and meta-analysis where appropriate. The recommendations were formulated using a considered judgement process which took into account the amount and quality of available evidence as well as its generalisability and applicability to current practice in Australia. Further points of relevance in the implementation of recommendations were made in clinical impact statements for each recommendation including consideration of resource implications.

In formulating the recommendations for this guideline, the guideline development groups recognised and took into account a number of factors and limitations pertaining to the available evidence. In many areas of PCOS, there is little or no evidence or the evidence is of poor quality and other potential biases in the trials resulting from different methods for diagnosis of PCOS, and differing endpoints. As a result of these limitations, several clinically important questions remain.

Key gaps in the evidence include inadequate study of the natural history of PCOS, its features and its complications, establishing the optimal model of care, optimal lifestyle intervention (specifically aiming to increase engagement, adherence and sustainability) and optimal fertility interventions. Another key gap was inadequate evidence about the role of bariatric surgery for improving fertility in PCOS. Hence well-considered research recommendations are made throughout the guideline.

It is intended that the guideline be considered according to the limitations outlined herein and used in conjunction with clinical judgement and patient preference.
Recommendations

This summary section provides a list of the evidence-based recommendations discussed in the text of chapters one through eight. Each of the evidence-based recommendations is given an overall grading from A to D based on the volume, consistency, generalisability, applicability and clinical impact of the body of evidence supporting each recommendation (as outlined in the National Health and Medical Research Council (NHMRC) levels of evidence and grades of recommendations for guideline developers) [14]. When insufficient evidence was available but there was consensus among the guideline development group, clinical consensus recommendations have been developed. Clinical practice points have also been included, where important issues (such as safety, side effects or risks) arose from discussion of evidence-based or clinical consensus recommendations. It is not possible to grade consensus recommendations and practice points according to NHMRC grading; instead a classification has been allocated according to its type of recommendation, i.e., a clinical consensus recommendation is classified ‘CR’ and a clinical practice point is classified ‘PP’.

The strength of the recommendations can be identified throughout the guideline with the following grades:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice.</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations.</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation but care should be taken in its application.</td>
</tr>
<tr>
<td>D</td>
<td>Body of evidence is weak and recommendation must be applied with caution.</td>
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Where a grade cannot be applied, the following classifications were used:

<table>
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<tr>
<th>Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>CR</td>
<td>In the absence of evidence, a clinical consensus recommendation has been made by the guideline development group.</td>
</tr>
<tr>
<td>PP</td>
<td>Evidence not sought. A practice point has been made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations.</td>
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</table>

The words “should”, “could” and “should not” do not directly reflect the grade or classification allocated to a recommendation and are independent descriptors intended to reflect the judgment of the multidisciplinary guideline development group on the practical application of the recommendation, balancing benefits and harms. Where the word “should” is used in the recommendations, the guideline development group judged that the benefits of the recommendation (whether evidence-based or clinical consensus) clearly exceed the harms, and that the recommendation can be trusted to guide practice. Where the word “could” is used, either the quality of evidence was underpowered, or the available studies demonstrated little clear advantage of one approach over another, or the balance of benefits to harm was unclear. Where the words “should not” are used, there is either a lack of appropriate evidence, or the harms outweigh the benefits.
Page numbers are provided in the table below to direct the reader to a discussion supporting the recommendation, including the clinical need for the question, the body of evidence identified to answer the question and the clinical impact of the recommendation, covering issues of applicability (such as potential changes in care and the way care is organised), organisational barriers and resource implications. The full evidence tables supporting the recommendations can be found in the supplementary document titled ‘Evidence report’, which can be found at [www.managingpcos.org.au/pcos-evidence-based-guidelines](http://www.managingpcos.org.au/pcos-evidence-based-guidelines).

The Project Board, the PCOS Australian Alliance Strategic Advisory Group and the guideline development groups support all 39 recommendations and intend that they be used in conjunction with clinical judgement and patient preferences.

<table>
<thead>
<tr>
<th>No.</th>
<th>Recommendations</th>
<th>Grade</th>
<th>Page</th>
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<tbody>
<tr>
<td>1.1a</td>
<td>Late-onset congenital adrenal hyperplasia, although rare, needs to be considered before the diagnosis of polycystic ovary syndrome is confirmed. In more severe clinical cases of hyperandrogenism, 21-hydroxylase deficiency, the most common form of congenital adrenal hyperplasia, can be excluded by measuring serum 17-hydroxyprogesterone in the follicular phase to explore this diagnosis.</td>
<td>CR</td>
<td>P51</td>
</tr>
<tr>
<td>1.1b</td>
<td>Calculated bioavailable testosterone, calculated free testosterone or free androgen index should be first-line investigation for biochemical determination of hyperandrogenism in polycystic ovary syndrome. The addition of androstenedione and dehydroepiandrosterone sulfate could be second-line investigation for biochemical determination of hyperandrogenism in polycystic ovary syndrome.</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>1.1c</td>
<td>It is difficult to assess androgen status in women on the oral contraceptive pill as effects include oestrogen mediated increases in sex hormone-binding globulin and reduction in androgens. Where the oral contraceptive pill has already been commenced, it should be withdrawn for at least three months before appropriate hormonal assessments for diagnosis of polycystic ovary syndrome are undertaken. Contraception should be otherwise managed during this time.</td>
<td>PP</td>
<td>P51</td>
</tr>
<tr>
<td>1.1d</td>
<td>If androgen levels are markedly above laboratory reference ranges, secondary causes may be considered. Mild elevations of androstenedione may be seen in polycystic ovary syndrome, whereas marked elevations are more indicative of non-classical adrenal hyperplasia. Reference ranges for different methods and different laboratories vary widely and clinical decisions should be guided by the reference ranges of the laboratory used.</td>
<td>PP</td>
<td></td>
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</table>
### Recommendations

1.2a In adolescent women (<18 years), after two years of irregular cycles (>35 or <21 days) following the onset of menarche, polycystic ovary syndrome should be considered and appropriate assessment should be undertaken.

As polycystic ovary syndrome is a diagnosis of exclusion, other causes of irregular cycles (such as thyroid dysfunction or hyperprolactinaloemia) need to be considered and excluded prior to the diagnosis of polycystic ovary syndrome.

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1.2b If oral contraceptive pill therapy is being considered or has commenced in adolescents (<18 years), the following are recommended:

- After twelve months of irregular cycles (>35 or <21 days) after onset of menarche, polycystic ovary syndrome should be considered before commencement of the oral contraceptive pill.
- Where the oral contraceptive pill has already been commenced, when girls are not sexually active, if biochemical hyperandrogenism is needed for the diagnosis of polycystic ovary syndrome, the oral contraceptive pill could be withdrawn for three months to facilitate appropriate hormonal assessments. Withdrawal of the oral contraceptive pill may facilitate assessment and early diagnosis of polycystic ovary syndrome as diagnosis can have important implications including optimisation of healthy lifestyle, regular metabolic screening and proactive fertility planning, with consideration of planning for conception at an earlier age. However, the risk of unplanned pregnancy needs to considered and weighed up against potential benefits of early diagnosis. Contraception may still need to be otherwise managed during this time.

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<th>P53</th>
<th>PP</th>
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1.3a Given the apparent lack of specificity of polycystic ovaries on ultrasound in adolescents, generally, ultrasound should not be recommended first-line in this age group for diagnosis of polycystic ovary syndrome pending further research. If pelvic ultrasounds are to be ordered in adolescents, the results should be interpreted with caution.

<table>
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<th>p54</th>
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1.3b Vaginal ultrasound is not appropriate in adolescents who have not been sexually active.

| PP |

CHAPTER TWO  Interdisciplinary model of care in PCOS

2.1a Interdisciplinary care, with multiple health professionals involved, should be offered to women with polycystic ovary syndrome, where appropriate based on the chronic and complex nature of the disease.

An interdisciplinary care model is the collaboration between a woman with polycystic ovary syndrome and a care team who have shared goals for her

| CR | p57 |  |
total wellbeing. It should have the following integral components:

- A care team, comprised of representation from varied health disciplines (e.g. may include dietetics, psychology, endocrinology, gynaecology, exercise physiology, general practice)
- A care plan which has been developed and agreed with the woman, and if relevant, the carer
- A designated care coordinator, who oversees the care plan and monitors and evaluates outcomes, which is often the general practitioner
- Clear and regular communication (e.g. information sharing via different forms of media, including internet, letters, case conferencing, email, teleconference)

The complexity of the woman’s need will determine the extent of interdisciplinary care required.

2.1b When referring a woman with polycystic ovary syndrome to other health professionals ie.. psychologists, a resource has been developed (Appendix IV) to inform the professional about polycystic ovary syndrome.

CHAPTER THREE  Assessment of cardiometabolic risk in PCOS

3.1a All women with polycystic ovary syndrome should be assessed for cardiovascular disease risk by assessing individual cardiovascular disease risk factors.

If screening in women with polycystic ovary syndrome shows that any of the following cardiovascular disease risk factors are present, these women with polycystic ovary syndrome should be considered at increased relative risk of cardiovascular disease (obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance, lack of physical activity) and those with metabolic syndrome and/or type 2 diabetes, at even greater risk.

3.1b All women with polycystic ovary syndrome should be assessed for excess weight at every visit.

In assessing women with polycystic ovary syndrome < 18 years, age appropriate and gender appropriate body mass index should be calculated at every visit.

All women with polycystic ovary syndrome should be assessed for cigarette smoking.

3.1c Body mass index should be assessed in all women with polycystic ovary syndrome using the following criteria:

Body mass index ≤ 25kg/m² = lean
<table>
<thead>
<tr>
<th>Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Body mass index ≥ 25.1-30kg/m² = overweight</td>
<td></td>
</tr>
<tr>
<td>Body mass index ≥ 30.1-35kg/m² = obese</td>
<td></td>
</tr>
<tr>
<td>Body mass index ≥ 35kg/m² = morbidly obese</td>
<td></td>
</tr>
<tr>
<td>Significant benefits have been demonstrated with 5-10% weight loss in overweight women with polycystic ovary syndrome and is a feasible initial target (see 5.4c).</td>
<td></td>
</tr>
<tr>
<td>BMI doesn’t always reflect adverse body fat stores and waist circumference will be useful.</td>
<td></td>
</tr>
<tr>
<td>Waist circumference should be assessed using the following criteria [15]:</td>
<td></td>
</tr>
<tr>
<td>Waist circumference &gt;80cm = increased risk of metabolic complications</td>
<td></td>
</tr>
<tr>
<td>Waist circumference &gt;88cm = substantially increased risk of metabolic complications</td>
<td></td>
</tr>
</tbody>
</table>
| **3.1d** | A complete lipid profile should be measured every two years in women with polycystic ovary syndrome who have normal lipid profiles.  
A complete lipid profile should be measured annually in women with polycystic ovary syndrome who have abnormal lipid profiles and/or excess weight.  |
| **3.1e** | In women with polycystic ovary syndrome, a lipid profile should include:  
- **Total cholesterol** - total cholesterol should be <4 mmol/L [16]  
- **Low density lipoprotein cholesterol (LDL-C)** - in women without additional cardiovascular disease risk factors, LDL-C levels should be <3.4 mmol/L [17]. In women with metabolic syndrome or type 2 diabetes, LDL-C levels should be < 1.8–2.6 mmol/L or 1.8 mmol/L, respectively [17]  
- **High density lipoprotein cholesterol (HDL-C)** - HDL-C levels should be > 1.0 mmol/L [18]  
- **Triglycerides** - Triglyceride levels should be < 1.7 mmol/L [17].  |
| **3.1f** | Prediabetes and/or type 2 diabetes should be assessed in all women with polycystic ovary syndrome (see 3.2a and 3.2b).  |
| **3.1g** | Blood pressure should be measured annually in women with polycystic ovary syndrome and a body mass index ≤ 25kg/m² (lean).  
Blood pressure should be routinely measured at each visit in women with polycystic ovary syndrome and a body mass index ≥ 25kg/m² (overweight/obese).  |
| **3.1h** | In women with polycystic ovary syndrome who are at high risk of type 2 |
Recommendations

| 3.2a | To assess for risk of type 2 diabetes, in addition to polycystic ovary syndrome status, the following diabetes risk factors should be considered [20, 21]:
|      | • Age
|      | • Gender
|      | • Ethnicity
|      | • Parental history of diabetes
|      | • History of high blood glucose level
|      | • Use of antihypertensive medications
|      | • Smoking
|      | • Physical inactivity
|      | • Waist circumference

| 3.2b | An oral glucose tolerance test should be performed every second year in all women with polycystic ovary syndrome and annually in those found to have additional risk factors for developing type 2 diabetes as outlined in 3.2a.

| 3.2c | Reference ranges for [22]:
|      | • Impaired fasting glucose - fasting plasma glucose: 6.1-6.9 mmol/L
|      | • Impaired glucose tolerance -2 hour glucose level: 7.8-11 mmol/L
|      | • Type 2 diabetes - fasting plasma glucose: ≥7.0 mmol/L or 2 hour oral glucose tolerance test: ≥11.1 mmol/L.

Ideally 150 grams of carbohydrate per day should be consumed for three days before, and women should then fast for 8 hours immediately prior to the oral glucose tolerance test since low carbohydrate intake may lead to false positive glucose tolerance tests.

| CHAPTER FOUR  Assessment of emotional wellbeing in PCOS |

| 4.1a | Depression and/or anxiety should be *routinely screened* and assessed by all appropriately qualified health professionals in women with polycystic ovary syndrome.

If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for depression and/or anxiety.

If depression and/or anxiety are detected, appropriate management should be offered.

| 4.1b | To screen for depression and/or anxiety, the following questions could be asked [23]:
|      | 1) During the last month, have you often been bothered by feeling down,
Recommendations

1) Have you been feeling depressed, or hopeless?

2) During the last month, have you often been bothered by having little interest or pleasure in doing things?

3) During the last month, have you been bothered by feeling excessively worried or concerned?

If any of the screening questions are positive further depression and/or anxiety assessment could be by either:

a) Referring the patient to an appropriate professional if they do not feel competent to perform a further mental health assessment. If the health professional is not the patient’s usual GP, inform the GP of the referral.

b) If they feel competent, perform a clinical interview and according to level of competence, choose from one or more of the following:
   • Kessler Psychological Distress Scale 10 (K-10)
   • Depression Anxiety Stress Scale (DASS-21)
   • Patient Health Questionnaire (PHQ9)
   • Generalised Anxiety Disorder 7 item scale (GAD7).

4.2a Negative body image should be considered in women with polycystic ovary syndrome.

If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for negative body image.

If negative body image is detected, appropriate management should be offered.

4.2b To screen for negative body image, the following questions could be asked:

1) Do you worry a lot about the way you look and wish you could think about it less?

2) On a typical day, do you spend more than 1 hour per day worrying about your appearance? (More than 1 hour a day is considered excessive)

3) What specific concerns do you have about your appearance?

4) What effect does it have on your life?

5) Does it make it hard to do your work or be with your friends and family?

If an issue is identified, the practitioner could further assess negative body image by:

a) Identifying any focus of concern of the patient and respond appropriately

b) Assessing the level of depression and/or anxiety (if they have not done so
| 4.3a | Disordered eating, including eating disorders, should be *considered* in women with polycystic ovary syndrome.  
If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for disordered eating and eating disorders.  
If disordered eating, or an eating disorder is detected, appropriate management should be offered. | CR | P68 |
|---|---|---|---|
| 4.3b | To screen for disordered eating and eating disorders, the following questions could be asked:  
1) Do you worry you have lost control over your eating?  
2) Do you ever feel disgusted, depressed, or guilty about eating?  
3) Have you tried fasting or skipping meals in an attempt to lose weight?  
4) Have you tried vomiting, laxatives or diuretics in an attempt to lose weight?  
5) Have you had significant (e.g. >5-7%), recurrent fluctuation in body weight?  
If a woman with polycystic ovary syndrome answers yes to any of the above questions the practitioner should further assess for the diagnosis of an eating disorder by either:  
--- | 4.4a | Psychosexual dysfunction should be *considered* in women with polycystic ovary syndrome.  
If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for psychosexual dysfunction.  
If psychosexual dysfunction is detected, appropriate management should be offered. | CR | P71 |

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1 Disordered eating refers to eating and weight related symptoms commonly associated with an eating disorder; this can include behavioural (e.g. bingeing, restriction), cognitive (e.g. dietary restraint, negative body image), and emotional (e.g. emotional eating) factors.

2 Psychosexual dysfunction refers to sexual problems or difficulties that have a psychological origin based in cognitions and/or emotions such as depression, low self-esteem and negative body image.
To screen for psychosexual dysfunction, the following questions could be asked:

1) During the last few months, have you often been bothered by problems with your sex life such as reduced satisfaction, diminished desire, pain, or any other problems?
2) Do you feel that polycystic ovary syndrome affects your sex life?
3) (If relevant) Do sexual problems affect your current relationship and/or have sexual problems affected your past relationships?

If a woman with polycystic ovary syndrome answers yes to any of the above questions or where sexual function is a concern, the practitioner should assess this through more detailed clinical interview, and in particular screen for depression and/or anxiety if not already done (see 4.1) and negative body image (see 4.2) or refer to a more appropriately qualified health practitioner.

Specific validated scales could be used as outcome measures at baseline to monitor progress over time. The choice of scale selected should be at the discretion of the clinician, based on the specific sexual problem, accessibility and expertise of the practitioner.

CHAPTER FIVE  Lifestyle management in PCOS

5.1a Lifestyle management (single or combined approaches of diet, exercise and/or behavioural interventions) for weight loss, prevention of weight gain, or for general health benefits should be recommended in women with polycystic ovary syndrome.

5.2a Lifestyle management targeting weight loss (in women with a body mass index ≥25kg/m² (overweight)) and prevention of weight gain (in women with a body mass index ≤25kg/m² (lean)) should include both reduced dietary energy (caloric) intake and exercise and should be first-line therapy for all women with polycystic ovary syndrome.

5.2b Psychological factors should be considered and managed to optimise engagement and adherence to lifestyle interventions.

5.3a Weight loss should be targeted in all women with polycystic ovary syndrome and body mass index ≥25kg/m² (overweight) through reducing dietary energy (caloric) intake in the setting of healthy food choices, irrespective of diet composition.

5.3b Prevention of weight gain should be targeted in all women with polycystic ovary syndrome through monitored caloric intake, in the setting of healthy food choices, irrespective of diet composition.
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<tr>
<td><strong>5.3c</strong></td>
<td>Weight loss (in women with a body mass index ≥25kg/m² (overweight)) and prevention of weight gain (in women with a body mass index ≤25kg/m² (lean)) is the joint responsibility of all health professionals, partnering with women with polycystic ovary syndrome. Where complex dietary issues arise (or obesity is present), referral to a dietitian should be considered as part of an enhanced primary care plan. Tools such as Lifescripts could be used for engagement in dietary change: <a href="http://www.health.gov.au/lifescripts">www.health.gov.au/lifescripts</a></td>
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<td>PP P78</td>
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<tr>
<td><strong>5.4a</strong></td>
<td>Face to face, tailored dietary advice, including education, behavioural change techniques and ongoing support should be provided to women with polycystic ovary syndrome and a body mass index ≥25kg/m² (overweight). Dietary modification is the joint responsibility of all health professionals, partnering with women with polycystic ovary syndrome.</td>
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<td>C</td>
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<tr>
<td><strong>5.4b</strong></td>
<td>Behaviour change techniques should target prevention of weight gain in all women with polycystic ovary syndrome including those with a body mass index ≤25kg/m² (lean).</td>
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<td>CR</td>
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<tr>
<td><strong>5.4c</strong></td>
<td>Behavioural change techniques, including motivational interviewing, should be used in addition to advice/education. Simple strategies, including self-monitoring, pedometers and time management techniques should be encouraged. Interventions could be individual, group or mixed mode, in a range of settings, delivered by a range of health professionals. Individual techniques should not be used in isolation and should be part of a coherent multidisciplinary interventional model. Key messages should be reinforced with women with polycystic ovary syndrome, including that achievable goals (5% to 10% loss of body weight in overweight women) yield significant clinical improvements.</td>
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<td>PP P80</td>
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<tr>
<td><strong>5.5a</strong></td>
<td>Exercise participation of at least 150 minutes per week should be recommended to all women with polycystic ovary syndrome, especially those with a body mass index ≥25kg/m² (overweight), given the metabolic risks of polycystic ovary syndrome and the long term metabolic benefits of exercise. Of this, 90 minutes per week should be aerobic activity at moderate to high intensity (60% - 90% of maximum heart rate) to optimise clinical outcomes.</td>
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<td>D P83</td>
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<tr>
<td><strong>5.5b</strong></td>
<td>Encouraging exercise is the joint responsibility of all health professionals, partnering with women with polycystic ovary syndrome. Where appropriate, referral to an exercise physiologist or specialist could be considered as part of an enhanced primary care plan. Where there are significant co-morbidities, assessment for exercise participation should be undertaken by the relevant healthcare professionals.</td>
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<td>PP P83</td>
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</table>

**CHAPTER SIX  Non-pharmacological first-line management of infertility in PCOS**

| 6.1a | Lifestyle management, including diet and exercise programs, should be used throughout the lifespan in women with polycystic ovary syndrome to optimise health generally and to alleviate polycystic ovary syndrome clinical severity including infertility. | C |
| 6.1b | In women with polycystic ovary syndrome and body mass index ≥30kg/m² with due consideration given to age-related infertility, intensive (frequent multidisciplinary contact) lifestyle modification alone (and not in combination with pharmacological ovulation induction therapy) should be first-line therapy for 3 to 6 months to determine if ovulation is induced. | C |
| 6.1c | Pharmacological ovulation induction should not be recommended for first-line therapy in women with polycystic ovary syndrome who are morbidly obese (body mass index ≥35kg/m²) until appropriate weight loss has occurred either through diet, exercise, bariatric surgery, or other appropriate means. | C |
| 6.1d | Pharmacological ovulation induction could be second-line therapy, after intensive lifestyle modification has been undertaken. | C |
| 6.1e | Morbid obesity (body mass index ≥35kg/m²) increases risks during pregnancy and should be regarded as a relative contraindication to assisted fertility. | PP |
| 6.1f | Psychological factors should be considered and managed in infertile women with polycystic ovary syndrome, to optimise engagement and adherence with lifestyle interventions. | PP |

**CHAPTER SEVEN  Pharmacological management of infertility in PCOS**

| 7.1a | Clomiphene citrate should be first-line pharmacological therapy to improve fertility outcomes in women with polycystic ovary syndrome and anovulatory infertility, with no other infertility factors. | A |
| 7.1b | The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring is recommended. | PP |
| 7.2a | Metformin should be combined with clomiphene citrate to improve fertility outcomes rather than persisting with further treatment with clomiphene citrate alone in women with polycystic ovary syndrome who are clomiphene citrate resistant, anovulatory and infertile with no other infertility factors. | A |

Recommendations 21
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Text</th>
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<tr>
<td>7.2b</td>
<td>Metformin could be used alone to improve ovulation rate and pregnancy rate in women with polycystic ovary syndrome who are anovulatory, have a body mass index ≤30kg/m² and are infertile with no other infertility factors. <strong>B</strong></td>
</tr>
<tr>
<td>7.2c</td>
<td>If one is considering using metformin alone to treat women with polycystic ovary syndrome who are anovulatory, have a body mass index ≥30kg/m², and are infertile with no other infertility factors, clomiphene citrate should be added to improve fertility outcomes. <strong>A</strong></td>
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<tr>
<td>7.3a</td>
<td>Gonadotrophins should be second-line pharmacological therapy in women with polycystic ovary syndrome who have clomiphene citrate resistance and/or failure, are anovulatory and infertile, with no other infertility factors. <strong>B</strong></td>
</tr>
<tr>
<td>7.3b</td>
<td>Gonadotrophins could be considered as first-line pharmacological therapy in women with polycystic ovary syndrome who are therapy naïve, anovulatory and infertile, with no other infertility factors. <strong>C</strong></td>
</tr>
</tbody>
</table>
| 7.3c          | Where gonadotrophins or laparoscopic ovarian surgery (see 8.1) are to be prescribed, the following should be considered:  
- Cost of either intervention for ovulation induction  
- Expertise required for the use of either intervention for ovulation induction  
- The degree of intensive monitoring that is required for gonadotrophin therapy  
- Implications of potential multiple pregnancy for gonadotrophin therapy  
- Implications of the potential risk of ovarian hyperstimulation syndrome for gonadotrophin therapy  
- Laparoscopic surgery in women who are overweight or obese is associated with both intra-operative and post-operative risks. **PP P96** |
| 7.4a          | Letrozole, under caution, could be offered as a pharmacological treatment for ovulation induction indicated for infertile anovulatory women with polycystic ovary syndrome with no other infertility factors **A** |
| 7.4b          | Letrozole, under caution, could be considered as a first line pharmacological treatment for ovulation induction in therapy naïve, infertile anovulatory women with polycystic ovary syndrome with no other infertility factors **B** |
| 7.4c          | Where letrozole is to be prescribed, the following should be considered:  
- Local therapeutic regulatory requirements  
- Potential cost implications  
Need for patient explanation and consent for off label use. **PP** |
| 8.1a | Laparoscopic ovarian surgery should be second line therapy in women with polycystic ovary syndrome who are clomiphene citrate resistant, anovulatory, and infertile, with no other infertility factors. | B |
| 8.1b | If undergoing laparoscopic ovarian surgery, the patient should be advised of the risks (see 7.3c) | PP |
| 8.1c | Where ovulation induction would be considered appropriate, laparoscopic ovarian surgery can be used as first-line treatment if laparoscopy is indicated for another reason in infertile women with PCOS. | CR |
| 8.1d | Where laparoscopic ovarian surgery or gonadotrophins (see 7.3) are to be prescribed, the following should be considered:  
• Cost of either intervention for ovulation induction  
• Expertise required for the use of either intervention for ovulation induction  
• The degree of intensive monitoring that is required for gonadotrophin therapy  
• Implications of potential multiple pregnancy for gonadotrophin therapy  
• Implications of the potential risk of ovarian hyperstimulation syndrome for gonadotrophin therapy  
• Laparoscopic surgery in women who are overweight or obese is associated with both intra-operative and post-operative risks. | P103 PP |
| 8.2a | Bariatric surgery could be considered second-line therapy to improve fertility outcomes in adult women with polycystic ovary syndrome who are anovulatory, have a body mass index ≥35kg/m², and who remain infertile despite undertaking an intensive (frequent multidisciplinary contact) structured lifestyle management program involving reducing dietary energy (caloric) intake, exercise, behavioural and/or drug interventions for a minimum of 6 months. | CR P105 |
| 8.2b | If bariatric surgery is to be prescribed, the following key issues should be considered:  
• A structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health should continue post-operatively.  
• The patient should be made aware of the risk of pre-and post-operative nutritional deficiencies and should be managed in a specialist interdisciplinary care setting, including a bariatric surgeon, a dietitian and/or other multidisciplinary staff trained to work with patients who | PP |
If bariatric surgery is to be prescribed, the following key issues should be considered:

- Bariatric surgery should not be conducted in patients who are known to be pregnant [24]
- Pregnancy should be avoided during periods of rapid weight loss
- Patients should be counselled to avoid pregnancy for at least 12-18 months after bariatric surgery [24, 25]
- Contraception should be discussed prior to surgery
- If pregnancy occurs, the patient should be made aware of the risk of pre- and post-operative nutritional deficiencies and should ideally be managed in a specialist interdisciplinary care setting which includes an obstetrician, bariatric surgeon and a dietitian and/or other multidisciplinary staff trained to work with patients who have had bariatric surgery to ensure that nutritional deficiencies and complications are avoided
- Fetal growth should be monitored during pregnancy
- A structured weight management program involving diet and physical activity, and interventions to improve psychological, musculoskeletal and cardiovascular health should continue post-operatively.
Algorithms

The algorithms summarise the recommendations of the guideline and provide an accessible desktop tool.

There are five algorithms:

1) A detailed flow chart covering challenges in diagnostic assessment of PCOS and assessment of cardiometabolic risk
2) A detailed flow chart for the assessment of emotional wellbeing
3) A detailed flow chart for lifestyle management of PCOS
4) A summary flow chart of options for management of infertility
5) A detailed flow chart of options for management of infertility.
### DIAGNOSTIC AND METABOLIC RISK ASSESSMENT FOR ALL WOMEN WITH POLYCYSTIC OVARY SYNDROME

#### The 2003 Rotterdam criteria for diagnosis of Polycystic Ovary Syndrome (PCOS) – requires two of the following three criteria:

1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries, exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen-secreting tumours, Cushing’s syndrome

#### CHALLENGES IN DIAGNOSTIC ASSESSMENT

- **Late-onset congenital adrenal hyperplasia**, although rare, needs to be considered before the diagnosis of polycystic ovary syndrome is confirmed. In more severe clinical cases of hyperandrogenism, 21-hydroxylase deficiency, the most common form of congenital adrenal hyperplasia, can be excluded by measuring serum 17-hydroxyprogesterone in the follicular phase to explore this diagnosis. [CR]
- Calculated bioavailable testosterone, calculated free testosterone or free androgen index should be first line investigation for biochemical determination of hyperandrogenism in PCOS.
- The addition of androstenedione and dehydroepiandrosterone sulfate could be second line investigation for biochemical determination of hyperandrogenism in PCOS. [CR]

#### ASSESSMENT OF CARDIOMETABOLIC RISK

- **All women with PCOS should be assessed for cardiovascular disease risk by assessing individual cardiovascular disease risk factors.**
- If screening in women with polycystic ovary syndrome shows that any of the following cardiovascular disease risk factors are present, these women with polycystic ovary syndrome should be considered at increased relative risk of cardiovascular disease (obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance, lack of physical activity) and those with metabolic syndrome and/or type 2 diabetes, at even greater risk. [CR]
- **All women with PCOS should be assessed for excess weight at every visit.** In assessing women with PCOS ≤ 6 years age, appropriate and gender appropriate body mass index should be calculated at every visit. Women with polycystic ovary syndrome should be assessed for cigarette smoking [CR]

#### GOOD PRACTICE POINT

- **It is difficult to assess androgen status in women on the oral contraceptive pill as effects include oestrogen mediated increases in sex hormone-binding globulin and reduction in androgens. Where the oral contraceptive pill has already been commenced,** it should be withdrawn for at least three months before appropriate hormonal assessments for diagnosis of polycystic ovary syndrome are undertaken. Contraception should be otherwise managed during this time. [PP]

#### GOOD PRACTICE POINT

- **If androgen levels are markedly above laboratory reference ranges, secondary causes may be considered.** Mild elevations of androstenedione may be seen in polycystic ovary syndrome, whereas marked elevations are more indicative of non-classical adrenal hyperplasia. Reference ranges for different methods and laboratories vary widely and clinical decisions should be guided by the reference ranges of the laboratory used. [PP]

#### GOOD PRACTICE POINT

- **In adolescent women (<18 years), after two years of irregular cycles (>21 or <21 days) following the onset of menarche, PCOS should be considered and appropriate assessment should be undertaken.** As polycystic ovary syndrome is a diagnosis of exclusion, other causes of irregular cycles (such as thyroid dysfunction or hyperprolactinaemia) need to be considered and excluded prior to the diagnosis of polycystic ovary syndrome. [CR]

#### GOOD PRACTICE POINT

- **If oral contraceptive pill therapy is being considered or has commenced in adolescents (<18 years), the following are recommended:**
  - After twelve months of irregular cycles (>35 or <21 days) after onset of menarche, PCOS should be considered before commencement of the oral contraceptive pill.
  - Where the oral contraceptive pill has already been commenced, when girls are not sexually active, if biochemical hyperandrogenism is needed for the diagnosis of PCOS, the oral contraceptive pill could be withdrawn for three months to facilitate appropriate hormonal assessments. Withdrawal of the oral contraceptive pill may facilitate assessment and early diagnosis of PCOS as diagnosis can have important implications including optimisation of healthy lifestyle, regular metabolic screening and proactive fertility planning, with consideration of planning for conception at an earlier age. However, the risk of unplanned pregnancy needs to be considered and weighed up against potential benefits of early diagnosis. Contraception may still need to be otherwise managed during this time.

#### GOOD PRACTICE POINT

- **Vaginal ultrasound is not appropriate in adolescents who have not been sexually active.** [PP]

### ASSESSMENT OF DIABETIC RISK

- **In women with PCOS, a lipid profile should include:**
  - **Total cholesterol** - total cholesterol should be < 4 mmol/L. Low density lipoprotein cholesterol (LDL-C) - in women without additional cardiovascular disease risk factors, LDL-C levels should be < 3.4 mmol/L. In women with metabolic syndrome or type 2 diabetes, LDL-C levels should be < 1.8–2.6 mmol/L or 1.8 mmol/L, respectively. High density lipoprotein cholesterol (HDL-C) - HDL-C levels should be > 1.0 mmol/L.
  - **Triglycerides** - triglyceride levels should be < 1.7 mmol/L. [PP]

#### GOOD PRACTICE POINT

- **Blood pressure should be measured annually in women with PCOS and a Body mass index ≤ 25kg/m² (lean). Blood pressure should be routinely measured at each visit in women with PCOS and a body mass index ≥ 25kg/m² (overweight-obese).** [CR]

#### GOOD PRACTICE POINT

- **In women with PCOS who are at high risk of type 2 diabetes, the ideal day time blood pressure should not exceed 135 mmHg systolic and 85 mmHg diastolic.** [PP]

#### GOOD PRACTICE POINT

- To assess for risk of type 2 diabetes, in addition to PCOS status, the following diabetes risk factors should be considered: age, gender, ethnicity, parental history of diabetes, history of high blood glucose level, use of antihyperglycaemic medications, smoking, physical inactivity, waist circumference. [CR]

#### GOOD PRACTICE POINT

- An oral glucose tolerance test should be performed every second year in all women with polycystic ovary syndrome and annually in those found to have additional risk factors for developing type 2 diabetes as outlined in 3.2a. [CR]

#### GOOD PRACTICE POINT

- Reference ranges for: Impaired fasting glucose - fasting plasma glucose: 6.1 - 6.9 mmol/L. Impaired glucose tolerance - 2 hour glucose level: 7.8-11.1 mmol/L. Type 2 diabetes - fasting plasma glucose: ≥ 7.0 mmol/L or 2 hour glucose tolerance test: ≥ 11.1 mmol/L. Ideally 150 grams of carbohydrate per day should be consumed for three days before, and women should then fast for 8 hours immediately prior to the oral glucose tolerance test since low carbohydrate intake may lead to false positive glucose tolerance tests. [PP]

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### Algorithms

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ALGORITHM 2:

**ASSESSMENT FOR EMOTIONAL WELLBEING FOR ALL WOMEN WITH POLYCYSTIC OVARY SYNDROME**

**INTERDISCIPLINARY CARE [CR]**

Interdisciplinary care, with multiple health professionals involved, should be offered to women with PCOS, where appropriate based on the chronic and complex nature of the disease. An interdisciplinary care model is the collaboration between a woman with PCOS and a care team who have shared goals for her total wellbeing. It should have the following integral components:

- A care team, comprised of and representation from, varied health disciplines (e.g., may include dietetics, psychology, endocrinology, gynaecology, exercise physiology, general practice)
- A care plan which has been developed and agreed with the woman, and if relevant, the carer
- A designated care coordinator, who oversees the care plan and monitors and evaluates outcomes, which is often the general practitioner
- Clear and regular communication (e.g., information sharing via different forms of media, including internet, letters, case conferencing, email, teleconference)

The complexity of the woman’s need will determine the extent of interdisciplinary care required.

**GOOD PRACTICE POINT**

When referring a woman with PCOS to other health professionals i.e., psychologists, a resource has been developed (Appendix IV) to inform the professional about PCOS.

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**STEP 1: SCREENING**

Depression and/or anxiety should be routinely screened and assessed by all appropriately qualified health professionals in women with PCOS. If a woman with PCOS is positive on screening, the practitioner should further assess for depression and/or anxiety. If depression and/or anxiety are detected, appropriate management should be offered.

The following questions could be asked:

1. During the last month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?
3. During the last month, have you been bothered by feeling excessively worried or concerned?

The following areas should be considered for further screening according to presented clinical symptoms:

**Assessing Body Image**

1. Do you worry a lot about the way you look and wish you could think about it less?
2. On a typical day, do you spend more than 1 hour per day worrying about your appearance? (More than 1 hour a day is considered excessive)
3. What specific concerns do you have about your appearance?
4. What effect does it have on your life?
5. Does it make it hard to do your work or be with your friends and family?

**Assessing Disordered Eating**

1. Do you worry you have lost control over your eating?
2. Do you ever feel disgusted, depressed, or guilty about eating?
3. Have you tried fasting or skipping meals in an attempt to lose weight?
4. Have you tried vomiting, laxatives or diuretics in an attempt to lose weight?
5. Have you had significant (e.g., >5-7%), recurrent fluctuation in body weight?

**Assessing Psychosexual Dysfunction**

1. During the last few months, have you often been bothered by problems with your sex life such as reduced satisfaction, diminished desire, pain, or any other problems?
2. Do you feel that PCOS affects your sex life?
3. (If relevant) Do sexual problems affect your current relationship and/or have sexual problems affected your past relationships?

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**STEP 2: ASSESSMENT**

If issues of depression and/or anxiety, body image, disordered eating or psychosexual dysfunction are identified on screening, explore the assessment further by undertaking a clinical interview using one of the recommended tools.

- If you do not feel confident to do so refer to an appropriate specialist.

**STEP 2: Suggested tools to use for depression and/or anxiety:**

- Kessler Psychological Distress Scale 10 (K-10)
- Depression Anxiety Stress Scale (DASS-21)
- Patient Health Questionnaire (PHQ9)
- Generalised Anxiety Disorder Tool (GAD7)

**STEP 2: Further questions for body image:**

- Assessing the level of depression and/or anxiety (if they have not done so already) (see 4.1a)
- Identify if there is any distortion of body image (e.g., presence of anorexia nervosa or body dysmorphic disorder)

**STEP 2: Suggested tools to use for disordered eating:**

- EAT 26
- If you have not already done so assess the level of depression and/or anxiety using the above questions and tools

**STEP 2: The choice of scale selected should be at the discretion of the clinician, based on specific sexual problem, accessibility and expertise of the practitioner.**

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**STEP 3: MANAGEMENT**

If issues of depression and/or anxiety, body image, disordered eating or psychosexual dysfunction are identified appropriate management should be offered.
**ALGORITHM 3:**

**MANAGEMENT OF LIFESTYLE FOR ALL WOMEN WITH POLYCYSTIC OVARY SYNDROME**

**LIFESTYLE MODIFICATION & BEHAVIOUR CHANGE**

* Lifestyle management (single or combined approaches of diet, exercise and/or behavioural interventions) for weight loss, prevention of weight gain, or for general health benefits should be recommended in women with PCOS. [CR]

* Face to face, tailored dietary advice, including education, behavioural change techniques and ongoing support should be provided to women with PCOS and a body mass index $\geq 25$kg/m² (overweight). Dietary modification is the joint responsibility of all health professionals, partnering with women with PCOS. [C]

* Behaviour change techniques should target prevention of weight gain in all women with PCOS including those with a body mass index $\leq 25$kg/m² (lean). [CR]

* Behavioural change techniques, including motivational interviewing, should be used in addition to advice/education. Simple strategies, including self-monitoring, pedometers and time management techniques, should be encouraged. Interventions could be individual, group or mixed mode, in a range of settings, delivered by a range of health professionals. Individual techniques should not be used in isolation and should be part of a coherent multidisciplinary interventional model. [PP]

* Key messages should be reinforced with women with PCOS, including that achievable goals (5% to 10% loss of body weight in overweight women) yield significant clinical improvements. [PP]

**COMBINED LIFESTYLE MANAGEMENT**

Lifestyle management targeting weight loss (in women with a body mass index $\geq 25$kg/m² (overweight)) and prevention of weight gain (in women with a body mass index $\leq 25$kg/m² (lean)) should include both reduced dietary energy (caloric) intake and exercise and should be first line therapy for all women with PCOS. [C]

**GOOD PRACTICE POINT**

Psychological factors should be considered and managed to optimise engagement and adherence to lifestyle interventions. [PP]

**DIET**

Weight loss should be targeted in all women with PCOS and body mass index $\geq 25$kg/m² (overweight) through reducing dietary energy (caloric) intake in the setting of healthy food choices, irrespective of diet composition. [C]

Prevention of weight gain should be targeted in all women with PCOS through monitored caloric intake, in the setting of healthy food choices irrespective of diet composition. [D]

**GOOD PRACTICE POINT**

Weight loss (in women with a body mass index $\geq 25$kg/m² (overweight)) and prevention of weight gain (in women with a body mass index $\leq 25$kg/m² (lean)) is the joint responsibility of all health professionals, partnering with women with polycystic ovary syndrome. Where complex dietary issues arise (or obesity is present), referral to a dietician should be considered as part of an enhanced primary care plan.

Tools such as **Lifescripts** could be used for engagement in dietary change: [www.health.gov.au/lifescripts](http://www.health.gov.au/lifescripts)

**EXERCISE**

Exercise participation of at least 150 minutes per week should be recommended in all women with PCOS, especially those with a body mass index $\geq 25$kg/m² (overweight), given the metabolic risks of PCOS and the long term metabolic benefits of exercise. [D]

Of this, 90 minutes per week should be aerobic activity at moderate to high intensity (60% - 90% of maximum heart rate) to optimise clinical outcomes. [D]

**GOOD PRACTICE POINT [PP]**

Encouraging exercise is the joint responsibility of all health professionals, partnering with women with PCOS. Where appropriate, referral to an exercise physiologist or specialist could be considered as part of an enhanced primary care plan. Where there are significant co-morbidities, assessment for exercise participation should be undertaken by the relevant healthcare professionals.

Tools such as **Lifescripts** could be used for engagement in physical activity: [www.health.gov.au/lifescripts](http://www.health.gov.au/lifescripts)
**ALGORITHM 5:**

### THERAPY FOR INFERTILITY FOR ALL WOMEN WITH POLYCYSTIC OVARY SYNDROME

#### NON-PHARMACOLOGICAL

- Lifestyle management, including diet and exercise programs, should be used throughout the lifespan in women with PCOS to optimise health generally and to alleviate PCOS clinical severity including infertility. [C]

- Women with PCOS and body mass index ≥ 30kg/m² with due consideration given to age-related infertility, intensive (frequent multidisciplinary contact visits) lifestyle modification alone (and not in combination with pharmacological ovulation induction therapy) should be offered first line therapy for 3 to 6 months to determine if ovulation is induced. [C]

#### PHARMACOLOGICAL MANAGEMENT

- Clomiphene citrate should be first line pharmacological therapy to improve fertility outcomes in women with PCOS and anovulatory infertility, with no other infertility factors. [A]

- Metformin should be combined with clomiphene citrate to improve fertility outcomes rather than persisting with further treatment with clomiphene citrate alone in women with PCOS who are clomiphene citrate resistant, anovulatory and infertile with no other infertility factors. [A]

- Metformin could be used alone to improve ovulation rate and pregnancy rate in women with PCOS who are anovulatory, have a body mass index ≥ 30kg/m², and are infertile with no other infertility factors. [B]

#### SURGICAL MANAGEMENT

- Laparoscopic ovarian surgery should be second line therapy in women with PCOS who are clomiphene citrate resistant, anovulatory, and infertile, with no other infertility factors. [B]

- If undergoing laparoscopic ovarian surgery, the patient should be advised of the risks (see 7.3). [PP]

- Where ovulation induction would be considered appropriate, laparoscopic ovarian surgery can be used as first line therapy if laparoscopic surgery is indicated for another reason in infertile women with PCOS. [C]

- Where laparoscopic ovarian surgery or gonadotrophins (see 7.3) are to be prescribed, the following should be considered:
  - Cost of other intervention for ovulation induction
  - Expertise required for the use of other intervention for ovulation induction
  - The degree of intensive monitoring that is required for gonadotrophin therapy
  - Implications of potential multiple pregnancy for gonadotrophin therapy
  - Implications of the potential risk of ovarian hyperstimulation syndrome for gonadotrophin therapy
  - Laparoscopic surgery in women who are overweight or obese is associated with both intra-operative and post-operative risks. [PP]

- Bariatric surgery could be considered second line therapy to improve fertility outcomes in adult women with polycystic ovary syndrome who are anovulatory, have a body mass index ≥ 30kg/m², and who remain infertile despite undertaking an intensive (frequent multidisciplinary contact visits) lifestyle management program involving reducing dietary energy (caloric) intake, exercise, and/or drug interventions for a minimum of 6 months. [C]

- If bariatric surgery is to be prescribed, the following key issues should be considered:
  - Bariatric surgery should not be conducted in patients who are known to be pregnant
  - Pregnancy should be avoided during periods of rapid weight loss
  - Patients should be counselled to avoid pregnancy for at least 12-18 months after bariatric surgery
  - Contraception should be discussed prior to surgery
  - If pregnancy occurs, the patient should be made aware of the risk of pre- and post-operative nutritional deficiencies and should ideally be managed in a specialist interdisciplinary care setting which includes an obstetrician, bariatric surgeon, and a dietician and/or other multidisciplinary staff trained to work with patients who have had bariatric surgery to ensure that nutritional deficiencies and complications are avoided
  - Fetal growth should be monitored
  - A structured weight management program involving diet and physical activity, and interventions to improve psychological, musculoskeletal, and cardiovascular health should continue post-operatively. [PP]

- Letrozole, under caution, could be considered as a pharmacological treatment for ovulation induction indicated for infertile anovulatory women with PCOS with no other infertility factors. [A]

- Letrozole, under caution, could be considered as a first line pharmacological treatment in therapy naïve, infertile anovulatory women with polycystic ovary syndrome with no other infertility factors. [B]
Introduction

Background

Polycystic ovary syndrome (PCOS) is one of the most common conditions in Australian women affecting 12-21% of reproductive-aged women [5, 26, 27] with 70% of these affected women with PCOS remaining undiagnosed [5]. In IndigenousAustralian women the prevalence is 21% [6]. Women with PCOS can present with a range of features including psychological (poor self-esteem, anxiety, depression) [11, 28, 29], reproductive (menstrual irregularity, hirsutism, infertility and pregnancy complications) [30], and metabolic features (insulin resistance (IR), metabolic syndrome, prediabetes, type 2 diabetes (DM2) and cardiovascular disease (CVD)) [31, 32](Figure 1). Not all women demonstrate all symptoms and there is considerable heterogeneity. Presentation can also vary across the lifecycle. PCOS is a chronic condition with manifestations that begin most commonly in adolescence with menstrual irregularity and hyperandrogenism with transition over time into problems including infertility and metabolic complications. PCOS is the most common cause of anovulatory infertility, and once pregnant, these women have higher risks of pregnancy-related diabetes and pregnancy complications.

Figure 1. Published with permission from the Royal Australian College of General Practitioners [33].

Screening in unselected women with obesity showed 28% had PCOS, compared to 5% of women who were lean [34]. The prevalence of PCOS will likely increase in line with the increasing prevalence of obesity in Australia. Other important long-term implications include a 4-7 fold increased risk of DM2 and CVD [21, 35]. Challenges to feminine identity and body image due to obesity, acne and excess hair compromise quality of life (QoL) in women with PCOS and social stigmas around symptoms adversely impact on self efficacy [10]. Increased rates of depression and anxiety are found in women with PCOS [28].

In 2006, the estimated health care costs of PCOS in the US were $6 billion/year. This equated to $400 million in Australia (anovulation 31%, infertility 12% and PCOS related DM2 40% of total costs), representing a major health and economic burden [36].

3 With acknowledgment that different terms are used, in this context, the word ‘Indigenous’ refers to all Aboriginal or Torres Straight Islanders.
Clinical need for this guideline

PCOS has been identified as an area of clinical need and as a public health issue by key stakeholder groups and by the Australian government. This was affirmed recently in an Australian community-based prevalence study where unselected women were screened for PCOS using NIH, Rotterdam and AES criteria. This study demonstrated that 9% have PCOS based on NIH criteria and 18% based on Rotterdam criteria. Of these women, 70% with PCOS were undiagnosed and only 30% aware of the diagnosis at the time of screening [5]. Furthermore, other Australian research has shown 21% prevalence of PCOS in Indigenous women [6].

Given its heterogeneous clinical features across the lifespan, PCOS is a condition that engages many health disciplines. The associated complications are serious yet are largely preventable, however there is a lack of awareness of PCOS among consumers and health professionals. The need for consumers and health professionals to recognise the lifecourse implications of PCOS, identify the early signs and symptoms and partner together in managing PCOS and preventing the complications is essential. The burden and cost of PCOS complications, including infertility, DM2, mental health issues and CVD are significant.

The impact of obesity on PCOS

Obesity or excess weight is a major cause of chronic disease in western countries. In Australia 56% of the adult population is overweight or obese (body mass index (BMI) ≥ 25kg/m^2) with 18% obese (BMI ≥ 30kg/m^2). In 2007, 31% of women were overweight and 24% of women were obese. Recent data from the Australian Longitudinal study of women’s health show that in women aged 26-31 years 20.4% were overweight and a further 13.9% were obese [37]. The proportion of adults who are obese is increasing and has approximately doubled in the past 20 years in Australia and the majority of other western countries [38]. Indeed, obesity is now the primary cause of chronic disease in Australian women with primary adverse outcomes including DM2 and CVD [39]. Obesity also has a specific impact on women’s reproductive health, increasing the prevalence and severity of PCOS, infertility, pregnancy complications, DM2 in pregnancy and fetal pregnancy complications, with substantial and escalating economic costs [40, 41]. Obesity exacerbates PCOS through increasing IR and hyperandrogenism. The major and increasing burden of infertility, especially when combined with condensed reproductive features in women with delayed child bearing, is resulting in a significant social, health and economic burden in Australia. With dramatic increases in obesity in our society, the impact of obesity on reproductive health in women is of critical importance. With increasing obesity, known to increase prevalence and exacerbate all features of PCOS, the prevalence of PCOS is expected to rise further.

Long term metabolic complications of PCOS: Prediabetes, type 2 diabetes and cardiovascular disease

In PCOS, prospective trials have shown a 35% prevalence of prediabetes, a 10% prevalence of DM2, a 5-10 fold risk of progression from prediabetes to DM2 and a 4-7 fold higher risk of DM2. CVD appears increased in PCOS despite inadequate long-term studies to appropriately address this question [35]. It is proposed in the international Androgen Excess and PCOS Society (AE-PCOS) consensus statement [17] that those with PCOS and obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance, and subclinical vascular disease are at increased relative CVD risk, and those with metabolic syndrome and/or DM2 are at even greater relative risk. In the general population IR is a predictor of CVD [42, 43]. Women with PCOS also have an increased prevalence of metabolic syndrome (associated with an increased risk for DM2 and CVD) [31], risk factors for CVD and clinical signs of atherosclerosis [44, 45] which are all exacerbated by obesity. Women with PCOS are therefore a population with a high relative risk of developing DM2 and CVD with this predisposition greatly worsened by obesity. It is acknowledged that data on absolute risk of CVD in women with PCOS suggests
an increase, however data in this area is limited. As DM2 and subsequent CVD are the primary cause of death in Australian women, any increase in prevalence will have significant public health implications.

Considerations for Indigenous women

The prevalence of PCOS in Indigenous women is as high as 21% by the ESHRE/Rotterdam criteria [6, 46] and increases with increasing BMI [46]. In a group of Indigenous women with PCOS, 30.3% were obese and 7.0% had a normal BMI [46].

DM2 and obesity are health issues associated with major morbidity in Indigenous women. DM2 is the second most common cause of mortality and disability-adjusted life years (DALY) in Indigenous women [47]. The DALY rate ratio (age standardised to total Indigenous population) for ischaemic heart disease in Indigenous women compared to all Australian women is 6.6 and for DM2 is 6.3, whilst the mortality rate ratio is 5.0 for ischaemic heart disease and 18.9 for DM2 [47]. Obesity, as previously noted, is a significant problem for non-Indigenous women and is even more so for Indigenous women. The National Aboriginal and Torres Strait Islander health survey (NATSIHS) found that Indigenous Australians are 1.2 times more likely to be overweight/obese than non-Indigenous Australians and this disparity is greatest for women in every age group [48].

Eleven selected risk factors have been identified under the broad categories of lifestyle behaviours, physiological states and social and environmental factors that together were responsible for half the discrepancy of disease burden between Indigenous and non-Indigenous people [47]. BMI was the second leading cause of Indigenous burden of disease in 2003 at 11.4%. For females aged 35–54 years, high body mass was responsible for the largest amount of burden among eleven risks examined and DM2 and ischaemic heart disease accounted for 89% of the total burden due to high body mass in Indigenous Australians; over half of this burden was experienced by females [47]. High blood cholesterol, physical inactivity, high blood pressure and low fruit and vegetable intake were also identified as causes.

The risk of metabolic complications is already high in Indigenous women, independent of PCOS and therefore PCOS has the potential to amplify the risk of metabolic complications in these women. Given that these metabolic complications are largely preventable, it is important to provide early access to care.

It is important to highlight that access to culturally appropriate care, services and programs is currently not optimal and the cost of maintaining a healthy diet in rural and remote locations is high, hence the translation and implementation of recommendations may be difficult. Socioeconomic factors such as poverty and overcrowding make the use of fridges and kitchen equipment to cook healthy food difficult.

Insufficient existing guidance

Currently, there is no consensus among different medical specialties as to the optimal management of PCOS in Australia [12]. Diagnosis and treatment of PCOS can therefore differ depending on the medical professional consulted (e.g. general practitioner, endocrinologist or gynaecologist) [12]. There are limited clinical guidelines and no evidence-based guidelines either in Australia or internationally for assessment or management of PCOS; rather PCOS is sometimes mentioned within guidelines for the management of obesity and DM2 [15, 49].

Where international clinical guidelines for the screening and treatment of women with PCOS exist, they are not evidence-based, they do not consider psychological issues and offer simplistic advice on lifestyle management of PCOS. There is no guidance on the assessment and management of PCOS in Indigenous women, nor any adaptation for the Australian context.
Purpose

The purpose of this guideline is to integrate the best available evidence with clinical expertise and consumer preferences to provide health professionals, consumers and policy makers with guidance on timely diagnosis, accurate assessment and optimal management of women with PCOS and to promote consistency of care and prevention of complications in primary care and specialist settings.

Patient population

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

Setting and audience

These guidelines will apply in all health care settings and to a broad audience, including:

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

Scope

The scope of this guideline was driven by the clinical priorities identified by the PCOS Australian Alliance during a two day workshop in 2008. The clinical priorities were:

- Development of evidence-based guidelines for the care of women with PCOS in order to facilitate:
  a. Early diagnosis of PCOS
  b. Early detection and treatment of depression, anxiety and mood disorders
  c. Early detection and diagnosis of risk factors for pre-diabetes, DM2 and CVD
  d. Early detection and treatment of fertility problems and prevention of pregnancy complications.
- Interdisciplinary co-ordinated care. Effective care for chronic conditions cannot take place unless there are well trained health professionals to ensure appropriate assessment and treatment. The features of PCOS require an interdisciplinary approach to care potentially including general practitioners, dietitians,

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4 This workshop was funded by the Helen McPherson Smith Trust as a competitive grant.
psychologists, exercise physiologists and nurse practitioners, endocrinologists, obstetricians and gynaecologists. Optimally trained practitioners armed with evidence-based guidance need to take an integrated approach to care for women with PCOS to improve outcomes.

- Decisional support and education is needed to translate evidence into practice, including a website, webcasts, CHECK program (continuing education for general practitioners), Active Learning Modules (ALM), video conference case support, outreach services with advice, clinical attachments, clinical nurse support. This will be addressed in guideline translation activities currently underway.
- Self-management and training, particularly around treatment options including lifestyle management, is needed in PCOS (i.e., dietary, exercise and behavioural advice).

Using these clinical priorities, the Alliance identified the four key clinical areas and corresponding clinical questions to be addressed in the guideline:

1. **Challenges in diagnostic assessment of PCOS**
   - In women with suspected PCOS, what is the most effective measure to diagnose PCOS-related hyperandrogenism? (See [1.1 Hyperandrogenism](#))
   - In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction? (See [1.2 Irregular cycles in adolescents](#))
   - In adolescents, what are the most effective criteria to diagnose polycystic ovaries on ultrasound? (See [1.3 Polycystic ovaries in adolescents](#))
   - In women with PCOS, what is the most effective tool/method to assess risk of cardiovascular disease? (See [3.1 Risk of cardiovascular disease](#))
   - In women with PCOS, what is the most effective tool/method to assess risk of type 2 diabetes? (See [3.2 Risk of type 2 diabetes](#))

2. **Assessment of emotional wellbeing in women with PCOS**
   - What is the effectiveness of an interdisciplinary model of care compared to usual care in terms of biopsychosocial wellbeing? (See [CHAPTER TWO Interdisciplinary care](#))
   - In women with PCOS, what is the most effective tool/method to screen and assess depression and/or anxiety? (See [4.1 Depression and/or anxiety](#))
   - In women with PCOS, what is the most effective tool/method to screen and assess body image? (See [4.2 Body image](#))
   - In women with PCOS, what is the most effective tool/method to screen and assess disordered eating? (See [4.3 Disordered eating](#))
   - In women with PCOS, what is the most effective tool/method to screen and assess psychosexual dysfunction? (See [4.4 Psychosexual dysfunction](#))

In this guideline, the term ‘screen’ refers to identifying whether the condition exists and is the first step in offering appropriate management; and the term ‘assess’ refers to identifying the severity of the condition.

3. **Lifestyle management of women with PCOS**
   - In women with PCOS, are lifestyle interventions (combined compared to minimal or nothing) effective for improving weight loss, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes? (See [5.1 Lifestyle modification](#))
• In women with PCOS, what is the effectiveness of diet compared to exercise for improving weight loss, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes? (See 5.2 Type of lifestyle modification: Diet or exercise)

• In women with PCOS, are diet interventions (compared to no diet or different diets) effective for improving weight loss, metabolic, fertility, and emotional wellbeing outcomes? (See 5.3 Diet)

• In women with PCOS, what is the most effective method to deliver dietary information for improving weight loss, QoL and emotional wellbeing outcomes? (See 5.4 Diet delivery)

• In women with PCOS, are exercise interventions (compared to no exercise or different exercises) effective for improving weight loss, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes? (See 5.5 Exercise)

4. Management of infertility in women with PCOS

• In women with PCOS, what is the effectiveness of lifestyle interventions compared to pharmacological interventions (ie., metformin and clomiphene citrate) for improving fertility, QoL and emotional wellbeing outcomes? (See 6.1 Lifestyle modification)

• In women with PCOS, is clomiphene citrate effective for improving fertility outcomes? (See 7.1 Clomiphene citrate)

• In women with PCOS, is metformin effective for improving fertility outcomes? (See 7.2 Metformin)

• In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes? (See 7.2 Metformin)

• In women with PCOS, are gonadotrophins effective for improving fertility outcomes? (See 7.3 Gonadotrophins)

• In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes? (See 7.4 Aromatase inhibitors)

• In women with PCOS, is ovarian surgery effective for improving fertility outcomes? (See 8.1 Laparoscopic ovarian surgery)

• In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility and adverse outcomes? (See 8.2 Bariatric surgery)

Agreed diagnostic criteria for PCOS

This guideline does not address diagnosis of PCOS. The Alliance has agreed to adopt the Rotterdam criteria (also called the ESHRE/ASRM consensus) for diagnosis of PCOS [2]. The Rotterdam criteria are the most accepted diagnostic criteria across Europe, Asia and Australia. It is acknowledged that the National Institutes of Health (NIH) criteria have a strong support base among clinicians as it is generally accepted that the NIH criteria define a more serious form of the syndrome, but exclude approximately 40% of those meeting Rotterdam criteria. Rotterdam criteria for diagnosis of PCOS is inclusive of NIH criteria (see Figure 2 below). The recent Androgen Excess and PCOS Society (AES) [50] consensus criteria were considered, but as yet these criteria are not widely adopted and the Rotterdam criteria were selected, consistent with international approaches.

5 This additional question was identified as important when the evidence review to answer the original question “In women with PCOS, is metformin effective for improving fertility outcomes?” and subsequent recommendations were discussed. It is apparent from the original evidence review that the effectiveness of metformin may be different according to BMI in women with PCOS. However the guideline development group is unable to rely on the available synthesized evidence identified for the original, more general question and more specific analysis of primary evidence was required to explore the effectiveness of metformin in women with PCOS and a BMI<30-32.
Rotterdam criteria

The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and polycystic ovary (PCO) morphology. PCOS remains a syndrome, and as such no single diagnostic criterion is sufficient for diagnosis. Clinical manifestations may include menstrual irregularities, infertility, signs of androgen excess, obesity and psychological features. IR and/or hyperandrogenism underpin the features of PCOS in the majority of cases.

Rotterdam diagnostic criteria requires two of:
1. Oligo- or anovulation;
2. Clinical and/or biochemical signs of hyperandrogenism;
3. Polycystic ovaries;
and exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing’s syndrome [2].

NIH diagnostic criteria requires:
1. Oligo- or anovulation; and
2. Clinical and/or biochemical signs of hyperandrogenism;
and exclusion of other aetiologies such as congenital adrenal hyperplasia, androgen-secreting tumours and Cushing’s syndrome [1].

Figure 2. Rotterdam criteria for diagnosis of PCOS is inclusive of NIH criteria, in that a woman diagnosed with PCOS using the NIH criteria will also meet Rotterdam criteria, however a woman diagnosed with PCOS using Rotterdam criteria may not meet NIH criteria.

This guideline does not address all aspects of PCOS, such as IVF therapy. Other factors may impact on the psychosocial wellbeing of women with PCOS including but not limited to compromised infertility, health related QoL and further depressive disorders such as bipolar disorder. These were beyond the resources and capacity of this guideline but may be addressed in future updates.

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 to the patient’s clinical profile and personal preferences. It is recommended that the reader consults the Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information including:

- indications
- drug dosage
- method and route of administration
- contraindications
- supervision and monitoring
- product characteristics
- adverse effects.
This guideline does not include a formal analysis of cost effectiveness of recommended practice versus current/established practice. Consideration of cost did occur in guideline development group meetings and did impact on recommendations. These considerations are discussed in the clinical impact of the recommendation sections in each chapter. It also does not cover the economic feasibility of the recommendations.

Funding

The development of this guideline was funded by the Australian Government Department of Health and Ageing, through the national Jean Hailes for Women’s Health on behalf of the PCOS Australian Alliance.

Editorial independence

This guideline is editorially independent. The funders, the Australian Government Department of Health and Ageing, were not involved in the development of the guideline and have not influenced the scope or recommendations of this guideline.
Methods used to develop this guideline

This guideline was developed as outlined in NHMRC standards and procedures for externally developed guidelines [51].

In 2008, Jean Hailes for Women’s Health facilitated a national meeting on PCOS with 25 leaders attending from the research, clinical and community sector. The outcome of this meeting was the formulation of the PCOS Australian Alliance and the mapping of an ambitious plan to improve health outcomes in women with PCOS.

The Alliance identified key clinical priorities for the guideline using the following criteria:

- highest clinical priority
- greatest knowledge gaps
- priorities identified by the commissioning Australian government
- expertise of Alliance members

The scope of this guideline is driven by the clinical priorities:

- Development of evidence-based guidelines for the care of women with PCOS in order to facilitate:
  a. early diagnosis of PCOS
  b. early detection and treatment of depression, anxiety and mood disorders
  c. early detection and diagnosis of risk factors for pre-diabetes, DM2 and CVD
  d. early detection and treatment of fertility problems and prevention of pregnancy complications.

- Interdisciplinary co-ordinated care. Effective care for chronic conditions cannot take place unless there are well trained health professionals to ensure appropriate assessment and treatment. The features of PCOS require an interdisciplinary approach to care potentially including general practitioners, dietitians, psychologists, exercise physiologists and nurse practitioners, endocrinologists, obstetricians and gynaecologists. Optimally trained practitioners, armed with evidence-based guidance, need to take an integrated approach to care in women with PCOS to improve outcomes.

- Decisional support and education is needed to translate evidence into practice, including a website, webcasts, CHECK program (continuing education for general practitioners), Active Learning Modules (ALM), video conference case support, outreach services with advice, clinical attachments, clinical nurse support. This will be addressed in guideline translation activities currently underway.

- Self management and training, particularly around treatment options including lifestyle management is needed in PCOS (ie. dietary, exercise and behavioural advice).

Using these clinical priorities, the Alliance identified the four key clinical areas:

1. Challenges in diagnostic assessment of PCOS
2. Assessment of emotional wellbeing in women with PCOS
3. Lifestyle management of women with PCOS
4. Management of infertility in women with PCOS

The scope of the guideline was reviewed and approved by the Project Board, PCOS Australian Alliance Strategic Advisory Group and the guideline development groups.
Multidisciplinary guideline development groups

Guideline development groups were convened to address each of the four key clinical areas. Expertise was sought through Alliance networks to ensure multidisciplinary participation within each guideline development group. Each guideline development group comprised a chair, professional group members with specific expertise in PCOS and the clinical area of interest (i.e. psychologist in the emotional wellbeing guideline development group), a consumer representative, evidence officers and where possible, a representative to provide context in the Indigenous setting. See Appendix II.

Each guideline development group met monthly to discuss the evidence to answer each clinical question and formulate resulting recommendations. The process for formulating recommendations is detailed below.

Consumer participation

The peak consumer body in PCOS, Polycystic Ovary Syndrome Association Australia (POSAA) provided consumer representatives who participated in the PCOS Australian Alliance Strategic Advisory Group and the guideline development groups. The President of POSAA is a member of the Project Board and the PCOS Australian Alliance. Consumers have been involved in every stage including formation of the Alliance, proposal to the Department of Health and Ageing for funding, development of the scope, public consultation of the scope and developing and refining the clinical questions and recommendations as part of the guideline development groups. Consumer representatives will also be extensively involved in the translation activities of the guidelines.

Indigenous representation

Indigenous representation was present on the PCOS Australian Alliance Strategic Advisory Group (a member of the Australian Indigenous Doctors Association) and the guideline development groups comprised clinicians with experience working with Indigenous communities. The Program Manager for Jean Hailes for Women’s Health National Indigenous Women’s Health Program provided oversight for Indigenous issues and considerations across all recommendations in the guideline.

Conflict of interest and confidentiality

Conflict of interest has been proactively managed throughout the guideline development process as outlined in NHMRC standards and procedures for externally developed guidelines [51]. All members of the guideline development groups have provided signed declarations of conflict of interest and a confidentiality agreement. Additionally, declarations of interest were a standing agenda item at each monthly meeting and guideline development group members were requested to detail areas for potential conflict. The process for managing conflict of interest and confidentiality and recorded declarations can be provided on request (linda.downes@monash.edu).

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

The chairs of each guideline development group attended a one day workshop, facilitated by Jean Hailes for Women’s Health and the Centre for Clinical Effectiveness, where the methods of reviewing evidence and guideline development were described in detail. The purpose of this workshop was to familiarise the chairs with:

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

At this workshop the chairs also participated in an exercise to generate potential clinical questions.
In addition, at the beginning of the first guideline development group monthly meeting, the evidence advisor briefly described the processes for evidence-based guideline development and these processes were reiterated as the evidence reviews were presented each month.

Clinical question development and prioritisation
Development and prioritisation of the clinical questions addressed in this guideline was conducted in three stages. First, in the workshop described above, attended by the chairs of each clinical area and the evidence officers, clinical questions were generated. Secondly, the clinical questions were distributed to all members of each corresponding guideline development group, the Project Board and the PCOS Australian Alliance Strategic Advisory Group. All members were invited to provide feedback on the suitability of the existing questions and to suggest additional clinical questions, if appropriate. Thirdly, the clinical questions were consolidated and distributed once again to guideline development group members who were asked to prioritise each question according to a ranking of 1-6. Rankings were compiled and 22 highly relevant and important clinical questions were agreed and form this guideline. The clinical questions are as follows:

1. Challenges in diagnostic assessment of PCOS
   • In women with suspected PCOS, what is the most effective measure to diagnose PCOS related hyperandrogenism? (See 1.1)
   • In adolescents, at what time point after onset of menarche do irregular cycles indicate ongoing menstrual dysfunction? (See 1.2)
   • In adolescents, what are the most effective criteria to diagnose polycystic ovaries on ultrasound? (See 1.3)
   • In women with PCOS, what is the most effective tool/method to assess risk of cardiovascular disease? (See 3.1)
   • In women with PCOS, what is the most effective tool/method to assess risk of type 2 diabetes? (See 3.2)
2. Assessment of emotional wellbeing in women with PCOS
   • What is the effectiveness of an interdisciplinary model of care compared to usual care in terms of biopsychosocial wellbeing? (See 2.0)
   • In women with PCOS, what is the most effective tool/method to screen and assess depression and/or anxiety? (See 4.1)
   • In women with PCOS, what is the most effective tool/method to screen and assess psychosexual dysfunction? (See 4.2)
   • In women with PCOS, what is the most effective tool/method to screen and assess disordered eating? (See 4.3)
   • In women with PCOS, what is the most effective tool/method to screen and assess body image? (See 4.4)
3. **Lifestyle management of women with PCOS**

- In women with PCOS, are lifestyle interventions (combined compared to minimal or nothing) effective for improving weight loss, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes? (See 5.1)
- In women with PCOS, what is the effectiveness of diet compared to exercise for improving weight loss, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes? (See 5.2)
- In women with PCOS, are diet interventions (compared to no diet or different diets) effective for improving weight loss, metabolic, fertility, and emotional wellbeing outcomes? (See 5.3)
- In women with PCOS, what is the most effective method to deliver dietary information for improving weight loss, QoL and emotional wellbeing outcomes? (See 5.4)
- In women with PCOS, are exercise interventions (compared to no exercise or different exercises) effective for improving weight loss, metabolic, reproductive, fertility, QoL and emotional wellbeing outcomes? (See 5.5)

4. **Management of infertility in women with PCOS**

- In women with PCOS, what is the effectiveness of lifestyle interventions compared to pharmacological interventions (i.e., metformin and clomiphene citrate) for improving fertility, QoL and emotional wellbeing outcomes? (See 6.1)
- In women with PCOS, is clomiphene citrate effective for improving fertility outcomes? (See 7.1)
- In women with PCOS, is metformin effective for improving fertility outcomes? (See 7.2)
- In women with PCOS and a BMI<30-32, what is the effectiveness of metformin compared to clomiphene citrate for improving fertility outcomes? (See 7.2)\(^6\)
- In women with PCOS, are gonadotrophins effective for improving fertility outcomes? (See 7.3)
- In women with PCOS, are aromatase inhibitors effective for improving fertility outcomes? (See 7.4)
- In women with PCOS, is ovarian surgery effective for improving fertility outcomes? (See 8.1)
- In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility and adverse outcomes? (See 8.2)

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**Search for existing evidence-based guidelines**

The evidence officers undertook a systematic search for existing guidelines that address the identified clinical questions (search conducted in January 2010).

**Internet searches to identify relevant websites**

The reviewers were aware of websites of guideline clearinghouses, guideline developers, centres of evidence-based practice, Australian government health services and websites of specific relevance known to contain evidence-based resources. Additional websites of specific relevance were sought via an internet search using the Google ‘Advanced Search’ function with the following string:

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\(^6\) This additional question was identified as important when the evidence review to answer the original question “In women with PCOS, is metformin effective for improving fertility outcomes?” and subsequent recommendations were discussed. It is apparent from the original evidence review that the effectiveness of metformin may be different according to BMI in women with PCOS. However the guideline development group are unable to rely on the available synthesized evidence identified for the original, more general question and more specific analysis of primary evidence was required to explore the effectiveness of metformin in women with PCOS and a BMI<30-32.
Methods used to develop this guideline

Website searches to identify relevant evidence-based guidelines

Where an internal search engine was available, websites were searched. If no search engine was available, lists of guidelines, publications or other resources identified on the site were scanned for relevant documents.

Internet searches to identify relevant evidence-based guidelines and systematic reviews

An internet search strategy was conducted to identify evidence-based guidelines and systematic reviews using the Google ‘Advanced Search’ function with the following string:

(((polycystic AND (ovary OR ovarian)) AND (disease OR syndrome)) OR PCOS OR PCOD) AND (guideline OR evidence OR systematic)

The search string was limited to pages in English.

There were no relevant existing evidence-based guidelines available for assessment or management of women with PCOS. There were guidelines that addressed components of the clinical questions, however they were not specific for use with women with PCOS ie. NICE guideline for Fertility: assessment and treatment for people with fertility problems.

Evidence reviews to answer the clinical questions

Evidence reviews were conducted for each clinical question and from the evidence reviews the guideline development groups were able to develop guideline recommendations. The evidence reviews for each question can be found in the supporting document titled ‘Evidence report’, which can be found at www.managingpcos.org.au/pcos-evidence-based-guidelines.

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, organisational barriers and resource implications are clearly explained in the accompanying discussion supporting the recommendation.

Selection criteria

The PICO (Population, Intervention, Comparison, Outcome) framework was used by the guideline development group to explore the components of each clinical question. These components were used to include and exclude studies in the evidence review. Details of the selection criteria for each question can be found in the supporting document titled ‘Evidence report’, which can be found at www.managingpcos.org.au/pcos-evidence-based-guidelines.

Systematic search for evidence

A broad-ranging systematic search for terms related to PCOS was developed by the evidence team. This PCOS search string was then combined with specific searches tailored for each clinical question according to the PICO developed by the guideline development group. The search terms used to identify studies addressing the population of interest (ie.. women with PCOS) were only limited to PCOS terms. Therefore
studies addressing women with PCOS in all cultural, geographical and socioeconomic backgrounds and settings would be identified by the search. The search strategy was limited to English language articles and there were no limits on year of publication. The literature was searched until November 2010.

In keeping with the outlined schedule to update the guideline (page 50), and to reflect recently published evidence on the effectiveness of aromatase inhibitors (Section 7.4) that had potential for significant clinical impact with change in practice, the systematic search for this section was searched until January 2015.

The following electronic databases were employed to identify relevant literature:

- Australasian Medical Index
- CINAHL
- The Cochrane Library
- Cochrane Database of Systematic Reviews (Cochrane Reviews)
- Database of Abstracts of Reviews of Effects (Other Reviews)
- Cochrane Central Register of Controlled Trials (Clinical Trials)
- Cochrane Database of Methodology Reviews (Methods Reviews)
- The Cochrane Methodology Register (Methods Studies)
- Health Technology Assessment Database (Technology Assessments)
- NHS Economic Evaluation Database (Economic Evaluations)
- EMBASE
- EBM Reviews (OVID)
- Medline (OVID)
- Medline in-process and other non-indexed citations (OVID)
- PsycInfo (OVID)

We also searched the bibliographies of relevant studies identified by the search strategy and relevant reviews/meta-analysis for identification of additional studies. Details of the search strategies and search results for each evidence review can be found in the supporting document titled ‘Evidence report’, which can be found at www.managingpcos.org.au/pcos-evidence-based-guidelines.

Where no evidence was found in women with PCOS (in emotional wellbeing evidence reviews), the emotional wellbeing guideline development group requested additional support to help frame their recommendations. The evidence officer for the emotional wellbeing guideline development group undertook an additional search for evidence-based clinical practice guidelines that included recommendations for the following in the general population: assessment of interdisciplinary models of care; assessment of body image; assessment of disordered eating; assessment of psychosexual dysfunction.

The following methodology and inclusion criteria were applied:

- Search known guideline service websites listed below for guidelines relevant to topic area in the general population (not in women with PCOS)
- Guidelines must not be more than 4 years old
- Guidelines must pass the following AGREE benchmark criteria:
  - Systematic methods were used to search for evidence
  - There is an explicit link between the recommendations and the supporting evidence
- The evidence officer provided any guidelines identified in this search to the guideline development group for consideration.
Inclusion of studies

To determine the literature to be assessed further, a reviewer scanned the titles, abstract sections and keywords of every record retrieved by the search strategy. Full articles were retrieved for further assessment if the information given suggested that the study met the inclusion criteria. Studies were selected and appraised by one reviewer in consultation with colleagues, using study selection (according to the PICO) and appraisal criteria established \textit{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.

Classification of included studies

Studies identified from the literature for inclusion in the evidence review were initially classified according to the NHMRC levels of evidence [14]. Classifications for intervention, accuracy and prognosis studies were applicable to the clinical questions in this guideline. The classifications for these types of studies are shown below in Tables 1a, 1b and 1c.

\textbf{Table 1a.} NHMRC levels of evidence for intervention studies (adapted from NHMRC levels of evidence and grades for recommendations for developers of guidelines [14]).

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial</td>
</tr>
</tbody>
</table>
| III-1 | A pseudo-randomised controlled trial  
\hspace{1cm} (ie.. alternate allocation or some other method) |
| III-2 | A comparative study with concurrent controls:  
\hspace{1cm} • Non-randomised, experimental trial  
\hspace{1cm} • Cohort study  
\hspace{1cm} • Case-control study  
\hspace{1cm} • Interrupted time series with a control group |
| III-3 | A comparative study without concurrent controls:  
\hspace{1cm} • Historical control study  
\hspace{1cm} • Two or more single arm studies  
\hspace{1cm} • Interrupted time series without a parallel control group |
| IV    | Case series with either post-test or pre-test/post-test outcomes |
Table 1b. NHMRC levels of evidence for accuracy studies (adapted from NHMRC levels of evidence and grades for recommendations for developers of guidelines [14]).

<table>
<thead>
<tr>
<th>Level</th>
<th>Accuracy studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies.</td>
</tr>
<tr>
<td>II</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation.</td>
</tr>
<tr>
<td>III-1</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation.</td>
</tr>
<tr>
<td>III-2</td>
<td>A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence.</td>
</tr>
<tr>
<td>III-3</td>
<td>Diagnostic case-control study.</td>
</tr>
<tr>
<td>IV</td>
<td>Study of diagnostic yield (no reference standard)</td>
</tr>
</tbody>
</table>

Table 1c. NHMRC levels of evidence for prognosis studies (adapted from NHMRC levels of evidence and grades for recommendations for developers of guidelines [14]).

<table>
<thead>
<tr>
<th>Level</th>
<th>Prognosis studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A systematic review of level II studies.</td>
</tr>
<tr>
<td>II</td>
<td>A prospective cohort study.</td>
</tr>
<tr>
<td>III-1</td>
<td>All or none.</td>
</tr>
<tr>
<td>III-2</td>
<td>Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial.</td>
</tr>
<tr>
<td>III-3</td>
<td>A retrospective cohort study.</td>
</tr>
<tr>
<td>IV</td>
<td>Case series, or cohort study of persons at different stages of disease.</td>
</tr>
</tbody>
</table>

Quality appraisal of the evidence

Methodological quality of the included studies was assessed using criteria developed *a priori* according to study design (ie., quality appraisal criteria used for an RCT is different to that used for a cohort study) [52]. Individual quality items were investigated using a descriptive component approach. Any disagreement or uncertainty was resolved by discussion among the guideline development team to reach a consensus. Using this approach, each study was allocated a risk of bias rating (see Table 2). Quality appraisal and data extraction tables for each evidence review can be found in the supporting document titled ‘Evidence report’, which can be found at www.managingpcos.org.au.
Table 2. Risk of bias ratings [52]

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

Data extraction

Data, according to the selection criteria, was extracted from included studies using a specially developed data extraction form [52]. Information was collected on general details (title, authors, reference/source, country, year of publication, setting), participants (age, sex, inclusion/exclusion criteria, withdrawals/losses to follow-up, subgroups), results (point estimates and measures of variability, frequency counts for dichotomous variables, number of participants, intention-to-treat analysis) and validity results. Quality appraisal and data extraction tables for each evidence review can be found in the supporting document titled ‘Evidence report’, which can be found at www.managingpcos.org.au

Data synthesis

Data was presented in summary form and descriptively, in tables or narratively in the evidence reviews for each clinical question. Where appropriate, meta-analyses were conducted. These can be found in the supporting document titled ‘Evidence report’, which can be found at www.managingpcos.org.au

Formulation of recommendations

Each of the four guideline development groups considered a new evidence review each month and drafted corresponding evidence-based recommendations as outlined in NHMRC levels of evidence and grades for recommendations for developers of guidelines [14].

The body of evidence supporting each recommendation was assessed in an NHMRC Evidence Statement form (Appendix III) and for each of the following components, a grade was assigned: the volume, consistency, generalisability, applicability and clinical impact of the body of evidence (see Table 3).
Table 3. Body of evidence assessment matrix (adapted from NHMRC levels of evidence and grades for recommendations for developers of guidelines [14]).

<table>
<thead>
<tr>
<th>Component</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of evidence</td>
<td>several level I or II studies with low risk of bias</td>
<td>one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias</td>
<td>level III studies with low risk of bias, or level I or II studies with moderate risk of bias</td>
<td>level IV studies, or level I to III studies with high risk of bias</td>
</tr>
<tr>
<td>Consistency</td>
<td>all studies consistent</td>
<td>most studies consistent and inconsistency may be explained</td>
<td>some inconsistency reflecting genuine uncertainty around clinical question</td>
<td>evidence is inconsistent</td>
</tr>
<tr>
<td>Clinical impact</td>
<td>very large</td>
<td>substantial</td>
<td>moderate</td>
<td>slight or restricted</td>
</tr>
<tr>
<td>Generalisability</td>
<td>population/s studied in body of evidence are the same as the target population for the guideline</td>
<td>population/s studied in body of evidence are similar to the target population for the guideline</td>
<td>population/s studied in body of evidence different to target population for guideline but it is clinically sensible to apply this evidence to target population</td>
<td>population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population</td>
</tr>
<tr>
<td>Applicability</td>
<td>directly applicable to Australian healthcare context</td>
<td>applicable to Australian healthcare context with few caveats</td>
<td>probably applicable to Australian healthcare context with some caveats</td>
<td>not applicable to Australian healthcare context</td>
</tr>
</tbody>
</table>

These component grades were then compiled and an overall grade was assigned to the recommendation. The overall grade reflects the strength of the recommendation in terms of trust or confidence practitioners can have in the recommendation when applied in a clinical situation (see Table 4).

Where there was insufficient or no evidence to make an evidence-based recommendation, a clinical consensus or research recommendation was made based on the clinical expertise of the multidisciplinary guideline development group. Where important issues arose from discussion of evidence-based or clinical consensus recommendations, and thus evidence was not sought, clinical practice points have been provided. They are essential tips on how to safely and effectively implement the recommendations. Clinical consensus
recommendations, clinical practice points and research recommendations, which are not based on a body of evidence but rather clinical expertise, are therefore not suitable for grading as outlined in NHMRC levels of evidence and grades for recommendations for developers of guidelines [14]. Instead, a classification has been allocated according to its type of recommendation i.e. a clinical consensus recommendation is classified ‘CR’ and a clinical practice point is classified ‘PP’ (see Table 5).

Table 4. The strength of the recommendations can be identified throughout the guideline with the following grades (from NHMRC levels of evidence and grades for recommendations for developers of guidelines [14]):

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Body of evidence can be trusted to guide practice.</td>
</tr>
<tr>
<td>B</td>
<td>Body of evidence can be trusted to guide practice in most situations.</td>
</tr>
<tr>
<td>C</td>
<td>Body of evidence provides some support for recommendation but care should be taken in its application.</td>
</tr>
<tr>
<td>D</td>
<td>Body of evidence is weak and recommendation must be applied with caution.</td>
</tr>
</tbody>
</table>

Table 5. Classifications of recommendations for which a Grade cannot be applied.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>In the absence of evidence, a clinical consensus recommendation is made by the guideline development group.</td>
</tr>
<tr>
<td>PP</td>
<td>Evidence not sought. A practice point is made by the guideline development group where important issues arose from discussion of evidence-based or clinical consensus recommendations.</td>
</tr>
</tbody>
</table>

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

All recommendations formulated from each evidence review were reviewed three times to ensure consensus among the guideline development group: 1) a first draft recommendation(s) was suggested by the evidence team and sent to the chair for input; 2) a second draft, formulated by the evidence team and the guideline development group chair, was sent to the guideline development group; 3) the second draft of the
recommendation(s) was discussed and revised in the monthly guideline development group meeting; 4) the revised recommendation was revisited and finalised upon consensus using a vote technique within the guideline development group in the following monthly guideline development group meeting.

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 the clinical impact of the resulting recommendation(s), including potential changes in usual care and the way care is organised, organisational barriers and resource implications. Such organisational issues are difficult to quantify without conducting methodologically rigorous assessments of relevant services and resources, therefore the clinical experience of the multidisciplinary guideline development groups was drawn upon for these discussions.

The Project Board, the PCOS Australian Alliance Strategic Advisory Group and the guideline development groups support all 38 recommendations and intend they be used in conjunction with clinical judgement and patient preferences. The guideline development groups acknowledge that lack of evidence is not evidence of lack of effect and have attempted to reflect this in the strength of the grading given to recommendations on interventions that are not supported by evidence. In addition, some interventions were not supported by evidence in the recommendations due to lack of evidence of effect. The guideline development groups acknowledge that this refers to lack of evidence of effect over placebo; that is, patients may receive some beneficial outcomes from the intervention but these do not exceed the beneficial effects that can be expected from a placebo therapy [53].

**Public consultation**

Public and targeted consultation was conducted for a period of 30 days commencing 5th March 2011 in accordance with the legislative requirements set out in section 14A of the *National Health and Medical Research Council Act 1992* as outlined in the NHMRC standards and procedures for externally developed guidelines (2007) [51]. Public consultation was invited via an advertisement in ‘The Australian’ which directed the reader to content on the Jean Hailes for Women’s Health website and a contact phone number.

The organisations approached for targeted consultation were:

- PCOS Australian Alliance Strategic Advisory Group
- PCOS Australian Alliance members
- Polycystic Ovary Syndrome Association of Australia (peak consumer group)
- Australian Indigenous Doctors Association
- Royal Australian College of General Practitioners
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists
- Royal Australasian College of Physicians
- Endocrine Society of Australia
- Fertility Society of Australia
- Androgen Excess and PCOS Society
- CRANA plus (remote area health professionals)
- Australian Nursing Federation
- Dietetics Association of Australia
- Australian Psychological Society
- PCOS UK (Professor Adam Balen)
• Therapeutic Goods Administration
• Australian Government, Department of Health and Ageing, Pharmaceutical Benefits Branch

Details of submissions arising from public consultation and the response of the guideline development groups as well as how the guidelines were altered as a result of their inclusion are available upon request (linda.downes@monash.edu).

In keeping with the outlined schedule to update the guideline (page 50), and to reflect recently published evidence on the effectiveness of aromatase inhibitors (Section 7.4) that had potential for significant clinical impact with change in practice, the evidence review for this section was updated. Public and targeted consultation was invited for a period of 30 days commencing 21st February 2015. Public consultation was invited via an advertisement in 'The Australian' which directed the reader to content on the Monash Centre for Health Research and Implementation website and a contact phone number. Details of submissions arising from public consultation and the response of the guideline development groups as well as how the guidelines were altered as a result of their inclusion are available upon request, email linda.downes@monash.edu.

External review

This guideline has been reviewed by the PCOS Australian Alliance Strategic Advisory Group, and independently by the Australasian Cochrane Centre, relevant professional colleges and societies and through public consultation.

Piloting of the guideline

This guideline has been piloted in a new, rigorously developed, evidence-based PCOS Jean Hailes for Women’s Health Service of Excellence since November 2010. Pre- and post-evaluation of the clinical service by consumers has been completed and notes improvement in QoL, physical and emotional wellbeing, awareness and understanding around PCOS and engagement in lifestyle modification programs. The pilot evaluation of this service is available upon request (linda.downes@monash.edu). The clinicians in the service reported that the draft guideline was a valuable resource which was useful to guide clinical practice.

Evaluation strategy

For an outline of the evaluation strategy, see Translation and implementation.

Scheduled review and update of the guideline

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

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

Challenges in diagnostic assessment of PCOS

There is a lack of awareness of PCOS among consumers and health professionals and 70% of women with PCOS remain undiagnosed [5].

1.1 Hyperandrogenism

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

Clinical need for the question

PCOS is a common hormonal and metabolic disorder affecting 12-21% of Australian women of reproductive age [5]. It is diagnosed based on two of three of menstrual disturbance and clinical/biochemical manifestations of hyperandrogenism and polycystic ovaries on ultrasound after exclusion of other conditions such as thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen-secreting tumours and Cushing’s syndrome [54]. Diagnosis of PCOS is challenging as the presenting symptoms and signs are heterogeneous depending on populations studied, degree of obesity and life stage of the women affected and indeed clinical features may vary over time within an individual woman.

Hyperandrogenism is a well established contributor to PCOS aetiology, detected in around 60–80% of cases, yet it is especially challenging to diagnose. It includes both clinical (hirsutism, central alopecia and acne) and biochemical hyperandrogenism. Clinical hyperandrogenism manifests differently depending on the population studied with Asian populations manifesting few features and South East Asian and Mediterranean populations displaying significant clinical hyperandrogenism. When determining biochemical hyperandrogenism, accurate diagnosis is hampered by a lack of ideal methods for measurement. Androgen assessment in women generally remains controversial. Within these limitations, a direct measure of androgens is testosterone. Calculated bioavailable testosterone and calculated free testosterone can be used interchangeably as a marker of testosterone, and can be derived using various different formulas, however calculated free testosterone is the most commonly measured marker, using the formula of Vermuelen et al. [55]. The FAI (100 x (total testosterone/SHBG)) is also a widely used measure of androgens. To diagnose hyperandrogenism, testosterone assays are widely used, however deficiencies in the accuracy of these assays limit their use in a setting where standardised testosterone measurements that are accurate, reliable and comparable over time are essential [56, 57]. Also, testosterone assays are generally designed for use in males with accuracy at lower androgen levels noted in females being much lower. Given the controversy, methodological challenges and variety of different options for the biochemical measurement of androgens and uncertainty in clinical practice, it is important to determine which measure is the most appropriate.

Evidence to answer the question

Three diagnostic studies (level III-2) with low, moderate and high risk of bias compared the diagnostic accuracy of different reproductive hormone markers in serum to detect PCOS [58-60]. The study with low risk of bias found that calculated bioavailable testosterone was better than androstenedione, SHBG and total
testosterone for diagnosis of PCOS and that the free androgen index (FAI) was better than androstenedione and SHBG for diagnosis of PCOS [59]. The same study also found that calculated free testosterone and total testosterone were better than androstenedione for diagnosis of PCOS.

There is supporting evidence from one medium quality, level III-2 study with a moderate risk of bias that FAI was better than calculated free testosterone for diagnosis of PCOS [58]. However, the authors note that their study did not have the statistical power to detect this small difference.

There was insufficient evidence from one low quality, level III-2 study with a high risk of bias to support any differences between total testosterone, SHBG and androstenedione [60].

A diagnostic study (level III-2) with high risk of bias compared the diagnostic accuracy of gas chromatographic mass spectrometry and radio-immunoassay to detect PCOS using serum reproductive hormone markers [61]. The authors reported that the FAI had a higher area under the receiver operating curve (AUC) than free testosterone, however they acknowledged that their study did not have the statistical power to detect such small differences. No other direct comparisons between techniques were made.

The evidence obtained from the included studies is generalisable to patient population in terms of age and BMI. The studies were conducted in Germany, Spain, Finland and Sweden and may be applied in the Australian setting as the tests addressed in the studies are available and routinely used in Australia.

**Recommendations**

<table>
<thead>
<tr>
<th>CLINICAL CONSENSUS RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1a Late-onset congenital adrenal hyperplasia, although rare, needs to be considered, before the diagnosis of polycystic ovary syndrome is confirmed. In more severe clinical cases of hyperandrogenism, 21-hydroxylase deficiency, the most common form of congenital adrenal hyperplasia can be excluded by measuring serum 17-hydroxyprogesterone in the follicular phase to explore this diagnosis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EVIDENCE-BASED RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1b Calculated bioavailable testosterone, calculated free testosterone or free androgen index should be first line investigation for biochemical determination of hyperandrogenism in polycystic ovary syndrome. The addition of androstenedione and dehydroepiandrosterone sulfate could be second line investigation for biochemical determination of hyperandrogenism in polycystic ovary syndrome.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL PRACTICE POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1c It is difficult to assess androgen status in women on the oral contraceptive pill as effects include oestrogen mediated increases in sex hormone-binding globulin and reduction in androgens. Where the oral contraceptive pill has already been commenced, it should be withdrawn for at least three months before appropriate hormonal assessments for diagnosis of polycystic ovary syndrome are undertaken. Contraception should be otherwise managed during this time.</td>
</tr>
</tbody>
</table>
Clinical impact of the recommendations: Moderate

There are currently no reliable direct assays for free testosterone but laboratories can provide calculated bioavailable testosterone, calculated free testosterone (more commonly provided than bioavailable, however both can be used interchangeably as markers of testosterone), FAI or total testosterone. Additionally, androstenedione and dehydroepiandrosterone sulfate may be used. When biochemical hyperandrogenism (elevated calculated bioavailable or free testosterone or FAI) has been confirmed, serum dehydroepiandrosterone sulfate and androstenedione measurement may be considered as second line investigations to exclude other causes of androgen excess. Dehydroepiandrosterone sulfate is predominantly an adrenal source of circulating androgen. Mild elevation may be seen with PCOS. However, markedly raised dehydroepiandrosterone sulfate in the setting of rapidly progressive virilisation should prompt one to investigate for possible androgen secreting adrenal tumour. Androstenedione is elevated in non-classical congenital adrenal hyperplasia.

Testosterone secretion may be increased during mid-cycle and assessment of androgen status should preferably be measured in the follicular phase in cycling women which can be determined by clinical menstrual history and by measurement of luteinizing hormone, FSH, oestradiol and progesterone. Diurnal variation may also occur [62] and morning levels may be most accurate.

The methodology of testosterone measurement may vary with respect to specificity, but this should be reflected in appropriate reference intervals. Davison et al describes a highly sensitive direct manual radioimmunoassay in the Australian setting that has more optimal accuracy for measuring total testosterone and provides reference values for androgens by age [63]. Automated immunoassay is readily available.

Current practice is unclear, so this recommendation may require changes in usual care. There may be resource implications as the cost of a calculated testosterone test is higher than a testosterone assay. However more limited first line androgen testing may also reduce costs. The field of androgen testing is constantly changing and is likely to keep changing in the future. New automated technology (liquid chromatography-mass spectrometry) is currently being introduced in many laboratories.
1.2 Irregular cycles in adolescents

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

Clinical need for the question

Physiologically, during the first year post-menarche, hormonal responses do not match adult patterns. During the second year, hormonal profiles are similar to control adult women during both phases of the menstrual cycle, although progesterone levels remain low [64].

The average adult menstrual cycle is 28 days, with a normal cycle range of 24 to 35 days [65]. However, during the first few years post-menarche, cycles vary considerably [65-67]. In the first post-menarcheal year, around half of cycles are anovulatory. Nonetheless, 80% of cycles occur within a predictable range of 21 to 45 days and last two to seven days [66-69]. By the third post-menarcheal year, 95% of cycles fall into this range and as such the 5% without regular cycles should be investigated for PCOS.

Regular ovulatory cycles onset are related to age at menarche [70]. In girls who begin menses at <12 years, between 12 and 13 years, and >13 years of age, 50% of cycles are ovulatory by one year, three years, and 4.5 years, respectively [70].

It still remains unclear at what developmental stage irregular cycles in adolescents reflect immaturity of the reproductive system or possible PCOS.

Evidence to answer the question

We did not identify any evidence in our patient population to answer the question and therefore a clinical consensus recommendation has been made informed by the natural history of menstrual cycles and ovulation in adolescents (aged <18 years).

Recommendations

<table>
<thead>
<tr>
<th>CLINICAL CONSENSUS RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2a</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL PRACTICE POINT</th>
</tr>
</thead>
</table>
| 1.2b | If oral contraceptive pill therapy is being considered or has commenced in adolescents (<18 years), the following are recommended:  
- After twelve months of irregular cycles (>35 or <21 days) after onset of menarche, polycystic ovary syndrome should be considered before commencement of the oral contraceptive pill.  
- Where the oral contraceptive pill has already been commenced, when girls are not sexually }
active, if biochemical hyperandrogenism is needed for the diagnosis of polycystic ovary syndrome, the oral contraceptive pill could be withdrawn for three months to facilitate appropriate hormonal assessments. Withdrawal of the oral contraceptive pill may facilitate assessment and early diagnosis of polycystic ovary syndrome as diagnosis can have important implications including optimisation of healthy lifestyle, regular metabolic screening and proactive fertility planning, with consideration of planning for conception at an earlier age. However, the risk of unplanned pregnancy needs to considered and weighed up against potential benefits of early diagnosis. Contraception may still need to be otherwise managed during this time.

Clinical impact of the recommendations: Very large

Irregular cycles (>35 or <21 days) that continue for more than two years after the onset of menarche are likely to reflect oligo-anovulation. Consideration should be given to age of menarche. Current practice is unclear. It is likely that current practice involves prescription of the oral contraceptive pill without diagnosis of PCOS in adolescents. This recommendation may increase referral for diagnostic testing and specialist care, however the benefits of early diagnosis and prevention of associated complications and infertility are likely to result in significant savings. Focus on lifestyle management, rather than medical management, may be increased.

1.3 Polycystic ovaries in adolescents

*In adolescents, what are the most effective criteria to diagnose polycystic ovaries on ultrasound?*

Clinical need for the question

Between the ages of two and nine years, the size and morphology of the ovaries are relatively stable with the volume of each ovary being less than 2 cm³; however from around nine years of age onward, the ovaries undergo progressive increases in size [71]. The number of large antral follicles and ovarian size reaches its maximum around the time of menarche [72, 73] and many girls with regular menstrual patterns may have polycystic ovaries [72]. Recently up to 68% of 19-21 year old Danish women were shown to have polycystic ovaries according to Rotterdam criteria on community based screening [74]. As follicle counts are high at a younger age, this needs to be considered to avoid over diagnosis of PCOS [74]. It seems unlikely that the adult criteria (presence of 12 or more follicles in each ovary measuring 2-9mm in diameter, and/or increased ovarian volume (>10ml)[2]) for diagnosing PCOS according to polycystic ovaries are directly applicable to adolescents. There is continuing discussion as to the quantitative characteristics of a polycystic ovary given increasing resolution of ultrasound.

Evidence to answer the question

One level III-3 case-control study with moderate risk of bias [75] was identified by our search to answer the question and was deemed insufficient evidence on which to base a recommendation. Therefore a clinical
consensus recommendation has been made based on the clinical expertise of the multidisciplinary guideline development group.

Recommendations

**CLINICAL CONSENSUS RECOMMENDATION**

1.3a Given the apparent lack of specificity of polycystic ovaries on ultrasound in adolescents, generally, ultrasound should not be recommended first line in this age group for diagnosis of polycystic ovary syndrome pending further research. If pelvic ultrasounds are to be ordered in adolescents, the results should be interpreted with caution.

**CLINICAL PRACTICE POINT**

1.3b Vaginal ultrasound is not appropriate in adolescents who have not been sexually active.

Clinical impact of the recommendations: Very large

The role of pelvic ultrasound in diagnosing PCOS in adolescents remains unclear. With inadequate evidence about its use for diagnosis of PCOS in adolescents, pelvic ultrasound should be used and interpreted with caution in this age group. Current practice is unclear, however it is anticipated that ultrasound will be less likely to be used for PCOS diagnosis in adolescents. There is a high prevalence of polycystic ovaries in adolescents and normal reference ranges for the age group have not been developed or validated. The guideline development group is not aware of resources implications, except for possible savings on ultrasound testing in adolescents.

**RESEARCH RECOMMENDATION**

Further methodologically rigorous trials are important to determine:

1) Natural history of menstrual cycles in PCOS compared to non-PCOS adolescents
2) Age-appropriate normal ranges for sonographic features of polycystic ovaries and for clinical and biochemical features of PCOS in adolescents (<18 years)
3) Accuracy of ovarian volume to diagnose polycystic ovary syndrome in adolescents (<18 years).

Assessment considerations for Indigenous women

It is acknowledged that the role of ultrasound is more limited and the recommendations may not be applicable in the Indigenous setting due to the limitations in care, access to ultrasound facilities and to service provision in rural and remote locations.
Interdisciplinary model of care in PCOS

Interdisciplinary care involves collaboration between a woman and her care team with shared goals for total wellbeing.

What is the effectiveness of an interdisciplinary model of care compared to usual care in terms of bio-psychosocial wellbeing?

Clinical need for the question

The literature shows a high incidence of psychological issues amongst women with PCOS such as depression, anxiety and eating disorders when compared to the general population. A woman with PCOS may benefit from care from a variety of health professionals to manage the biological, psychological and social issues that may manifest from PCOS. A woman with PCOS may need to see a general practitioner, dietitian, psychologist, exercise physiologist, endocrinologist, gynaecologist and infertility specialist. Although most women with PCOS do not adequately access those disciplines, when they do it is usually via a general practitioner referral to separate multidisciplinary health professionals.

Multidisciplinary team approaches have been used in the management of a number of chronic diseases. A multidisciplinary approach has been credited with improvements in health related behaviours, health parameters and general wellbeing. However there have been a number of criticisms with the multidisciplinary care model, namely the compartmentalisation of patient care and the limited communication between health professionals. As a consequence of these limitations and the need for more patient-centred care, an interdisciplinary model has been developed.

Interdisciplinary care is collaboration between health professionals and patients in addressing health issues with common care goals. Health professionals are responsible for complementary tasks, work interdependently with clear communication pathways and with a clear patient-centric focus. Elements of a successful collaboration include “a willingness to collaborate, trust in each other, mutual respect and communication” [76]. Successful collaboration also relies on adequate systems and organisational supports [77]. Interdisciplinary care has the advantages of providing more efficient and better coordinated care with better use of resources [78]. It also has the advantage of empowering patients in being active participants in their management.

A recent Cochrane review about interdisciplinary care identified the complexities of collaborative management [79]. The review did not show consistent improvements in clinical outcomes, but studies were not of high quality, highlighting both a considerable research gap and the vital need for evaluation strategies in development and implementation of interdisciplinary models of care.

Evidence to answer the question

We did not identify any evidence in women with PCOS to answer the question and therefore a clinical consensus recommendation has been made based on the clinical expertise of the multidisciplinary guideline development group and informed by the literature in other chronic disease areas.
Recommendations

**CLINICAL CONSENSUS RECOMMENDATION**

2.1a Interdisciplinary care, with multiple health professionals involved, should be offered to women with polycystic ovary syndrome, where appropriate based on the chronic and complex nature of the disease.

An interdisciplinary care model is the collaboration between a woman with polycystic ovary syndrome and a care team who have shared goals for her total wellbeing. It should have the following integral components:

- A care team, comprised of representation from varied health disciplines (e.g. may include dietetics, psychology, endocrinology, gynaecology, exercise physiology, general practice)
- A care plan which has been developed and agreed with the woman, and if relevant, the carer
- A designated care coordinator, who oversees the care plan and monitors and evaluates outcomes, which is often the general practitioner
- Clear and regular communication (e.g. information sharing via different forms of media, including internet, letters, case conferencing, email, teleconference)

The complexity of the woman’s need will determine the extent of interdisciplinary care required.

**CLINICAL PRACTICE POINT**

2.1b When referring a woman with polycystic ovary syndrome to other health professionals ie.. psychologists, a resource has been developed ([Appendix IV](#)) to inform the professional about polycystic ovary syndrome.

**RESEARCH RECOMMENDATION**

Further methodologically rigorous trials are important to address implementation and evaluation of interdisciplinary models of care in polycystic ovary syndrome, where an evaluation strategy for a service model needs to be designed from the outset of the interdisciplinary service. Implementation research/evaluation of health service models requires resources.

Clinical impact of the recommendations: Very large

Current management models for women with PCOS are single disciplinary, where a woman sees only one health professional or multidisciplinary where a women may be referred to a number of health professionals who manage a single component of the syndrome. An interdisciplinary care model is the collaboration between different health professionals and the patient. This model of care emphasises the need for shared decision making, mutual respect between all collaborating members of the team and a philosophy and culture of equality between all team members. This requires changes to the current systems of management, both organisational and systemic.

Currently the health system in Australia is not well set up to manage chronic complex diseases in an interdisciplinary model of care. Funding arrangements hinder the establishment of interdisciplinary clinic models especially in ambulatory care settings. Medicare funding to see allied health professionals is capped,
and often women with PCOS need to see multiple health professionals frequently. Although current care plans do facilitate chronic PCOS care, funding models need to be adapted for chronic, complex health problems like PCOS.

Whilst there are organisational changes that need to take place, there is also a need to change the cultural mindset and philosophy of clinicians. The single and multidisciplinary care models have been well established, where clinicians tend to work autonomously. The interdisciplinary model of care requires a considerable change in culture and in health service delivery. Clinicians need to shift to a philosophy of collaboration, trust and respect for all professional competences and recognise complementary skills and knowledge. This may require an education strategy aiming to break down impedance to this model of care.

Interdisciplinary care considerations for Indigenous women

We expect that the above recommendations are applicable to Indigenous women but acknowledge that they may not be applicable in the Indigenous setting due to the limitations in care and service provision in rural and remote locations. It is important to encourage and enable Indigenous women with PCOS to access services that are available.
Assessment of cardiometabolic risk in PCOS

Complications of PCOS such as type 2 diabetes and cardiovascular disease are serious yet largely preventable.

3.1 Risk of cardiovascular disease

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

Clinical need for the question

CVD remains one of the leading causes of death in women in Australia. There is an increased prevalence in metabolic syndrome in women with PCOS [80]. They also have abnormal traditional (hyperinsulinaemia, dyslipidaemia, hypertension) CVD risk factors. Dyslipidemia in PCOS occurs in the setting of abnormal lipid metabolism which may be due to a combination of overproduction of triglyceride-rich lipoproteins and increased catabolism of high density lipoprotein particles [81]. These abnormalities are thought to be a consequence of a global metabolic effect of IR and an excess of both visceral and hepatic fat [81]. Lifestyle interventions improve dyslipidemia [81].

In women with PCOS, other novel CVD risk factors (C-reactive protein [hsCRP], endothelial dysfunction and impaired fibrinolysis) [21, 31, 44, 45, 82-85] and early onset cardiovascular dysfunction (endothelial dysfunction, arterial stiffness, plaques and coronary artery calcification) [44, 45, 83], have been noted and are related to IR and obesity [32, 86, 87]. High androgens and low SHBG have also been linked to increased CVD risk in both pre- and post-menopausal women [88]. Studies to date suggest that women with PCOS have subclinical evidence of premature CVD [84, 89, 90]. Two large epidemiological studies have reported increased prevalence of CVD among women with anovulation [91, 92] but initial poor quality long term studies have not shown an increase in cardiovascular events or cardiovascular mortality with PCOS [84, 93]. However, recently Shaw et al. examined a subset of the Women’s Ischaemia Evaluation Study (WISE) and confirmed increased cardiovascular events and deaths in postmenopausal women with PCOS [35].

As CVD is the biggest killer of Australian women and ~80% is preventable, the public health impact of early identification and targeted prevention in high risk, young, reproductive age women with PCOS is likely to be very significant [94-97], however the best method for assessing cardiovascular risk in women with PCOS remains unclear.

Evidence to answer the question

We did not identify any evidence in women with PCOS to answer the question and therefore clinical consensus recommendations have been made based on the clinical expertise of the multidisciplinary guideline development group, an international position statement on CVD risk assessment in PCOS [17] and national guidelines on absolute CVD risk assessment [98], management of obesity [15], lipids [16, 18] and hypertension [19] for the general population.
## Recommendations

### CLINICAL CONSENSUS RECOMMENDATION - CARDIOVASCULAR RISK

3.1a All women with polycystic ovary syndrome should be assessed for cardiovascular disease risk by assessing individual cardiovascular disease risk factors.

If screening in women with polycystic ovary syndrome shows that any of the following cardiovascular disease risk factors are present, these women with polycystic ovary syndrome should be considered at increased relative risk of cardiovascular disease (obesity, cigarette smoking, dyslipidemia, hypertension, impaired glucose tolerance, lack of physical activity) and those with metabolic syndrome and/or type 2 diabetes, at even greater risk.

### CLINICAL CONSENSUS RECOMMENDATION – WEIGHT & CIGARETTE SMOKING

3.1b All women with polycystic ovary syndrome should be assessed for excess weight at every visit.

In assessing women with polycystic ovary syndrome < 18 years, age appropriate and gender appropriate body mass index should be calculated at every visit.

All women with polycystic ovary syndrome should be assessed for cigarette smoking.

### CLINICAL PRACTICE POINT

3.1c **Body mass index should be assessed in all women with polycystic ovary syndrome using the following criteria [15]:**

- Body mass index <18.5kg/m² = underweight
- Body mass index 18.5 – 24.9kg/m² = lean
- Body mass index ≥ 25.0 – 29.9kg/m² = overweight
- Body mass index ≥ 30.0-34.9kg/m² = obese
- Body mass index ≥ 35kg/m² = morbidly obese

Significant benefits have been demonstrated with 5-10% weight loss in overweight women with polycystic ovary syndrome and is a feasible initial target (see 5.4c).

BMI doesn’t always reflect adverse body fat stores and waist circumference will be useful.

**Waist circumference should be assessed using the following criteria [15]:**

- Waist circumference >80cm = increased risk of metabolic complications
- Waist circumference >88cm = substantially increased risk of metabolic complications

### CLINICAL CONSENSUS RECOMMENDATION - LIPID PROFILE

3.1d A complete lipid profile should be measured every two years in women with polycystic ovary syndrome who have normal lipid profiles.

A complete lipid profile should be measured annually in women with polycystic ovary syndrome who...
have abnormal lipid profiles and/or excess weight.

CLINICAL PRACTICE POINT

3.1e In women with polycystic ovary syndrome, a lipid profile should include:

- **Total cholesterol** - total cholesterol should be <4 mmol/L [16]
- **Low density lipoprotein cholesterol (LDL-C)** - in women without additional cardiovascular disease risk factors, LDL-C levels should be <3.4 mmol/L [17]. In women with metabolic syndrome or type 2 diabetes, LDL-C levels should be < 1.8–2.6 mmol/L or 1.8 mmol/L, respectively [17]
- **High density lipoprotein cholesterol (HDL-C)** - HDL-C levels should be > 1.0 mmol/L [18]
- **Triglycerides** - Triglyceride levels should be < 1.7 mmol/L [17].

CLINICAL CONSENSUS RECOMMENDATION - TYPE 2 DIABETES

3.1f Prediabetes and/or type 2 diabetes should be assessed in all women with polycystic ovary syndrome (see 3.2a and 3.2b).

CLINICAL CONSENSUS RECOMMENDATION - BLOOD PRESSURE

3.1g Blood pressure should be measured annually in women with polycystic ovary syndrome and a body mass index ≤ 25kg/m² (lean).

Blood pressure should be routinely measured at each visit in women with polycystic ovary syndrome and a body mass index ≥ 25kg/m² (overweight/obese).

CLINICAL PRACTICE POINT

3.1h In women with polycystic ovary syndrome who are at high risk of type 2 diabetes, the ideal day time blood pressure should not exceed 135 mmHg systolic and 85 mmHg diastolic [19].

Clinical impact of the recommendations: Very large

All women with PCOS should be assessed for individual CVD risk factors to establish those who are at increased relative risk of CVD. Although the absolute risk of CVD in PCOS appears increased [17], this does require further research. CVD risk is often not considered in women with PCOS, however, women with PCOS have a high prevalence of metabolic abnormalities, high risk of prediabetes and DM2 and increased risk of CVD and therefore CVD risk factors should be routinely monitored. There may be resource implications here as this may result in more frequent ordering of metabolic tests in PCOS. However early detection of increased relative risk of CVD may motivate lifestyle changes, with long term benefits. A shift in cultural mindset to acknowledge the cardiovascular features of PCOS may be required. In some populations, where cardiometabolic and DM2 risk is high, the impact of weight gain appears to be more significant than in Caucasian populations and this needs to be considered when assessing and managing women with PCOS. In these populations consideration should be given to potentially lower BMI limits in high risk ethnic groups.
3.2 Risk of type 2 diabetes

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

Clinical need for the question

IR is a key etiological feature in PCOS, worsening reproductive and metabolic features, DM2 and CVD risk [45, 99, 100]. Obesity, DM2 and CVD are all national health priority areas. IR is present in around 65-80% of women with PCOS, independent of obesity [101] and is further exacerbated by excess weight [102-104]. Women with PCOS have increased risk of gestational diabetes [30] as well as increased risk of DM2 using the Finnish diabetes risk tool [105]. A meta-analysis reported increased risk of impaired glucose tolerance and DM2 in PCOS [21] independent of obesity. Earlier onset hyperglycaemia and rapid progression to DM2 is also reported in PCOS [106, 107]. DM2 risk in women with PCOS is independent of, yet exacerbated by, obesity. PCOS is listed by the International Diabetes Federation as a non-modifiable risk factor for DM2 [108]. Furthermore, DM2 is a major CVD risk factor, with 80% developing CVD. Lifestyle therapy has been shown to prevent or delay progression to DM2. Hence early screening and identification in this high risk group of women with PCOS is vital. Fasting blood glucose level alone has been shown to be inaccurate and results in under-diagnoses of DM2 in PCOS. International groups have recommended screening all women with PCOS with an oral glucose tolerance test [26]. Whilst the high risk of DM2 is recognised in PCOS and screening is important to facilitate effective lifestyle therapy to prevent DM2, the most appropriate measure to assess risks for glucose intolerance and DM2 in women with PCOS remains unclear.

Evidence to answer the question

One low quality systematic review (level I) with high risk of bias was identified by our search [109] that asked the question: How can women with PCOS be identified for Type 2 diabetes screening? The authors found no publications addressing the question and in the absence of evidence, the authors suggest that oligomenorrhoea, along with clinical or biochemical hyperandrogenism, obesity or a family history of risk of DM2 may be indicators of risk of DM2. The systematic review was deemed insufficient evidence on which to base a recommendation. Therefore clinical consensus recommendations have been made based on the systematic review, an international position statement on CVD risk assessment in PCOS [17] and national guidelines for case detection and diagnosis of type 2 diabetes [22].

Recommendations

<table>
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<tr>
<th>CLINICAL CONSENSUS RECOMMENDATION</th>
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<tbody>
<tr>
<td>3.2a To assess for risk of type 2 diabetes, in addition to polycystic ovary syndrome status, the following diabetes risk factors should be considered [20, 21]:</td>
</tr>
<tr>
<td>• Age</td>
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<tr>
<td>• Gender</td>
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<tr>
<td>• Ethnicity</td>
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<tr>
<td>• Parental history of diabetes</td>
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<tr>
<td>• History of high blood glucose levels</td>
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<td>• Use of antihypertensive medications</td>
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</table>
• Smoking
• Physical inactivity
• Waist circumference

CLINICAL CONSENSUS RECOMMENDATION

3.2b An oral glucose tolerance test should be performed every second year in all women with polycystic ovary syndrome and annually in those found to have additional risk factors for developing type 2 diabetes as outlined in 3.2a.

CLINICAL PRACTICE POINT

3.2c Reference ranges for [22]:
- Impaired fasting glucose - fasting plasma glucose: 6.1-6.9 mmol/L
- Impaired glucose tolerance -2 hour glucose level: 7.8-11 mmol/L
- Type 2 diabetes - fasting plasma glucose: ≥7.0 mmol/L or 2 hour oral glucose tolerance test: ≥11.1 mmol/L.

Ideally 150 grams of carbohydrate per day should be consumed for three days before, and women should then fast for 8 hours immediately prior to the oral glucose tolerance test since low carbohydrate intake may lead to false positive glucose tolerance tests.

RESEARCH RECOMMENDATIONS

Further methodologically rigorous trials in women with polycystic ovary syndrome are important to determine:

1) absolute risk of CVD in women with polycystic ovary syndrome across age ranges
2) the most appropriate way of identifying those with polycystic ovary syndrome at highest risk of developing type 2 diabetes and the value of utilising existing scores such as the AUSDiab risk score in women with polycystic ovary syndrome
3) the most effective method to prevent the development of type 2 diabetes.

Clinical impact of the recommendations: Very large

The impact of the significantly increased risk of developing DM2 amongst women with PCOS is very large, representing a significant disease burden and health care cost. Up to 80% of prediabetes will be missed on a fasting glucose test, therefore the guideline development group recommends the use of an oral glucose tolerance test in line with international recommendations [22]. The recommendation to perform an oral glucose tolerance test and not fasting blood glucose alone will result in earlier disease detection (prediabetes and early detection of DM2) and will present opportunities for prevention of DM2 and complications of DM2 and CVD. Early assessment of risk and detection of prediabetes is vital because lifestyle interventions can be commenced which will reduce the risk of developing DM2 as outlined in chapter five. There may be resource implications as screening tests will be ordered more frequently, but earlier detection of risk will facilitate early lifestyle intervention and may result in a reduction of progression.
to DM2 and CVD. It is acknowledged that oral glucose tolerance tests increase inconvenience for patients and may impact on compliance. In some populations where cardiometabolic and DM2 risk is high, the impact of weight gain appears to be more significant than in Caucasian populations and this needs to be considered when assessing and managing women with PCOS. In these populations consideration should be given to potentially lower BMI limits in high risk ethnic groups. It is important to note that assessment of insulin resistance has no current role in clinically assessing for risk of DM2.

Metabolic risk assessment considerations for Indigenous women

CVD and DM2 are major causes of mortality and morbidity in Indigenous women. This is due to a number of causes, including dyslipidaemia, obesity, physical inactivity, poor diet [47] and other non-traditional risk factors including high C-reactive protein, albuminuria and the long-term effects of low birth weight [110-112].

HDL-C has been noted to be low in a number of studies in Indigenous Australians and to be inversely related to triglyceride level, LDL particle size and waist-to-hip ratio, as has been reported in other populations [110, 113, 114]. Further, O’Neal et al. also found for any given level of these factors, the corresponding HDL-C was disproportionately reduced in Indigenous participants compared to non-Indigenous participants [114]. In populations of European origin, women have higher HDL-C than men but Indigenous men and women have similarly low levels of HDL-C [114]. This may be related to the higher insulin levels and IR in the Indigenous women, secondary to high levels of abdominal obesity.

We expect that the above recommendations are applicable to Indigenous women but that the clinical impact may be even more significant in this group of women given the higher underlying burden of risk factors for DM2 and CVD.
CHAPTER FOUR

Assessment of emotional wellbeing in PCOS

Challenges to feminine identity and body image due to obesity, acne and excess hair adversely impact on mood and self efficacy, compromise quality of life and impact on the effectiveness of lifestyle intervention in women with PCOS.

4.1 Depression and/or anxiety

In women with PCOS, what is the most effective tool/method to assess depression and/or anxiety?

Clinical need for the question

Prevalence of depression in women with PCOS is higher (28% - 64%) [11, 115, 116] than for women in the general population (7.1% - 8%) [117, 118]. Prevalence of anxiety in women with PCOS ranges from 34% [119] to 57% [11], yet again higher than in the general population (18%) [117]. Women with PCOS are also likely to experience more severe anxiety and depression [11, 29].

The reasons for higher prevalence and severity of anxiety and depression in women with PCOS are complex with hormonal, metabolic and reproductive features such as increased IR, androgen levels, acne, hirsutism, increased obesity and infertility likely to impact. While acne, hirsutism, infertility and increased BMI have been linked to increased mood and distress, the evidence is inconsistent [11, 119-121]. Further potential contributors to depression and anxiety in PCOS include the chronic [122-126], complex and frustrating nature of PCOS [127, 128].

The higher prevalence and severity of anxiety and depression in PCOS is likely to impact on ability to follow treatment and management plans and overall QoL. Lifestyle interventions are first line treatment for PCOS [129] and small changes to lifestyle are known to decrease weight, improve symptoms, increase ovulation and improve fertility. Yet to undertake lifestyle change requires motivation and self efficacy which are limited by depression and/or anxiety. Recognition of poor emotional wellbeing in PCOS may prompt intervention and improve clinical outcomes in this chronic and common condition. Assessment of depression and/or anxiety in women with PCOS is vital as recognition and treatment improves emotional wellbeing and QoL and is likely to improve effectiveness of lifestyle intervention in PCOS. With the routine need for screening and assessment of depression and/or anxiety in PCOS, effective, readily available tools are needed.

Evidence to answer the question

We did not identify any evidence in women with PCOS to answer the question and therefore a clinical consensus recommendation has been made based on key relevant sources of evidence-based information for the general population and the clinical expertise of the multidisciplinary guideline development group. The guideline development group has consulted the following guidelines:

- The treatment and management of depression in adults with chronic physical health problems, NICE, 2009 [23].
• Depression: the treatment and management of depression in adults, NICE, 2009 [130].
• Beyondblue Depression in Adolescents and Young Adults, Beyond Blue, 2010 [131].
• Anxiety: management of generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults in primary, secondary and community care – partial update, 2011 [132].

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [133] also informed the clinical consensus recommendation.

Recommendation

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<tr>
<th>CLINICAL CONSENSUS RECOMMENDATION</th>
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<tr>
<td>4.1a Depression and/or anxiety should be <em>routinely screened</em> and assessed by all appropriately qualified health professionals in women with polycystic ovary syndrome.</td>
</tr>
<tr>
<td>If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for depression and/or anxiety.</td>
</tr>
<tr>
<td>If depression and/or anxiety are detected, appropriate management should be offered.</td>
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<tr>
<th>CLINICAL PRACTICE POINT</th>
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<tbody>
<tr>
<td>4.1b To screen for depression and/or anxiety, the following questions could be asked [23]:</td>
</tr>
<tr>
<td>1) During the last month, have you often been bothered by feeling down, depressed, or hopeless?</td>
</tr>
<tr>
<td>2) During the last month, have you often been bothered by having little interest or pleasure in doing things?</td>
</tr>
<tr>
<td>3) During the last month, have you been bothered by feeling excessively worried or concerned?</td>
</tr>
</tbody>
</table>

If any of the screening questions are positive further depression and/or anxiety assessment could be by either:

a) Referring the patient to an appropriate professional if they do not feel competent to perform a further mental health assessment. If the health professional is not the patient’s usual GP, inform the GP of the referral.

b) If they feel competent, perform a clinical interview and according to level of competence, choose from one or more of the following:
   - Kessler Psychological Distress Scale 10 (K-10)
   - Depression Anxiety Stress Scale (DASS-21)
   - Patient Health Questionnaire (PHQ9)
   - Generalised Anxiety Disorder 7 item scale (GAD7).
Clinical impact of the recommendation: Very large

It is not usual practice to screen women with PCOS for depression and/or anxiety and doing so may identify affected patients who would otherwise be missed. Screening may have resource implications such as an impact on length of consultation, however this can be reduced by the use of the PCOS emotional wellbeing general screening tool (Appendix V) and other tools recommended here. If depression and/or anxiety are detected, intervention may require referral to other health practitioners. Additional time with the patient may also be required to complete a Mental Health Plan. It is important to note that all tools recommended are free to use in clinical practice, research and education. Access to appropriately trained and experienced health professionals will be required. It is the responsibility of all health professionals to understand the impact of PCOS on psychological health and to screen for and manage these disorders.

4.2 Body image

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

Clinical need for the question

Body image is complex and is influenced by many factors. For the purpose of this clinical question, body image is defined as the way a person may feel, think and view their body including their appearance. Physical factors affecting appearance (excess weight and hirsutism), psychological factors (self-esteem) and sociocultural influences all appear to influence the way women think and feel about their bodies. Body image includes attitudes to physical appearance, understanding of health, physical fitness and body size, the mental picture that individuals form of their bodies, values and self-esteem. Assessment of body image includes measures of body dissatisfaction and disordered eating [134], body size estimation [135] and weight [136, 137].

Two thirds of women from the general population are dissatisfied with their body, yet negative body image is more prevalent in PCOS and impacts on thoughts and feelings of health, appearance, QoL, mood and physical fitness. A recent study demonstrated that women with PCOS, compared with control women, had a greater negative body image in 7 out of 10 subscales of the validated Multidimensional Body-Self Relations Questionnaire [28]. Women with PCOS appear to feel less physically attractive, healthy or physically fit and are less satisfied with their body size and appearance than women without PCOS [138] and this negative body image predicts both depression and anxiety [139]. PCOS features, in particular hirsutism and increased weight, appear to impact negatively on body image and QoL [139, 140] and negative body image [141] is associated with depression in women with PCOS, even after controlling for weight [29].

Given that negative body image in PCOS may result in increased depression and poorer health-related QoL, body image of women with PCOS should be considered as part of a comprehensive assessment and management plan. Recommendations for screening and assessment that are easy to use and widely applicable are needed in PCOS. If identified, addressing negative body and associated mood disorders is important to improve emotional wellbeing and QoL in PCOS.

Evidence to answer the question

We did not identify any evidence in women with PCOS to answer the question and therefore a clinical consensus recommendation has been made based on key relevant sources of evidence-based information.
for the general population and the clinical expertise of the multidisciplinary guideline development group. The guideline development group has consulted the following guidelines:

- NICE Guideline 31 – Obsessive Compulsive Disorder: Core interventions in the treatment of obsessive compulsive disorder and body dysmorphic disorder [142].

Recommendation

<table>
<thead>
<tr>
<th>CLINICAL CONSENSUS RECOMMENDATION</th>
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<tbody>
<tr>
<td>4.2a Negative body image should be considered in women with polycystic ovary syndrome.</td>
</tr>
<tr>
<td>If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for negative body image.</td>
</tr>
<tr>
<td>If negative body image is detected, appropriate management should be offered.</td>
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<tr>
<th>CLINICAL PRACTICE POINT</th>
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<tbody>
<tr>
<td>4.2b To screen for negative body image, the following questions could be asked:</td>
</tr>
<tr>
<td>1) Do you worry a lot about the way you look and wish you could think about it less?</td>
</tr>
<tr>
<td>2) On a typical day, do you spend more than 1 hour per day worrying about your appearance? (More than 1 hour a day is considered excessive)</td>
</tr>
<tr>
<td>3) What specific concerns do you have about your appearance?</td>
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<tr>
<td>4) What effect does it have on your life?</td>
</tr>
<tr>
<td>5) Does it make it hard to do your work or be with your friends and family?</td>
</tr>
<tr>
<td>If an issue is identified, the practitioner could further assess negative body image by:</td>
</tr>
<tr>
<td>a) Identifying any focus of concern of the patient and respond appropriately</td>
</tr>
<tr>
<td>b) Assessing the level of depression and/or anxiety (if they have not done so already) (see 4.1a)</td>
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<tr>
<td>c) Identifying if there is any distortion of body image (e.g. presence of anorexia nervosa (see 4.3) or body dysmorphic disorder)</td>
</tr>
</tbody>
</table>

Clinical impact of the recommendation: Moderate

Negative body image is more prevalent in women with PCOS and is related to depression and reduced QoL, hence it is important and highly recommended that women with PCOS are screened and assessed for negative body image. It is not usual practice to screen women with PCOS for negative body image and doing so may identify affected patients who would otherwise be missed. 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. Screening may have resource implications in terms of impact on length of consultation, however this can be reduced by the use of the emotional wellbeing general screening tool (Appendix V) and
other tools recommended here. Intervention may require referral to other health practitioners. Where needed, access to appropriately trained and experienced health professionals is required. A shift in cultural mindset may be required to ensure the clinical impact of negative body image is understood.

4.3 Disordered eating

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

Clinical need for the question

Australian research [144] suggests that prevalence of diagnosable eating disorders is increasing with ~0.2% of women reporting anorexia nervosa, 1.1% bulimia nervosa, 2.6% binge eating disorder. The prevalence of disordered eating is likely to be higher with 7.5% of women noted binge eating, 2.1% purging, and 5.2% strict dieting or fasting. Disordered eating refers to eating and weight related symptoms and can include behavioural (e.g. bingeing, excessive restriction), cognitive (e.g. excessive dietary restraint, negative body image) and emotional factors. Disordered eating affects health and wellbeing and capacity to participate in and contribute to society. The consequences of eating disorders encompass medical, psychological, social and occupational difficulties [144, 145]. Eating disorders are also often linked with other psychiatric illness, particularly mood and anxiety disorders [145].

There is a lack of good prevalence data on eating disorders in women with PCOS [146, 147], with links between PCOS and bulimia nervosa [148, 149] and abnormal eating behaviour [148, 150, 151]. The prevalence of any eating disorder has been reported at 21% in PCOS [152]. This study also reported significant mood disturbances among women with PCOS and an eating disorder; 62% had major depression and 41% anxiety disorders.

Proposed mechanisms linking PCOS and eating disorders include hormonal links as well as the impact of PCOS on self-esteem and body image [153, 154]. Women with PCOS have higher prevalence of risk factors for eating disorders including excess weight, depression, anxiety, low self-esteem and poor body image [145]. There may also be more motivation for weight loss and prescribed and self-imposed dietary restriction in women with PCOS.

Available research suggests that fewer than half of patients with clinically significant eating disorders are identified in primary care, potentially related to ambivalence, secrecy and shame or health practitioner’s knowledge, attitudes and skills. Health practitioners are well placed to identify these problems and high-risk groups are often routinely screened for the presence of eating disorders. The NICE guidelines recommend initially screening using simple clinical questions and these have informed the recommendations below [154]. Once identified a range of more detailed assessment tools is available. Effective assessment is important as it should increase recognition and management of eating disorders and disordered eating, thereby improving the psychological functioning and overall QoL in women with PCOS and reduce health risks associated with disordered eating.

Evidence to answer the question

We did not identify any evidence in women with PCOS to answer the question and therefore a clinical consensus recommendation has been made based on key relevant sources of evidence-based information for the general population and the clinical expertise of the multidisciplinary guideline development group.
### Recommendation

<table>
<thead>
<tr>
<th><strong>CLINICAL CONSENSUS RECOMMENDATION</strong></th>
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</table>
| **4.3a** | Disordered eating, including eating disorders, should be considered in women with polycystic ovary syndrome.  
If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for disordered eating and eating disorders.  
If disordered eating, or an eating disorder is detected, appropriate management should be offered. |

<table>
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<tr>
<th><strong>CLINICAL PRACTICE POINT</strong></th>
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| **4.3b** | To screen for disordered eating and eating disorders, the following questions could be asked:  
1) Do you worry you have lost control over your eating?  
2) Do you ever feel disgusted, depressed, or guilty about eating?  
3) Have you tried fasting or skipping meals in an attempt to lose weight?  
4) Have you tried vomiting, laxatives or diuretics in an attempt to lose weight?  
5) Have you had significant (e.g. >5-7%), recurrent fluctuation in body weight?  
If a woman with polycystic ovary syndrome answers yes to any of the above questions the practitioner should further assess for the diagnosis of an eating disorder by either:  
 a) Referring the patient to an appropriate professional to perform a further mental health assessment.  
b) If the practitioner feels competent, performing a clinical interview which may be supplemented with standardised assessment tools (e.g. Eating Assessment Tool (EAT 26) [www.eat-26.com](http://www.eat-26.com)).  
c) Assessing the level of depression and/or anxiety (see 4.1a). |

**Clinical impact of the recommendation: Very large**

As eating disorders are more common in PCOS, screening should be considered. It is not usual practice to screen women with PCOS for disordered eating. It is likely that improved screening practices will improve the identification of disordered eating/eating disorders and that this will increase treatment. However, given that women with eating disorders have increased health service utilisation for weight management and general psychopathology, appropriate treatment may shift, or reduce, rather than increase health service utilisation. Effective treatment is available for the management of disordered eating/eating disorders [155-158]. Screening may have resource implications as appropriate disordered eating assessment will require longer consultation times, however this can be reduced by the use of the emotional wellbeing general screening tool ([Appendix V](#)) and other tools recommended here. It is important to note that the Eating Assessment Tool (EAT 26) requires some minor adaptation (metric measurements for height and weight) for use in the Australian setting. Increased detection of disordered eating will result in increased referrals to other health professionals. Access to appropriately trained and experienced health professionals will be
required. A shift in cultural mindset may be required to ensure the clinical impact of eating disorders is understood.

4.4 Psychosexual dysfunction

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

Clinical need for the question

Psychosexual dysfunction refers to sexual problems or difficulties that have a psychological origin based in cognitions and/or emotions such as depression, low self-esteem and negative body image [159]. It appears that women with PCOS suffer from greater psychosexual dysfunction than women in the general population [160]. Whilst there is limited quality research in this area, studies [120, 160, 161] do show a correlation between PCOS and reduced QoL, sexual satisfaction and feminine identity.

Physical PCOS symptoms such as hirsutism, obesity, menstrual irregularity and infertility may cause loss of feminine identity and a feeling of being unattractive which may impact on sexuality [120, 160, 162]. Women with PCOS also report less sexual satisfaction and lower sexual self-worth than women without PCOS and sexual dysfunction impacts more on relationships in women with PCOS [163].

Overall, psychosexual dysfunction appears to be more common in women with PCOS, may be an important issue for the individual woman and is likely to impact on QoL and relationships. Hence clinicians should be aware of potential psychosexual dysfunction in PCOS and screening and assessment should be considered. In this setting guidance on the most effective way to assess psychosexual dysfunction is needed.

Evidence to answer the question

We did not identify any evidence in women with PCOS to answer the question and therefore a clinical consensus recommendation has been made based on key relevant sources of evidence-based information for the general population and the clinical expertise of the multidisciplinary guideline development group.

Recommendation

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>4.4a Psychosexual dysfunction should be <em>considered</em> in women with polycystic ovary syndrome.</td>
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<tr>
<td>If a woman with polycystic ovary syndrome is positive on screening, the practitioner should further assess for psychosexual dysfunction.</td>
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<tr>
<td>If psychosexual dysfunction is detected, appropriate management should be offered.</td>
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<tr>
<td>4.4b To screen for psychosexual dysfunction, the following questions could be asked:</td>
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<tr>
<td>1) During the last few months, have you often been bothered by problems with your sex life such as reduced satisfaction, diminished desire, pain, or any other problems?</td>
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2) Do you feel that polycystic ovary syndrome affects your sex life?
3) (If relevant) Do sexual problems affect your current relationship and/or have sexual problems affected your past relationships?

If a woman with polycystic ovary syndrome answers yes to any of the above questions or where sexual function is a concern, the practitioner should assess this through more detailed clinical interview, and in particular screen for depression and/or anxiety if not already done (see 4.1) and negative body image (see 4.2) or refer to a more appropriately qualified health practitioner.

Specific validated scales could be used as outcome measures at baseline to monitor progress over time. The choice of scale should be selected by the discretion of the clinician, based on the specific sexual problem, accessibility and expertise of the practitioner.

Clinical impact of recommendation: Moderate

As prevalence and severity of psychosexual dysfunction is increased in women with PCOS, screening and assessment should be considered in sexually active women facilitating appropriate intervention aiming to optimise sexual function, limit the social impact of PCOS and improve QoL. It is not usual practice to screen and assess women with PCOS for psychosexual dysfunction and screening for psychosexual dysfunction may pick up affected patients who would otherwise be missed. Screening may have resource implications such as an impact on length of consultation and intervention may require referral to other specialist health professionals. The guideline development group is not aware of barriers to implementation of these recommendations.

Emotional wellbeing assessment considerations for Indigenous women

The leading cause of burden of disease in Indigenous women in the National and Torres Strait Islander Health Survey was anxiety and depression, accounting for 10% of the burden [48]. Little is known about the prevalence of eating disorders and disordered eating in Indigenous women. We expect that the above recommendations are applicable to Indigenous women but acknowledge that they may not be applicable in the Indigenous setting due to the limitations in care and service provision in rural and remote locations. We also acknowledge that social and cultural factors influence emotional wellbeing and that the challenges facing many Indigenous women are likely to amplify the impact of PCOS on emotional wellbeing. Further research in this area is needed.

RESEARCH RECOMMENDATIONS

Further methodologically rigorous trials in women with polycystic ovary syndrome are important to determine the most effective tool to assess and optimal approaches to manage:

- Depression and/or anxiety
- Psychosexual dysfunction
- Eating disorders and disordered eating
- Negative body image
- Overall health related quality of life

This body of research should consider emotional wellbeing across the different cultural and age groups affected by PCOS.
CHAPTER FIVE

Lifestyle management in PCOS

As weight gain increases, the potent combination of obesity and PCOS is adversely affecting health in up to 1 in 5 young Australian women, presenting a major public health challenge which needs addressing to limit adverse health outcomes.

5.1 Effectiveness of lifestyle interventions

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

Clinical need for the question

The aetiology of PCOS is unknown although abnormalities in steroidogenesis, gonadotrophin action and IR are proposed as significant aetiological factors. Of these, IR is present in a high proportion of lean and overweight women with PCOS [101, 164] and increases free androgens via insulin stimulated ovarian androgen production [165] and decreased hepatic production of SHBG [166]. Women with PCOS who are relatively more insulin resistant also present with worsened reproductive and metabolic features compared to women with PCOS who are relatively more insulin sensitive [101]. IR is inherent in PCOS but is also further exacerbated by excess weight [102]. Excess weight increases the prevalence and severity of PCOS including reproductive [103, 104], psychological and metabolic features [32, 86]. Where the features of PCOS are worsened by obesity, weight loss or prevention of excess weight gain reduce the contribution of obesity to the features of PCOS.

Treatment of PCOS aims to improve biochemical and clinical hyperandrogenism, reproductive function, psychological features and metabolic (diabetic and cardiovascular) outcomes. Where the clinical features of PCOS are worsened by IR or obesity, lifestyle (diet, exercise and/or behavioural) interventions to reduce weight or IR are preferable and cost-effective [167, 168] compared to surgical and pharmacological options. There is a large number of small, uncontrolled trials demonstrating that weight loss achieved through lifestyle management decreases abdominal fat, hyperandrogenism and IR, and improves lipid profiles, menstrual cyclicity, fertility, risk factors for DM2 and CVD and psychological health in women with PCOS who are overweight [167, 169-171]. Lifestyle management is also useful in preventing excess weight gain, especially relevant as women with PCOS appear to have an increased rate of weight gain and higher weight than the general population [172, 173]. As such, weight loss, weight management and lifestyle management may be feasible treatment options for a large proportion of women with PCOS. Lifestyle management may also improve PCOS independent of weight loss, with exercise intervention improving metabolic risk factors associated with PCOS, including hypertension, IR and elevated blood glucose, even when no weight loss occurs [174-176]. It is difficult to be certain about the effectiveness of lifestyle interventions in women with PCOS based on small uncontrolled trials addressing different outcomes in different subgroups of women with PCOS.
Evidence to answer the question

One high quality systematic review (level I) with a low risk of bias was identified to answer this question. The systematic review appraised six randomised controlled trials (RCTs) (low to moderate quality and moderate to high risk of bias) for the effectiveness of lifestyle treatment compared to minimal treatment in improving reproductive, metabolic, anthropometric and QoL factors in women with PCOS [177]. Due to the inconsistencies and methodological weaknesses of included studies, caution is recommended when interpreting the combined meta-analyses and results of the systematic review. There were three studies that used exercise and three that used combined lifestyle modification programmes (including diet, exercise and behaviour), with the outcome measurements reported at various times (12, 16, 24, and 48 weeks). None of the studies addressed fertility outcomes. Lifestyle intervention was better than minimal treatment for total testosterone (mean difference (MD) -0.27 nmol/L [-0.46 to -0.09] p=0.004), hirsutism by Ferriman-Galwey score (MD -1.19 [-2.35 to -0.03] p=0.04), weight (MD -3.47 kg [-4.94 to -2.00] p<0.00001), waist circumference (MD -1.95 cm [-3.34 to -0.57] p=0.006), waist-hip ratio (MD -0.04 [-0.07 to -0.00] p=0.02), fasting insulin (MD -2.02 µU/mL [-3.28 to -0.77] p=0.002) and oral glucose tolerance test insulin (standardised mean difference -1.32 [-1.73 to -0.92] p<0.00001) and percent weight change (MD -7.00% [-10.1 to -3.90] p<0.00001). There was no difference between the two interventions for BMI, FAI, SHBG, glucose or lipids. QoL, patient satisfaction and acne were not reported.

Recommendations

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<th>EVIDENCE-BASED RECOMMENDATION</th>
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<td>5.1a</td>
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<th>RESEARCH RECOMMENDATION</th>
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<tr>
<td>Further methodologically rigorous trials in women with polycystic ovary syndrome are important to address:</td>
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<tr>
<td>1) The extent of the benefits of lifestyle management compared to no or minimal therapy for all clinically relevant outcomes</td>
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<tr>
<td>2) Comparing efficacy of different types of lifestyle management (diet alone, exercise alone, behavioural modification alone, or combinations of the three)</td>
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<td>3) The effect of lifestyle management in prevention of weight gain/weight maintenance compared to weight loss</td>
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<tr>
<td>4) The effect of lifestyle management for women who are both overweight and not overweight and specific reproductive outcomes such as menstrual regularity, ovulation and fertility and the relative efficacy of lifestyle management either compared to or in combination with pharmacological therapy.</td>
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</table>

Clinical impact of the recommendations: Moderate

Given the high prevalence and important adverse impact of excess weight in PCOS as well as the efficacy of lifestyle intervention in improving outcomes, lifestyle management is important in PCOS. It is likely that the
recommendation will reduce variation in practice and ensure lifestyle advice is prescribed to all women with PCOS, targeting prevention of weight gain and promoting weight loss, where appropriate. The recommendation may result in increased consultation times, increased utilisation of care plans and increased referral to allied health professionals and as such, higher associated healthcare costs, however long term benefits of lifestyle change are anticipated to reduce the health and economic burden of PCOS. Barriers to implementation of these recommendations include the engagement of health practitioners, access to allied health professionals and financial barriers. Insufficient consultation time allocated by general practitioners and other health professionals may also be a barrier and a shift in cultural mindset may be required to focus on lifestyle interventions especially around prevention of weight gain which is not traditionally a focus of health professionals. In high risk populations where cardiometabolic and DM2 risk is increased, the impact of weight gain appears to be more significant than in Caucasian populations and this needs to be considered when assessing and managing women with PCOS.

5.2 Optimal components of lifestyle interventions

In women with PCOS, what is the effectiveness of diet compared to exercise for improving weight loss, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

With the high prevalence of PCOS likely to increase secondary to increasing rates of obesity, identifying key components of successful lifestyle interventions, particularly dietary modifications and exercise, has the potential to effectively treat symptoms and to reduce the risk of longer-term complications including DM2, CVD and infertility in women with PCOS.

As recommended above, lifestyle management including diet, exercise and weight loss is recommended as the first line of treatment for women with PCOS and should precede and/or accompany pharmacological treatment [177]. In women with PCOS and excess weight, a reduction of as little as 5% of total body weight has been shown to reduce insulin levels, improve menstrual function, reduce testosterone levels, improve hirsutism and acne, improve ovulation and fertility and improve psychological outcomes [167, 169-171, 178-196]. However, despite these benefits, there are no specific dietary or exercise recommendations for women with PCOS and few studies have compared the effectiveness of diet or exercise in PCOS management. The literature on interventions for promoting changes in lifestyle in adults at risk of DM2 shows that interventions which target both exercise and diet are most successful, yet lifestyle interventions have low engagement and adherence rates and it is clear that more research is needed to identify key successful components.

Evidence to answer the question

One low quality non-randomised controlled trial (level III-2) with a high risk of bias investigated the changes in anthropometric, fertility, non-fertility, metabolic, QoL, and adverse events by comparing a structured exercise training (SET) programme to a low caloric, high protein diet in women with PCOS [197]. SET was better than diet for increased menses frequency (SET: 28 observed menses/107 expected cycles (26.2%), hypocaloric hyperproteic diet group (HCHP): 18 observed menses/118 expected cycles (15.3%), p=0.043),
increased ovulation rate (SET: 28 ovulatory cycles/113 observed cycles (24.8%), HCHP: 18 ovulatory cycles/119 observed cycles (15.1%), p=0.032) and increased cumulative ovulation rate (SET: 13 ovulatory patients/20 patients (65.0%), HCHP: 5 ovulatory patients/20 patients (25.0%), p=0.011). In the SET group, there were thirteen ovulatory women, compared to the diet group of just three ovulatory women. There was no difference between the interventions for anthropometric, metabolic, non-fertility or QoL outcomes, however upon subgroup analysis in women who were ovulatory, SET was better than diet for fasting insulin (SET: -23.4 ± 10.0, HCHP: -13.1 ± 8.6, p<0.05), fasting glucose-to-insulin ratio (SET: 37.5 ± 19.6, HCHP: 19.0 ± 10.1, p<0.05), homeostasis model of assessment-insulin resistance (HOMA-IR) (SET: -41.0 ± 15.9, HCHP: -9.1 ± 4.1, p<0.05), SHBG (SET: 82.5 ± 30.6, HCHP: 41.9 ± 19.1, p<0.05) and FAI (SET: -27.2 ± 9.2, HCHP: -18.1 ± 9.7, p<0.05). Diet was better than SET for weight (SET: -5.6 ± 1.6, HCHP: -10.5 ± 4.1, p<0.05) and BMI (SET: 10.0 ± 3.7, HCHP: -15.4 ± 3.9, p<0.05). The evidence from the included study is directly generalisable to the patient population of women with PCOS, particularly to women who have BMI ≥33 kg/m².

There may be limitations to generalising these findings to other ethnic groups, especially to non-European populations. The usability of the evidence is limited to the particular exercise (bicycling) and diet (high protein, low carbohydrate) interventions used in this study.

Recommendation

<table>
<thead>
<tr>
<th>EVIDENCE-BASED RECOMMENDATIONS</th>
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<tr>
<td>5.2a Lifestyle management targeting weight loss (in women with a body mass index ≥25kg/m² (overweight)) and prevention of weight gain (in women with a body mass index ≤25kg/m² (lean)) should include both reduced dietary energy (caloric) intake and exercise and should be first line therapy for all women with polycystic ovary syndrome.</td>
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<tr>
<th>CLINICAL PRACTICE POINT</th>
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<tr>
<td>5.2b Psychological factors should be considered and managed to optimise engagement and adherence with lifestyle interventions.</td>
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</table>

Clinical impact of the recommendation: Moderate

PCOS is integrally linked to excess weight, and lifestyle interventions improve outcomes. Successful lifestyle components, including diet and exercise, separately and in combination, in both the general population and in PCOS, have significant health benefits. Hence the recommendation to combine diet and exercise approaches was made. It is acknowledged that there may be changes to usual care and the way care is organised and there are potentially greater barriers to integration of exercise in lifestyle interventions in young women. However it is expected that the cost of lifestyle interventions will be less than the cost of pharmacological intervention.
5.3 Dietary interventions

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

Clinical need for the question

If a woman with PCOS is overweight, lifestyle therapy should be first line, as recommended above, as weight loss improves reproductive, metabolic and psychological features of PCOS [129]. With regards to the recommendations for obesity management in the general population on dietary components of lifestyle interventions, a low-fat high fibre (~30% of energy, saturated fat ~10%, <300 mg cholesterol daily), moderate protein (~15%) and high carbohydrate diet (~55%) in conjunction with moderate regular exercise is recommended for the management of obesity and related co-morbidities [15, 198, 199]. An area of increasing focus in PCOS is the macronutrient composition of the dietary component of a lifestyle intervention. Specific dietary approaches (including modifying the amount of type of dietary carbohydrate, protein or fat) are proposed to have either more favourable hormonal or metabolic effects or be more effective in achieving and sustaining long-term weight loss. Systematic reviews in the general population report similar or less weight loss and compliance for a low fat diet compared to other approaches [200, 201] whilst a large RCT reported similar changes in weight for a range of reduced energy diets with different macronutrient content over two years [202]. It appears that the calorific (energy) restriction per se, rather than macronutrient composition, is effective for weight loss and clinical benefits. However, there is limited research assessing the effect of modifying dietary macronutrients in women with PCOS.

Evidence to answer the question

Six articles reporting five RCTs were identified to answer this question. Two articles [170, 203] report different outcomes of the same study and therefore have been reported together. Three RCTs had a moderate risk of bias [170, 182, 193, 203] and two had a high risk of bias [204, 205]. The studies compared various macronutrient dietary compositions, including low carbohydrate, low glycaemic index, monounsaturated fatty acid-enriched, conventional healthy diet, high protein, carbohydrate-counting, or fat-counting dietary approaches. There was no difference for the majority of the anthropometric, metabolic, fertility, non-fertility, QoL and emotional wellbeing outcomes, however, regardless of the type of diet, the overall finding was that a diet aimed at reducing weight was of benefit to women with PCOS. The evidence from the included studies is directly generalisable to the patient population of women with PCOS, particularly to women >30 years of age and who have BMI ≥30kg/m². However, the majority of the women studied were European Caucasian, so there may be limitations to generalizing these findings to other ethnic groups.

Recommendations

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<tr>
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<tr>
<td><strong>5.3a</strong> Weight loss should be targeted in all women with polycystic ovary syndrome and body mass index ≥25kg/m² (overweight) through reducing dietary energy (caloric) intake in the setting of healthy food choices, irrespective of diet composition.</td>
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</table>
5.3b Prevention of weight gain should be targeted in all women with polycystic ovary syndrome through monitored caloric intake, in the setting of healthy food choices, irrespective of diet composition.

**CLINICAL PRACTICE POINT**

5.3c Weight loss (in women with a body mass index ≥25kg/m² (overweight)) and prevention of weight gain (in women with a body mass index ≤25kg/m² (lean)) is the joint responsibility of all health professionals, partnering with women with polycystic ovary syndrome. Where complex dietary issues arise (or obesity is present), referral to a dietitian should be considered as part of an enhanced primary care plan.

Tools such as *Lifescrpts* could be used for engagement in dietary change: [www.health.gov.au/lifescrpts](http://www.health.gov.au/lifescrpts)

**RESEARCH RECOMMENDATION**

Further methodologically rigorous trials in women with polycystic ovary syndrome are important to address:

1) A range of diet compositions including low glycaemic index for both prevention of weight gain/weight maintenance and weight loss in women who are overweight and in women who are lean
2) Monitoring of safety and harms of diets and longer follow-up
3) Increasing engagement and compliance with intervention studies.

Clinical impact of the recommendations: Moderate

Healthy food choices, irrespective of diet composition, are recommended in overweight and obese women (BMI ≥25kg/m²) with PCOS for weight loss and in lean women (BMI ≤25kg/m²) with PCOS, for prevention of weight gain. Based on the presumption that most practitioners are not recommending a specific dietary composition about diet due to time restriction, there may not be changes to usual care. However consumer targeted evidence about PCOS purports the use of specific macronutrient composition in PCOS and a shift in mindset to ensure consumers understand the lack of evidence to support these approaches and the need for more research is important. The guideline development group is not aware of resource implications, changes to the way care is organised or barriers to implementation of these recommendations.

Diet management considerations for Indigenous women

The largest differences in the contribution of risk factors for disease burden between Indigenous and non-Indigenous Australians includes low fruit and vegetable intake [47]. There is a low intake of these substances and the replacement foods are often high in saturated fat and refined carbohydrates. There are many reasons why diet quality is poor for many Indigenous people; certainly the high cost of fresh fruit and vegetables compared to processed foods rich in saturated fat, sugars and salt plays a significant role in food choices in remote communities [206]. Programmes are in place to try and address these issues but in the
short term, combined with lack of access to services in rural and remote areas, implementation of the dietary recommendations may be difficult in some settings.

5.4 Delivery of dietary interventions

_In women with PCOS, what is the most effective method to deliver dietary information for improving weight loss, quality of life and emotional wellbeing outcomes?_

Clinical need for the question

Despite weight loss being first line treatment in PCOS, there are few comparative studies on the most effective method to deliver diet and lifestyle information to improve weight loss in PCOS. Motivational interviewing and established behaviour techniques appear more effective than traditional advice-giving for changes in weight, diet and/or exercise [207]. Providing instruction, establishing self-monitoring (including pedometer use), time management techniques, incorporation of relapse prevention techniques, individual tailoring, engaging social support and setting goals have all been shown to be useful. Individual, group, and mixed interventions have been shown to be effective [208-210]. Also, a wide range of providers (with appropriate training) including doctors, nurses, dietitians, nutritionists, exercise specialists, can deliver effective interventions for changing diet and/or exercise [209-212].

Greater intensity, behaviour change techniques, contact time and duration generate significantly more weight loss [213]. The impact of intervention setting on effectiveness remains unclear, although evidence suggests that there is no difference in outcomes (either dietary or exercise change) between interventions in primary care, community and workplace settings.

Overall interventions to promote changes in diet and/or exercise in adults with increased risk of DM2 or CVD are more likely to be effective if they combine intensive lifestyle interventions and sustainable behaviour change methods. However the interventions to optimise engagement, adherence and successful outcomes in young women with PCOS remain unclear.

Evidence to answer the question

Eight articles reporting seven RCTs were identified by the search to answer this question. Five RCTs were of moderate risk of bias [170, 189, 193, 203, 214] and three were of high risk of bias [204, 205, 215]. The included studies used various diet delivery methods/tools (and associated support mechanisms) and various macronutrient diet compositions, including low carbohydrate diet, low glycaemic index diet, monounsaturated fatty acid-enriched diet, conventional healthy diet, high protein diet, carbohydrate-counting, or fat-counting dietary approaches.

Consistency across studies included the involvement of a dietitian consultation. Furthermore, all studies used compliance and progress monitoring, but the timing varied from daily monitoring [204], to weekly [193], to monthly monitoring [170, 189, 203, 214, 215], or a mixture of intervals [189, 205].

Of the diet delivery methods used, two studies reported explaining and using official dietary guidelines with participants [189, 193, 205] and three studies provided food for participants [189, 204, 214]; of these, two used partial meal replacement [189, 214]. Other studies advocated changing the composition of whole foods consumed for their dietary changes [170, 189, 193, 203, 205, 214, 215]. One study used a food preparation kitchen to support the study [204]. Diet changes were made to all daily meals, except in the case of one
study where only breakfast was altered [214]. Exercise was only increased in two studies [170, 203]. Other studies reported participants having regular exercise [189, 205], or having no change in exercise levels [193, 214]. One study offered participants other lifestyle support mechanisms such as menu plans, emails, newsletters, articles, recipes, and motivational support [189, 205].

There was no difference between the diet delivery methods for the majority of the anthropometric, QoL, and emotional wellbeing outcomes. Two studies reported differences for anthropometric outcomes [204, 214] and another study reported a difference in an emotional wellbeing outcome [205], however the studies varied by the diet delivery regime and by degree of dietary support, so it is difficult to make a recommendation about the use of one method over another.

The evidence from the included studies is directly generalisable to the patient population of women with PCOS, particularly to women >30 years of age and who have BMI ≥30kg/m². However, the majority of the women in the studies were European Caucasian, so there may be limitations to generalising these findings to other ethnic groups. The multidisciplinary guideline development group included evidence comparing diet compositions as different diets have inherent differences in the method of their delivery and on the behaviour of the participant.

Overall, the diet delivery approaches that were consistently reported included face to face advice and education about diet composition, food types and practical approaches to healthy eating, including behaviour change techniques.

Recommendations

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<tr>
<td>5.4a Face to face, tailored dietary advice, including education, behavioural change techniques and ongoing support should be provided to women with polycystic ovary syndrome and a body mass index ≥25kg/m² (overweight). Dietary modification is the joint responsibility of all health professionals, partnering with women with polycystic ovary syndrome.</td>
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<tr>
<td>5.4b Behaviour change techniques should target prevention of weight gain in all women with polycystic ovary syndrome including those with a body mass index ≤25kg/m² (lean).</td>
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<tr>
<td>5.4c Behavioural change techniques, including motivational interviewing, should be used in addition to advice/education. Simple strategies, including self-monitoring, pedometers and time management techniques should be encouraged. Interventions could be individual, group or mixed mode, in a range of settings, delivered by a range of health professionals. Individual techniques should not be used in isolation and should be part of a coherent multidisciplinary interventional model. Key messages should be reinforced with women with polycystic ovary syndrome, including that achievable goals (5% to 10% loss of body weight in overweight women) yield significant clinical improvements.</td>
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</table>
RESEARCH RECOMMENDATION

Further methodologically rigorous trials in women with polycystic ovary syndrome are important to address:

1) the types of diet delivery methods and diet support and tools that are effective - an initial study would be to have diet compositions the same and vary the delivery method or support tools between the groups
2) comparison of the delivery methods for lifestyle interventions including comparing settings and providers.

Clinical impact of the recommendations: Moderate

Face to face, tailored dietary advice, including education, behavioural change techniques and ongoing support should be provided to women with PCOS for weight loss in overweight women (BMI ≥25kg/m²) and for prevention of weight gain in lean women (BMI ≤25kg/m²). Current practice is unclear. Dietary modification is the joint responsibility of all health professionals, partnering with women with PCOS and these recommendations may result in increased referrals to allied health professionals. PCOS information to aid allied health management of PCOS has been developed (Appendix IV). There may be resource implications due to increased consultation times and increased utilisation of care plans. Engagement of health practitioners and financial barriers for patients may present implementation issues.

To find a dietitian, follow the links on the Dietitians Association of Australia website: www.daa.asn.au

5.5 Exercise interventions

In women with PCOS, are exercise interventions (compared to no exercise or different exercises) effective for improving weight loss, metabolic, reproductive, fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

Although not included in the diagnostic criteria, IR, underpinned by insulin signalling pathway defects, is strongly implicated in the aetiology of PCOS [216, 217] and is closely associated with the reproductive (hirsutism, infertility) and cardiometabolic (impaired glucose tolerance and metabolic syndrome) complications of the disorder [216-220]. Furthermore, approximately 40-60% of women with PCOS are either overweight (BMI ≥25kg/m²) or obese (BMI ≥30kg/m²) with increased central adiposity [103, 104], which exacerbates underlying IR and IR-associated metabolic and reproductive complications in PCOS [86, 104]. Exercise effectively ameliorates IR and offers a potentially effective intervention in PCOS.

Moderate aerobic exercise can be defined as an intensity between 50-80% of maximum oxygen consumption (VO₂ max) or 60-90% of maximal heart rate [221]. A single session of moderate exercise enhances whole-body glucose disposal and improves insulin sensitivity in skeletal muscle short-term [222]. Ongoing moderate exercise at least three to five times per week has consistently been shown in high risk
groups to reduce DM2 risk [223, 224] and improve cardiovascular risk factors (ie. weight, lipid profiles and blood pressure) [225, 226]. Similarly, resistance or weight-bearing exercise either alone or in combination with aerobic exercise has been shown to improve health outcomes in high risk groups [227-230]. When combined with dietary changes, exercise has been shown to potentiate the effects of diet on insulin sensitivity in obese DM2 patients [231].

Whilst diet and exercise should be combined in PCOS lifestyle interventions, there is significant evidence to support the role of exercise alone for improving overall health and insulin sensitivity, independent of any weight loss [174, 232]. Thus, it is important to determine whether the inclusion of moderate to high intensity exercise and different types of exercise may be effective in management of PCOS and its associated co-morbidities.

Evidence to answer the question

Eight RCTs, all with a high risk of bias, were identified by the search to answer this question. Two studies compared different exercises to each other [171, 233, 234]. Orio et al. showed that 24 weeks’ exercise was better than no exercise with diet for fasting glucose response, insulin area under the curve (AUC), glucose/insulin AUC, LDL-C, HDL-C, BMI, waist-to-hip ratio, and waist circumference [233].

The evidence was inconsistent among the five studies that compared exercise to no exercise [235-239]. Triglycerides were lower in the exercise group [235]. Bruner et al. reported no difference between the interventions for any outcomes [236]. In Giallauria et al. exercise was better than no exercise for fasting insulin (exercise group (E) change: -1.9 ± 4.61μU/ml, non-exercise group (NE) change: 0.4 ± 5.66μU/ml; p<0.01), insulin AUC (E change: -896 ± 1577, NE change: -30 ± 1353, p<0.001), AUC_{GLU}/AUC_{INS} ratio (E change: 0.06 ± 0.21, NE change: 0.02 ± 0.18, p<0.001), highly sensitive C-reactive protein (E change: -0.31 ± 0.86mg/L, NE change: 0.06 ± 1.20mg/L, p<0.01), SHBG (E change: 1.9 ± 9.62nmol/L, NE change: -1.2 ± 9.12nmol/L, p<0.05), BMI (E change: -1.3 ± 3.83, NE change: -0.2 ± 4.88, p<0.05), and waist-to-hip ratio (E change: -0.05 ± 0.14, NE change: -0.01 ± 0.14, p<0.05) [237]. BMI was better in the exercise group in the study by Stener-Victorin et al (E change: 0.4 ± 3.83, NE change: -0.2 ± 4.88, p<0.05), and waist-to-hip ratio (E change: -0.01 ± 0.28, p<0.001), systolic blood pressure (E change: -3.8 ± 14.71, NE change: 1.1 ± 13.02, p<0.01) and diastolic blood pressure at peak exercise (E change: -0.8 ± 5.70, NE change: 10.6 ± 5.25, p<0.01) [239]. There was no difference between exercise and no exercise for all other outcomes.

Three studies [171, 197, 234, 238] compared exercise to non-exercise lifestyle interventions. Palomba et al. reported that exercise was better for menses frequency (SET: 28 observed menses/107 expected cycles (26.2%), hypocaloric hyperproteic diet group (HCHP): 18 observed menses/118 expected cycles (15.3%), p=0.043), increased ovulation rate (SET: 28 ovulatory cycles/113 observed cycles (24.8%), HCHP: 18 ovulatory cycles/119 observed cycles (15.1%), p=0.032) and increased cumulative ovulation rate (SET: 13 ovulatory patients/20 patients (65.0%), HCHP: 5 ovulatory patients/20 patients (25.0%), p=0.011) [197]. Stener-Victorin et al. reported that there was no difference between exercise and low-frequency electro-acupuncture [238].

There was no difference between aerobic exercise and aerobic-resistance exercise for percent of body fat, fat mass, fat-free mass, depression scores and PCOS-related QoL [171, 234].

The evidence from the included studies is directly generalisable to overweight women with PCOS with practical exercise regimens used. There may be limitations to generalising these findings to other ethnic groups, especially to non-European populations.
It is important to note that while exercise has benefits for overweight women with PCOS, the evidence is limited, inconsistent and of low quality.

Recommendations

**EVIDENCE-BASED RECOMMENDATION**

5.5a Exercise participation of at least 150 minutes per week should be recommended to all women with polycystic ovary syndrome, especially those with a body mass index $\geq 25 \text{kg/m}^2$ (overweight), given the metabolic risks of polycystic ovary syndrome and the long term metabolic benefits of exercise. Of this, 90 minutes per week should be aerobic activity at moderate to high intensity (60% - 90% of maximum heart rate) to optimise clinical outcomes. 

**CLINICAL PRACTICE POINT**

5.5b Encouraging exercise is the joint responsibility of all health professionals, partnering with women with polycystic ovary syndrome. Where appropriate, referral to an exercise physiologist or specialist could be considered as part of an enhanced primary care plan. Where there are significant co-morbidities, assessment for exercise participation should be undertaken by the relevant healthcare professionals. Tools such as [Lifescripts](http://www.health.gov.au/lifescripts) could be used for engagement in physical activity:

**RESEARCH RECOMMENDATION**

Further methodologically rigorous trials in women with polycystic ovary syndrome are important to help define what types, intensities and delivery methods of exercise strategies are optimal for lean and overweight women for improved clinical outcomes.

Clinical impact of the recommendations: Moderate

Healthcare professionals can recommend 150 minutes of exercise per week based on current national and international guidelines for the general population [240-248] on exercise prescription for health and weight maintenance. Ninety minutes of exercise per week at moderate to high intensity can be recommended. In cases where there is risk from injury or barriers to exercise, due consideration should be given to involvement of exercise physiologists and specialists to assist in structured exercise training.

For most practices, this recommendation will result in changes to usual care. This recommendation will also reduce variation in practice and ensure exercise advice is prescribed to all women and may result in increased referral to exercise physiologists. There may also be additional cost to the healthcare system with potentially increasing: 1) referrals to Medicare-funded exercise physiologists 2) consultation times 3) referrals to allied health professionals 4) utilisation of care plans. Engagement of, and adequate access to,
health professionals including insufficient consultation time allocated by general practitioners, may be barriers. Drop-out or non-adherence to exercise programmes by patients may be a problem, but if there is adequate allied health and clinical support, then this issue may be reduced. A shift in cultural mindset may be required to ensure clinicians and women with PCOS understand the importance of exercise in PCOS management.

To find an exercise physiologist, follow the links on the Exercise and Sports Science Australia website: www.essa.org.au

**Lifestyle management considerations for Indigenous women**

Indigenous Australians preferentially deposit fat abdominally when they gain weight. With their traditionally linear body build for any given BMI they have a greater central distribution of body fat than Australians of European background [249, 250]. Thus, even in the “healthy” BMI range for Europeans (20–25kg/m²) they can have excess central fat. Central fat conveys a higher health risk with greater IR and cardiovascular risk than peripheral fat distribution [251]. Remaining lean (BMI ≤20kg/m²) has been shown, to a large extent, to protect even older Indigenous people from dyslipidaemia, IR and DM2 [250]. Therefore it may be that due to differences in body build the “healthy” BMI may be lower in Indigenous people [252, 253].

There is little information about the patterns of exercise in Indigenous Australians. However, the National Aboriginal and Torres Strait Islander Health Survey (NATSIHS) 2004–2005 reported that fewer than half of those surveyed aged >15 years had played sport or participated in any physical activity in the last 12 months and that the amount of activity decreased with age and was less in women than men [48].

Knowledge of the health benefits of exercise among urban Indigenous adults appears to be well understood and most people would like to be more active than they are. However, a number of barriers to exercise have been identified. For Indigenous women, as for those from other backgrounds and cultures, domestic work takes up much of their time and having children negatively affects the physical activity of mothers. Cost and safety concerns have also been identified as barriers to activity [254].

In attempting to address the lack of activity, consideration should be given to findings from studies with urban Indigenous adults which report that family/community activity is more important than individual exercise and that there is a lack of opportunity to participate in ongoing team activities [254, 255].

We therefore expect that the above recommendations are applicable to Indigenous women but acknowledge that exercise programs may need to be applied in different ways to engage Indigenous women and incorporate exercise into daily activities, especially in rural and remote locations due to a lack of service provision and facilities.
Non-pharmacological first line management of infertility in PCOS

With increasing obesity exacerbating infertility in women with PCOS and weight loss improving reproductive, metabolic and psychological features, lifestyle interventions should be first line PCOS therapy.

6.1 Lifestyle interventions for infertility

In women with PCOS, what is the effectiveness of lifestyle interventions compared to pharmacological interventions (ie. metformin and clomiphene citrate) for improving fertility, quality of life and emotional wellbeing outcomes?

Clinical need for the question

Lifestyle therapy is deemed first line for women with PCOS targeting prevention of weight gain and promoting weight loss where required [129]. Diet, weight loss and exercise induces significant benefits in women with PCOS [177, 256]. Fertility rates are low in women with a BMI ≥30-32kg/m² and the benefits of lifestyle intervention are wide ranging and extend beyond fertility (including DM2 prevention). There is a dramatically rising prevalence of obesity in Australian women with greater rates of weight gain in PCOS [173]. Lifestyle therapy is clearly critical in PCOS women. Implementation challenges include engagement and sustainability of lifestyle programme uptake rates are often low and drop out rates can be high. There is inadequate high quality evidence on pregnancy outcomes with lifestyle intervention in women with PCOS [177]. Pharmacological therapy, including clomiphene citrate, metformin and gonadotrophins, is available and effective in improving fertility in women with PCOS [257]. However there is little comparative literature on the benefits of lifestyle versus pharmacological therapy in women with PCOS who are overweight or obese.

Evidence to answer the question

Ten RCTs (level II) of moderate [194, 258, 259] to high [182, 191, 192, 260-263] risk of bias compared various types of lifestyle interventions (including low carbohydrate or healthy diets, exercise programmes and group sessions) to pharmacological therapy (including metformin or clomiphene citrate) in women with PCOS and BMI ≥25kg/m².

Statistical significance values have been presented where differences between interventions were found. For detailed results for each individual RCT, please see section 6.1 in the ‘Evidence report’, found at www.managingpcos.org.au/pcos-evidence-based-guidelines.

There was no difference between lifestyle (diet) therapy (with or without placebo) and pharmacological therapy (with or without lifestyle (diet) therapy) for fertility outcomes. In two studies [191, 260], metformin plus diet was better than placebo plus diet for menstruation frequency. In one study, lifestyle plus clomiphene citrate was better than clomiphene citrate alone or lifestyle alone for ovulation rate and
menstrual frequency (p<0.05) [259]. There was no difference between lifestyle (diet) therapy (with or without placebo) and pharmacological therapy.

When comparing lifestyle (diet) therapy (with or without placebo) to pharmacological therapy plus lifestyle (diet) therapy, five out of the eight studies reported that there was no difference between the interventions. Gambineri et al. reported that metformin was better than placebo plus diet for menstrual pattern after six months (p=0.03) and 12 months (p=0.003) [182, 260] and frequency of menstruation at both baseline to six months (p=0.05) and baseline to 12 months (p=0.01). Pasquali et al. reported that metformin plus diet was better than placebo plus diet (p<0.05) for menstruation frequency [191]. Another study reported that lifestyle plus clomiphene citrate was better than lifestyle alone for ovulation rate and menstrual frequency (p<0.05) [259].

Adverse events were not consistently reported. Two patients had adverse events in the metformin group [261] and Qublan et al. [192] reported that 11 women withdrew due to side-effects in the metformin plus diet group. Six women withdrew from the placebo plus diet group due to side effects within the first 2 months of the study, however the side effects were not defined.

It is important to note that there was inconsistency in the components of lifestyle (diet) therapy and therefore a recommendation cannot be made about a specific intervention; however given that there is no difference between lifestyle and pharmacological therapy overall, the guideline development group deemed that there are clear benefits in using lifestyle interventions over pharmacological interventions.

**Recommendations**

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<tr>
<th>EVIDENCE-BASED RECOMMENDATIONS</th>
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<tr>
<td><strong>6.1a</strong> Lifestyle management, including diet and exercise programs, should be used throughout the lifespan in women with polycystic ovary syndrome to optimise health generally and to alleviate polycystic ovary syndrome clinical severity including infertility.</td>
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<td><strong>6.1b</strong> In women with polycystic ovary syndrome and body mass index ≥30kg/m² with due consideration given to age-related infertility, intensive (frequent multidisciplinary contact) lifestyle modification alone (and not in combination with pharmacological ovulation induction therapy) should be first line therapy for 3 to 6 months to determine if ovulation is induced.</td>
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<td><strong>6.1c</strong> Pharmacological ovulation induction should not be recommended for first line therapy in women with polycystic ovary syndrome who are morbidly obese (body mass index ≥35kg/m²) until appropriate weight loss has occurred either through diet, exercise, bariatric surgery, or other appropriate means.</td>
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<td><strong>6.1d</strong> Pharmacological ovulation induction could be second line therapy, after intensive lifestyle modification has been undertaken.</td>
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<th>CLINICAL PRACTICE POINT</th>
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<td><strong>6.1e</strong> Morbid obesity (body mass index ≥35kg/m²) increases risks during pregnancy and should be regarded as a relative contraindication to assisted fertility.</td>
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<td><strong>6.1f</strong> Psychological factors should be considered and managed in infertile women with polycystic ovary</td>
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syndrome, to optimise engagement and adherence to lifestyle interventions.

**RESEARCH RECOMMENDATIONS**

Further methodologically rigorous trials are important to investigate the impact of lifestyle improvement on fertility outcomes including live birth. Implementation research into the optimal engagement, adherence and delivery of lifestyle intervention is needed to inform consumers, health professionals and policy makers.

Clinical impact of the recommendations: Very large

Lifestyle management, including diet and exercise programs, should be used throughout the lifespan in women with polycystic ovary syndrome to optimise health generally and to improve fertility outcomes. Pharmacological ovarian stimulation and/or assisted fertility should not be prescribed in morbidly obese women (BMI $\geq$35kg/m$^2$) unless appropriate weight loss has occurred in accordance with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists recommendations [264]. With lifestyle intervention as first line for overweight women with PCOS, initial therapy for infertility can be commenced at the primary care level. Barriers to implementation of these recommendations may include impact on workloads in general practice, increased referral to allied health professionals and availability and funding for lifestyle programs. Barriers to implementation of these recommendations may also include availability and funding for interventions. A shift in cultural mindset may be required to focus on lifestyle interventions especially around prevention of weight gain which is not traditionally a focus of health professionals.

Non-pharmacological management considerations for Indigenous women

We expect that the above recommendations are applicable to Indigenous women but acknowledge that they may not be applicable in the Indigenous setting due to the limitations in care and service provision in rural and remote locations and potential barriers presented by cultural and traditional health practices.
CHAPTER SEVEN
Pharmacological management of infertility in PCOS

Hormonal disturbances can affect ovulation, making it more difficult for women with PCOS to conceive naturally. Pharmacological ovulation induction can be used to induce ovulation but is generally second line after intensive lifestyle therapy in overweight women with PCOS.

7.1 Clomiphene citrate

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

Clinical need for the question

Clomiphene citrate is a selective oestrogen receptor modulator with both oestrogenic and anti-oestrogenic properties [265]. It was first approved for use in women with anovulation in 1967 and has been used as a first line ovulation induction agent for over 40 years [266]. Acting as an anti-oestrogen, clomiphene citrate competitively inhibits the binding of estradiol to its receptors in the hypothalamus and pituitary which in turn blocks the negative feedback effect of endogenous oestrogens including estradiol. This release of the hypothalamus from negative inhibition results in an increased secretion of pulsatile gonadotrophin-releasing hormone secretion from the hypothalamus leading to an increase in FSH and luteinizing hormone production and secretion from the pituitary gland. This increase in FSH secretion stimulates follicular growth and estradiol production inducing a midcycle luteinizing hormone surge and ovulation [267].

Standard practice is to administer clomiphene citrate for 5 days, commencing on menstrual cycle day 2 to 5, starting with 50mg/day and increasing to 150 mg/day. If ovulation cannot be achieved with clomiphene citrate administration at doses of 150mg/day, clomiphene citrate resistance is reached. If pregnancy cannot be achieved after six ovulatory cycles with clomiphene citrate, then the patient is described as having clomiphene citrate failure [268].

Studies with clomiphene citrate have shown an ovulation rate of 60–85% and a pregnancy rate of 30–50% after 6 ovulatory cycles. This apparent discrepancy between good ovulation rates and lower pregnancy rates has been attributed to the anti-oestrogenic effects of clomiphene citrate on the endometrium and cervical mucus. The rates of twin pregnancy and triplets with clomiphene citrate are 5–7% and 0.3%, respectively. The incidence of ovarian hyperstimulation syndrome is less than 1% [269]. Although more studies are required, it is best to limit a patient’s lifetime exposure to clomiphene citrate to 12 treatment cycles, as additional cycles may place the patient at increased risk of borderline ovarian tumours [270]. It is important to establish the effectiveness of clomiphene citrate, particularly in comparison to other treatments, in infertile women with PCOS in light of the potential risks.
Evidence to answer the question

One high quality systematic review (level I) with low risk of bias found that clomiphene citrate was better than placebo for pregnancy rate per patient (OR 5.77 [1.55 to 21.48] I²=0% p<0.009; 3 studies, 133 participants) and ovulation rate per patient (OR 7.47 [3.24 to 17.23] I²=0% p<0.00001; 3 studies, 133 participants) in women with PCOS, including those whose sensitivity to clomiphene citrate was not reported [271]. The evidence obtained from this systematic review is generalisable to patient population in terms of age and BMI. The setting was varied and study locations included USA and Canada. None of the studies were conducted in Australia and may not be generalisable to Indigenous populations.

Recommendations

| EVIDENCE-BASED RECOMMENDATION | 7.1a Clomiphene citrate should be first line pharmacological therapy to improve fertility outcomes in women with polycystic ovary syndrome and anovulatory infertility, with no other infertility factors. |
|CLINICAL PRACTICE POINT | 7.1b The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring is recommended. |

Clinical impact of the recommendations: Slight

First line clomiphene citrate therapy should be prescribed in specialist care. It should be noted that there are limitations which differ across states in terms of those specialists who are able to prescribe and monitor clomiphene citrate therapy. There may be resource implications as adequate monitoring will require additional resources. Costs to the patient of having adequate monitoring (tests and specialist visits) and accessibility to specialist care may be barriers to the use of clomiphene citrate, however it is anticipated that increased costs will be offset by reduced multiple pregnancy related costs.

7.2 Metformin

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

Clinical need for the question

IR with compensatory hyperinsulinaemia is a prominent feature of PCOS [164] affecting approximately 65 to 80% of women with PCOS [101]. Hyperinsulinaemia results in increased ovarian androgen biosynthesis in vivo and in vitro and decreased SHBG synthesis from the liver, leading to increased bioavailability of free androgens. This excess in local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation [272].

The association of IR contributing to anovulation in PCOS has led to the introduction of insulin-sensitizing drugs in an attempt to restore ovulation and enhance pregnancy. Of the insulin-sensitizing drugs, metformin has been the one studied most widely in PCOS and has the most reassuring safety profile [273]. Metformin
is a biguanide which is used as an oral antihyperglycaemic agent in the treatment of DM2 [274]. The first published report on the use of metformin as a treatment for PCOS was in 1994 [275]. The early studies examining the reproductive system effects of metformin in women with PCOS showed promising results but most of the studies had relatively small sample sizes [272].

Metformin is available in two formulations: immediate and extended-release. Therapeutic regimens of metformin administration in PCOS are not well standardized in clinical practice, and various protocols have been used in the studies available in literature with an extremely variable target dose of 1500 to 2550 mg per day having been proposed [258].

Evidence to answer the question

Forty four articles met the selection criteria, however only the most current, high level and high quality evidence for each comparison was used to answer this question. Four systematic reviews (level I) and five RCTs (level II) were used to answer the question.

Three systematic reviews (two high quality systematic reviews (level I) with low risk of bias [257, 276] and a medium quality systematic review (level I) with moderate risk of bias [277]) and one high quality RCT (level II) with low risk of bias (that was published after publication of the most current systematic review) [278] found that:

- Metformin was better than placebo for ovulation rate in overall women with PCOS\(^7\) (OR 2.12 [1.50, 3.00] \(I^2=69\%\) \(p=0.000019\); 13 studies, 875 participants) [257], women with PCOS and a BMI \(\leq 30\text{kg/m}^2\) (OR 2.33 [1.43–3.81] \(I^2=88\%\) \(p=0.00071\); 4 studies, 417 participants) [257], women with PCOS and a BMI \(\geq 30\text{kg/m}^2\) (OR 1.94 [1.20–3.15] \(I^2=39\%\) \(p=0.0073\); 9 studies, 458 participants) [257] and women with non-clomiphene citrate resistant (non-CCR\(^8\)) PCOS (OR 3.55 [1.46–8.65]; 6 studies, 401 participants) [276]. However, there was significant statistical heterogeneity in overall women with PCOS and women with PCOS and a BMI \(\leq 30\text{kg/m}^2\). There was no difference in ovulation rate between metformin and placebo in women with CCR PCOS.

- Metformin was better than placebo for pregnancy rate in overall women with PCOS (OR 3.86 [2.18, 6.84] \(I^2=0\%\) \(p<0.00001\); 6 studies, 479 participants) [257] and women with PCOS and a BMI \(\leq 30\text{kg/m}^2\) (OR 4.41 [2.24–8.66] \(I^2=40\%\) \(p=0.000017\); 3 studies, 250 participants) [257] but no difference in women with PCOS and a BMI \(\geq 30\text{kg/m}^2\), women with clomiphene citrate naïve PCOS, women with CCR PCOS or women with non-CCR PCOS.

- There was no difference between metformin and placebo for live birth rate in overall women with PCOS, women with CCR PCOS and women with PCOS and a BMI \(\geq 30\text{kg/m}^2\).

- There was no difference between metformin and placebo for miscarriage rate in overall women with PCOS.

- Metformin had a higher incidence of gastrointestinal related adverse events compared to placebo (OR 9.23 [4.18, 20.37] \(I^2=25\%\) \(p<0.00001\); 5 studies, 253 participants) in women with PCOS [257].

Two systematic reviews (one high quality systematic review (level I) with low risk of bias [257] and a medium quality systematic review (level I) with moderate risk of bias [277]) and two RCTs (one high quality RCT (level II) with low risk of bias [278] and a medium quality RCT (level II) with moderate risk of bias [262] (both RCTs were published after publication of the most current systematic review) found that:

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7 “Overall women with PCOS” is defined as all the women with PCOS in the relevant study or studies regardless of BMI or clomiphene citrate exposure or sensitivity.

8 Non-CCR PCOS is defined as clomiphene citrate sensitive or unknown clomiphene citrate sensitivity.
• Clomiphene citrate was better than metformin for ovulation rate in overall women with PCOS (OR 0.48 [0.41, 0.57] I²=78% p<0.00001; 3 studies, 2470 participants) [257] and women with PCOS and a BMI ≥30kg/m² (OR 0.43 [0.36–0.51] I²=0% p<0.00001; 2 studies, 2044 participants) [257]. However, there was significant statistical heterogeneity seen in overall women with PCOS. There was no difference in ovulation rate between metformin and clomiphene citrate in women with PCOS and a BMI ≤30kg/m².

• Clomiphene citrate was better than metformin for ovulation rate in overall women with PCOS (OR 0.48 [0.41, 0.57] I²=78% p<0.00001; 3 studies, 2470 participants) [257] and women with PCOS and a BMI ≥30kg/m² (OR 0.43 [0.36–0.51] I²=0% p<0.00001; 2 studies, 2044 participants) [257]. However, there was significant statistical heterogeneity seen in overall women with PCOS. There was no difference in ovulation rate between metformin and clomiphene citrate in women with PCOS and a BMI ≤30kg/m².

• Clomiphene citrate was better than metformin for pregnancy rate in overall women with PCOS (OR 0.63 [0.43, 0.92] I²=91% p=0.018; 3 studies, 600 participants) [257] and women with PCOS and a BMI ≥30kg/m² (OR 0.34 [0.21–0.55] I²=0% p=0.00001; 2 studies, 500 participants) [257]. However, there was significant statistical heterogeneity seen in overall women with PCOS. Metformin was better than clomiphene citrate for pregnancy rate in women with PCOS and a BMI ≤30kg/m², however this was based on a single study (OR 3.47 [1.52–7.90] I²=NA p=0.0031; 1 study, 100 participants) [257].

• There was no difference in live birth rate between metformin and clomiphene citrate in overall women with PCOS with statistical heterogeneity. Clomiphene citrate was better than metformin for live birth rate in women with PCOS and a BMI ≥30kg/m² without statistical heterogeneity (OR 0.30 [0.17–0.52] I²=0% p=0.000021; 2 studies, 500 participants) [257]. Metformin was better than clomiphene citrate for live birth rate in women with PCOS and a BMI ≤30kg/m², however this was based on a single study (OR 4.94 [1.99–12.26] I²=NA p=0.00059; 1 study, 100 participants) [257].

• There was no difference in multiple pregnancy rate (without statistical heterogeneity) and miscarriage rate (with statistical heterogeneity) between metformin and clomiphene citrate in overall women with PCOS.

Three systematic reviews (two high quality systematic reviews (level I) with low risk of bias [257, 276] and a medium quality systematic review (level I) with moderate risk of bias [277]) and five RCTs (three high quality RCT (level II) with low risk of bias [278-280], a medium quality RCT (level II) with moderate risk of bias [262] and a low quality RCT (level II) with high risk of bias [281]) (all RCTs were published after publication of the most current systematic review) found that:

• Metformin plus clomiphene citrate was better than clomiphene citrate alone for ovulation rate in overall women with PCOS (OR 1.76 [1.51, 2.06] I²=74% p<0.00001; 11 studies, 2668 participants) [257], women with PCOS and a BMI ≤30kg/m² (OR 1.61 [1.13–2.31] I²=65% p=0.0091; 5 studies, 525 participants) [257], women with PCOS and a BMI ≥30kg/m² (OR 1.80 [1.51–2.14] I²=81% p<0.00001; 6 studies, 2143 participants) [257], women with CCR PCOS (OR 4.86 [2.43, 9.74] I²=0% p<0.00001; 5 studies, 179 participants) [257], women with non-CCR PCOS (OR 3.84 [1.38–10.68]; 5 studies, 832 participants) [276], and women with unknown clomiphene citrate sensitivity PCOS (ie. clomiphene citrate sensitivity not defined) (OR 1.65 [1.40, 1.94] I²=85% p<0.00001; 5 studies, 2433 participants) [257]. However, there was significant statistical heterogeneity seen in all these types of PCOS women except in the women with CCR PCOS. There was no difference in ovulation rate between metformin plus clomiphene citrate and clomiphene citrate alone in women with clomiphene citrate sensitive PCOS.

• Metformin plus clomiphene citrate was better than clomiphene citrate alone for pregnancy rate in overall women with PCOS (OR 1.48 [1.12, 1.95] I²=58% p=0.0058; 7 studies, 976 participants) [257], women with PCOS and a BMI ≥30kg/m² (OR 1.67 [1.18–2.36] I²=41% p=0.0038; 5 studies, 643 participants) [257], women with clomiphene citrate naïve PCOS (RR 1.5 [1.2–1.8] I²=78% p<0.0001; 7 studies, 985 participants) [277] and women with CCR PCOS (RR 5.6 [2.3–13] I²=0% p=0.0001; 5 studies, 212 participants) [277]. However, there was significant statistical heterogeneity seen in all these types of PCOS women except in women with PCOS and a BMI ≥30kg/m² and women with CCR PCOS. There was no difference in pregnancy rate between metformin plus clomiphene citrate and clomiphene citrate
alone in women with PCOS and a BMI ≤30kg/m², women with non-CCR PCOS and women with unknown clomiphene citrate sensitivity PCOS.

- Metformin plus clomiphene citrate was better than clomiphene citrate alone for live birth rate in women with CCR PCOS, without significant statistical heterogeneity (RR 6.4 [1.2–34] I²=0% p=0.03; 2 studies, 107 participants) [277]. There was no difference in live birth rate between metformin plus clomiphene citrate and clomiphene citrate alone in overall women with PCOS women, women with PCOS and a BMI ≤30kg/m², women with PCOS and a BMI ≥30kg/m², or women with clomiphene citrate naive PCOS.

- There was no difference between metformin plus clomiphene citrate and clomiphene citrate alone for miscarriage rate in overall women with PCOS and women with PCOS and a BMI ≤30kg/m².

- There was no difference between metformin plus clomiphene citrate and clomiphene citrate alone for multiple pregnancy rate in overall women with PCOS, women with PCOS and a BMI ≤30kg/m² and women with unknown clomiphene citrate sensitivity PCOS.

- Clomiphene citrate alone had fewer gastrointestinal related adverse events compared to metformin plus clomiphene citrate in overall women with PCOS.

One high quality systematic review (level I) with low risk of bias evaluating two RCTs with a mean BMI ≥ 30 kg/m² [282] and two RCTs (one high quality RCT (level II) with low risk of bias [278] and one medium quality RCT (level II) with moderate risk of bias [262] (both RCTs were published after publication of the most current systematic review)) and found that:

- Metformin plus clomiphene citrate was better than metformin alone for ovulation rate (OR 0.23 [0.15, 0.34] Q=0.948 (p=0.330 test for heterogeneity) p<0.0001 (for test of overall effect); 2 studies, 741 participants), pregnancy rate (OR 0.23 [0.14, 0.37] Q=0.244 (p=0.622 test for heterogeneity) p<0.0001 (for test of overall effect); 2 studies, 741 participants) and live birth rate (OR 0.23 [0.13, 0.40] Q=0.533 (p=0.465 test for heterogeneity) p<0.0001 (for test of overall effect); 2 studies, 741 participants) in overall women with PCOS [282].

- There was no difference between metformin plus clomiphene citrate and metformin alone for miscarriage rate or adverse events in overall women with PCOS.

The included studies provide supporting evidence for the use of metformin alone as well as for the use of metformin combined with clomiphene citrate. The included studies also provide supporting evidence for the use of clomiphene citrate over metformin, therefore we suggest that metformin be used (alone or in combination with clomiphene citrate) only in women with PCOS who have not responded to clomiphene citrate as first line therapy either in terms of ovulation or pregnancy. There is evidence that the use of metformin may be associated with gastrointestinal related adverse events and therefore women with PCOS who are prescribed metformin (alone or in combination with clomiphene citrate) to improve fertility outcomes should be informed about associated gastrointestinal related side effects.

There is heterogeneity in the evidence about efficacy of metformin for rates of ovulation, pregnancy and live birth across the subgroups, including BMI (≤ or ≥30kg/m²) and sensitivity to clomiphene citrate.

Additionally, we conducted a meta-analysis of four RCTs (level II) comparing metformin and clomiphene citrate in women with PCOS and a BMI ≤30-32kg/m² [262, 278, 283, 284], since this was not performed in any of the included systematic reviews. There was no difference between metformin and clomiphene citrate in women with PCOS and a BMI≤30-32kg/m². Due to significant heterogeneity across the RCTs and wide confidence intervals in the results, we were unable to make an evidence-based recommendation. For more detail about this evidence review and analysis, see section 7.2b in the ‘Evidence report’ (www.managingpcos.org.au/pcos-evidence-based-guidelines).
The evidence is generalisable to patient population in terms of age and BMI. The setting was varied and only one of the RCTs within one systematic review was conducted in New Zealand which may be generalisable to the Australian setting but may not be generalisable to Indigenous populations.

Recommendations

**EVIDENCE-BASED RECOMMENDATIONS**

| 7.2a | Metformin should be combined with clomiphene citrate to improve fertility outcomes rather than persisting with further treatment with clomiphene citrate alone in women with polycystic ovary syndrome who are clomiphene citrate resistant, anovulatory and infertile with no other infertility factors. | A |
| 7.2b | Metformin could be used alone to improve ovulation rate and pregnancy rate in women with polycystic ovary syndrome who are anovulatory, have a body mass index ≤30kg/m² and are infertile with no other infertility factors. | B |
| 7.2c | If one is considering using metformin alone to treat women with polycystic ovary syndrome who are anovulatory, have a body mass index ≥30kg/m², and are infertile with no other infertility factors, clomiphene citrate should be added to improve fertility outcomes. | A |

**RESEARCH RECOMMENDATIONS**

Further methodologically rigorous trials are important to address:

1) whether the addition of metformin to clomiphene citrate improves live birth rate in anovulatory PCOS women with no other infertility factors
2) whether there is a difference in effectiveness between clomiphene citrate and metformin in PCOS anovulatory, infertile women with a body mass index ≤30kg/m² to improve fertility outcomes.

**Clinical impact of the recommendations: Moderate**

Metformin should be added to clomiphene citrate in women with CCR PCOS; metformin alone could be used in women with PCOS and a BMI ≤30kg/m²; and clomiphene citrate should be added to metformin in women with PCOS and a BMI ≥30kg/m². This may result in a change in usual care as clinicians may now be more likely to prescribe metformin. There is evidence that the use of metformin may be associated with mild gastrointestinal related adverse events and therefore women with PCOS who are prescribed metformin (alone or in combination with clomiphene citrate) to improve fertility outcomes should be informed about potential associated gastrointestinal related side effects. The guideline development group is not aware of resource implications or changes to the way care is organised upon implementation of the recommendations, however a barrier may be that while metformin is listed as an unrestricted benefit on the Pharmaceutical Benefits Scheme, no application for metformin approval has been made to the TGA and
hence it is not approved for use in PCOS\(^9\). Whilst use is evidence-based, patient explanation and consent is appropriate.

### 7.3 Gonadotrophins

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

**Clinical need for the question**

Gonadotrophin therapy is often used as second-line therapy in anovulatory women with PCOS with either clomiphene citrate resistance or failure to conceive, however sensitivity to gonadotrophin therapy is increased in PCOS with increased multiple follicular development and cycle cancellation [285]. Gonadotrophins also increase the risk of multiple pregnancy and ovarian hyperstimulation syndrome. To overcome this risk a ‘low-dose step-up’ protocol is well established in fertility practice [286]. This regime involves commencing therapy with 50 or 75IU per day of FSH for 7 to 10 days and then increasing the dose incrementally by 37.5IU every week if there is not development of a follicle ≥12mm in size. Ovulation is triggered when there is development of a solitary follicle ≥18mm in size in the absence of any other follicles in excess of 14mm in size. A ‘step-down’ protocol is also used with a usual starting dose of 150IU of FSH until a dominant follicle develops and then the dose of FSH is decreased until the triggering of ovulation with human chorionic gonadotrophin [287]. The success of this regime is comparable to that of the ‘step-up’ protocol although it is believed that a step-up approach is safer with regard to the induction of monofollicular ovulation and potentially easier to monitor [288]. Despite a large body of observational evidence supporting the use of gonadotrophin therapy in anovulatory women with PCOS [286], its effectiveness, particularly in relation to other therapies, needs to be evaluated using the best available evidence.

**Evidence to answer the question**

One systematic review and one RCT was identified by our search. The systematic review compared gonadotrophins to laparoscopic ovarian surgery and is described in detail in 8.1 Ovarian surgery. Briefly, the systematic review found that there was no difference between gonadotrophins and laparoscopic ovarian surgery and this is reflected in the pathway of the algorithm for therapy for infertility (see Algorithms). The high quality RCT (level II) with low risk of bias compared recombinant FSH with clomiphene citrate in women with PCOS who were therapy naive and found that there was no difference between FSH and clomiphene citrate for all fertility outcomes [289]; however due to the small sample size and inadequate power, a recommendation cannot be based on this evidence alone.

A multi-centre RCT comparing clomiphene citrate versus low dose gonadotrophins, as the first line therapy for ovulation induction in anovulatory women with PCOS who were therapy naive, reported with intention to treat analysis that the clinical pregnancy rate was significantly higher in the gonadotrophin treated group. Furthermore the chance of pregnancy was almost double in the first treatment cycle when compared to clomiphene citrate [290]. This study to date has only been published in abstract form, hence it has informed the guideline development group in formulating the recommendation, but is not included in the evidence.

\(^9\) For TGA approval, industry must propose metformin for approval and as metformin is generic and produced by many companies, no one company will fund and support an application to TGA. This technical challenge is independent of effectiveness or evidence.

The evidence obtained from the included studies is generalisable to patient population in terms of age and BMI. Where reported, studies were conducted in Spain and India. These studies may be applied in the Australian setting, but may not address issues of special importance, such as generalisability to Indigenous populations.

Recommendations

<table>
<thead>
<tr>
<th>EVIDENCE-BASED RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3a Gonadotrophins should be second line pharmacological therapy in women with polycystic ovary syndrome who have clomiphene citrate resistance and/or failure, are anovulatory and infertile, with no other infertility factors.</td>
</tr>
<tr>
<td>7.3b Gonadotrophins could be considered as first line pharmacological therapy in women with polycystic ovary syndrome who are therapy naïve, anovulatory and infertile, with no other infertility factors.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL PRACTICE POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.3c Where gonadotrophins or laparoscopic ovarian surgery (see 8.1) are to be prescribed, the following should be considered:</td>
</tr>
<tr>
<td>• Cost of either intervention for ovulation induction</td>
</tr>
<tr>
<td>• Expertise required for the use of either intervention for ovulation induction</td>
</tr>
<tr>
<td>• The degree of intensive monitoring that is required for gonadotrophin therapy</td>
</tr>
<tr>
<td>• Implications of potential multiple pregnancy for gonadotrophin therapy</td>
</tr>
<tr>
<td>• Implications of the potential risk of ovarian hyperstimulation syndrome for gonadotrophin therapy</td>
</tr>
<tr>
<td>• Laparoscopic surgery in women who are overweight or obese is associated with both intra-operative and post-operative risks.</td>
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</table>

<table>
<thead>
<tr>
<th>RESEARCH RECOMMENDATION</th>
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</thead>
<tbody>
<tr>
<td>Further methodologically rigorous trials are important to address the role of gonadotrophins in ovulation induction in polycystic ovary syndrome.</td>
</tr>
</tbody>
</table>

Clinical impact of the recommendations: Slight

Gonadotrophin therapy is suitable for improving infertility in women with PCOS in specialist care. The guideline development group is not aware of resource implications, changes to the way care is organised or barriers to implementation of these recommendations. Gonadotrophins appear to be as effective as laparoscopic ovarian surgery (comparison described in 8.1) and therefore the issues covered in the clinical practice point should be considered when deciding between the two therapy options.
7.4 Aromatase inhibitors

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

Clinical need for the question

Aromatase inhibitors are oral ovulation-inducing drugs that were first proposed as new ovulation-inducing agents in anovulatory women (with an inadequate response to clomiphene citrate) in 2001 [291]. The most commonly used aromatase inhibitors in ovulation induction are letrozole and anastrozole, with letrozole being the most widely used [274].

The enzyme aromatase is a member of the cytochrome P450 hemoprotein containing enzyme complex super family and catalyses the conversion of androgens to oestrogens, specifically the conversion of testosterone and androstenedione to estradiol and estrone respectively in the ovary. Therefore, aromatase inhibitors inhibit oestrogen biosynthesis, thereby releasing the hypothalamus/pituitary axis from oestrogenic negative feedback and increasing the secretion of FSH by the pituitary. As a result, the ovary receives increased FSH stimulation, allowing for greater follicular growth and development. In addition, androgens that are normally converted to oestrogens accumulate in the ovary and these androgens increase follicular sensitivity to FSH [292].

The main incentives for the proposal of aromatase inhibitors as ovulation induction agents were to avoid some of the adverse effects of clomiphene citrate including the effects on the endometrium and cervical mucus [293] and the increased risk of multiple pregnancy [294]. The increasing estradiol levels secreted by the multiple developing ovarian follicles which first appear on day 7 results in normal negative feedback on FSH secretion later in the follicular phase and those follicles that are smaller than the dominant follicle undergo atresia, resulting, in most cases, in single follicle ovulation [294].

Letrozole is typically administered on days 3–7 of the menstrual cycle at doses of 2.5–7.5 mg per day in 2.5mg increments [266]. Adverse effects include gastrointestinal disturbances, asthenia, hot flushes, headache and back pain [292]. The potential teratogenic effect of letrozole for infertility treatment was first raised at an American Society for Reproductive Medicine meeting in 2005 where an oral abstract presentation suggested that the use of letrozole for infertility treatment might be associated with a higher risk of congenital cardiac and bone malformations in newborns [295]. However, four subsequent publications suggest that letrozole use for ovulation induction may not be associated with significant increased risk of fetal anomaly [296-298], where congenital anomalies found in the letrozole group were 0%, 2.4%, 0% and 1% compared with 2.6%, 4.8%, 2% and 0.3% in the clomiphene citrate group, respectively.

Given that aromatase inhibitors have recently been used in the treatment of infertile women with PCOS, it is important to evaluate their effectiveness in improving fertility outcomes in this group of women.

Evidence to answer the question

Twenty-five studies were identified by our search. The four systematic reviews were found to have a low risk of bias. Nine of the RCTs were found to have a low risk of bias, three had a moderate risk of bias and nine had a high risk of bias. The systematic reviews contain the same studies (and therefore do not provide any additional evidence and in some cases are not as comprehensive or current) as the meta-analyses conducted thus far in the original 2011 Australian PCOS guideline and the 2014 update by our team on behalf of the World Health Organisation (WHO), which are further updated here to incorporate new evidence. Therefore we have incorporated the newly published RCTs into the existing meta-analyses. One of
the identified systematic reviews contains the meta-analyses conducted in the initial Australian PCOS guideline and thus will not be referred to further [299]. The remaining three systematic reviews will only be referred to where they provide evidence not already addressed in this evidence review [300-302].

Aromatase inhibitors compared to placebo

Our search did not identify any studies addressing the effectiveness of letrozole as first line therapy in women with PCOS (ie. letrozole versus placebo in treatment naïve patients).

Studies identified by our search addressed the effectiveness of letrozole as second line therapy in women with PCOS. One high quality RCT (level II) with a low risk of bias compared letrozole to placebo in women with CCR PCOS and found that letrozole was better than placebo for ovulation rate per patient but there was no difference between letrozole and placebo for pregnancy rate per patient or live birth rate per patient [303].

Type, duration and dose of aromatase inhibitors

One high quality RCT with low risk of bias found that there was no statistical difference between letrozole and anastrozole for ovulation rate per cycle, pregnancy rate per cycle and miscarriage rate per pregnancy in clomiphene-resistant women with PCOS [304]. A low quality RCT with high risk of bias (Al-Omari 2004) addressing this comparison and outcomes found that letrozole is better than anastrozole for ovulation rate per cycle (p=0.05) and pregnancy rate per cycle (p = 0.05), however it is possible that the effect may be overestimated in a study with high risk of bias and therefore the results should be interpreted with caution.

One high quality RCT with low risk of bias found that long term therapy (10 days) of letrozole may be better than short term therapy (5 days) for pregnancy rate per cycle in clomiphene-resistant women with PCOS (p = 0.03) but that there is no statistical difference between short and long term therapy for ovulation rate per patient and miscarriage rate per pregnancy [305]. This is the only study identified addressing the duration and dose of letrozole and the 10 day protocol using 2.5mg per day appeared optimal.

One low quality RCT with low risk of bias found that there was no statistical difference between 5mg/day and 7.5mg/day of letrozole for ovulation rate per patient and per cycle, pregnancy per patient and per cycle, miscarriage rate per pregnancy and multiple pregnancies per pregnancy [306]. No OHSS was reported in either group.

Aromatase inhibitors compared to clomiphene citrate

Thirteen RCTs (level II) compared letrozole with clomiphene citrate. Seven of these RCTs had a high risk of bias [307-313], two had a moderate risk of bias [298, 314] and four had a low risk of bias [315-318]. Upon meta-analysis, we found that letrozole was better than clomiphene citrate for ovulation rate per patient [298, 307, 308, 310, 312, 314, 317, 318]; pregnancy rate per patient [298, 307-318]; and per cycle [310, 311, 318]; and live birth rate per patient [298, 308, 315, 317, 318]. There was no difference between letrozole and clomiphene citrate for ovulation rate per cycle [310, 311, 315, 316, 318]; multiple pregnancy rate per patient [298, 307, 309, 310, 313, 316-318]; and miscarriage rate per patient [298, 308-310, 314-318]. When subgroup analysis was conducted for studies that included women with PCOS who were therapy naïve, there was no difference between the two interventions for any outcome though we note that for pregnancy rate per patient the OR 1.68 [95% CI 0.96, 2.94] had an I2 of 0% and a p value of 0.07.
### Aromatase inhibitors compared to clomiphene citrate plus metformin

One medium quality RCT (level II) with moderate risk of bias compared letrozole to clomiphene citrate plus metformin and found that there was no difference between letrozole and clomiphene citrate plus metformin for ovulation rate per cycle, pregnancy rate per cycle, miscarriage rate per pregnancy and multiple pregnancy rate per pregnancy in women with CCR PCOS [319].

### Aromatase inhibitors compared to laparoscopic ovarian surgery

Two high quality RCTs with low risk of bias [320, 321] compared letrozole to laparoscopic ovarian surgery (LOD). One of the RCTs in 147 women with CCR PCOS found that letrozole was better than laparoscopic ovarian surgery for ovulation rate per cycle (p < 0.001), however there was no statistical difference between letrozole and LOD for pregnancy rate per patient, live birth rate per patient and miscarriage rate per pregnancy [320]. Another high quality RCT with low risk of bias in 260 women with CCR PCOS compared the same interventions over the same follow-up time periods and found that there were no statistical differences for ovulation rate per cycle, pregnancy rate per cycle, pregnancy rate per patient, live birth rate per pregnancy, biochemical miscarriage rate per patient and clinical miscarriage rate per pregnancy between letrozole and LOD [321].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RCTs*</th>
<th>PCOS &amp;**</th>
<th>Effect estimate***</th>
<th>Favours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation rate per patient</td>
<td>2L 2M 5H</td>
<td>TN CCR U</td>
<td>OR 2.01 [95% CI 1.47, 2.76], I²=35%, P&lt;0.0001</td>
<td>letrozole</td>
</tr>
<tr>
<td>Ovulation rate per cycle</td>
<td>3L 2H</td>
<td>TN U</td>
<td>rate ratio 0.97 [95% CI 0.87, 1.07], I²=0%, P=0.51</td>
<td>ND</td>
</tr>
<tr>
<td>Pregnancy rate per patient</td>
<td>4L 2M 7H</td>
<td>TN CCR U</td>
<td>OR 1.56 [95% CI 1.22, 2.00], I²=31%, P=0.0004</td>
<td>letrozole</td>
</tr>
<tr>
<td>Pregnancy rate per cycle</td>
<td>1L 2H</td>
<td>TN CCR U</td>
<td>rate ratio 1.45 [95% CI 1.03, 2.05], I²=0%, P=0.03</td>
<td>letrozole</td>
</tr>
<tr>
<td>Live birth rate per patient</td>
<td>3L 1M 1H</td>
<td>TN CCR U</td>
<td>OR 1.78 [95% CI 1.37, 2.32], I²=0%, P&lt;0.0001</td>
<td>letrozole</td>
</tr>
<tr>
<td>Multiple pregnancy rate per patient</td>
<td>3L 1M 4H</td>
<td>TN CCR U</td>
<td>OR 0.54 [95% CI 0.22, 1.33], I²=0%, P=0.18</td>
<td>ND</td>
</tr>
<tr>
<td>Miscarriage rate per patient</td>
<td>4L 2M 3H</td>
<td>TN CCR U</td>
<td>OR 1.47 [95% CI 0.98, 2.20], I²=0%, P=0.06</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Risk of bias: L, low risk of bias, high quality; M, moderate risk of bias, medium quality; H, high risk of bias, low quality.

**Includes women with PCOS and one or more of: TN, therapy naïve; CCR, clomiphene citrate-resistant; U, unknown whether therapy naïve or clomiphene citrate-resistant.

***OR, odds ratio
The evidence obtained from the included studies is generalisable to patient population in terms of age and BMI. Detail about the study setting was often not reported but studies were conducted in Egypt, Iraq, Bangladesh, Iran, India, Saudi Arabia, Turkey and the USA. These studies may be applied in the Australian setting, but may not address issues of special importance, such as generalisability to Indigenous populations and those of ethnicities not yet studied. It should also be noted that the evidence does not provide clear guidance on the role of aromatase inhibitors across the different treatment subgroups (eg. Treatment naïve and clomiphene citrate-resistant women) or ethnic groups.

**Recommendations**

<table>
<thead>
<tr>
<th>EVIDENCE BASED RECOMMENDATIONS</th>
<th></th>
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<tbody>
<tr>
<td>7.4a Letrozole, under caution, could be offered as a pharmacological treatment for ovulation</td>
<td>A</td>
</tr>
<tr>
<td>induction indicated for infertile anovulatory women with polycystic ovary syndrome with no</td>
<td></td>
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<tr>
<td>other infertility factors</td>
<td></td>
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<tr>
<td>7.4b Letrozole, under caution, could be considered as a first line pharmacological treatment for</td>
<td>B</td>
</tr>
<tr>
<td>ovulation induction in therapy naïve, infertile anovulatory women with polycystic ovary</td>
<td></td>
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<tr>
<td>syndrome with no other infertility factors</td>
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</table>

**CLINICAL PRACTICE POINT**

7.4d Where letrozole is to be prescribed, the following should be considered:

- Local therapeutic regulatory requirements
- Potential cost implications
- Need for patient explanation and consent for off label use [322] ¹⁰

**Clinical impact of the recommendations: Moderate**

We recommend exercising caution when using letrozole. It is important to note that aromatase inhibitors have not been approved for use in ovulation induction and in women with PCOS, furthermore, costs are not currently subsidised on the Pharmaceuticals Benefits Scheme. It is likely that they would currently not be routinely used as first line treatment in women with PCOS and therefore these recommendations may increase use. The costs are likely to be similar overall to other routinely used ovulation induction agents. The evidence about the risk of congenital abnormalities with the use of aromatase inhibitors is unclear and the potential for such a negative impact of aromatase inhibitors should not be ruled out. Patient explanation and consent is appropriate. Use could be considered in those with an adverse reaction to clomiphene citrate.

¹⁰ The Council of Australian Therapeutic Advisory Groups (CATAG) includes the following recommendation with regard to “off-label” prescribing: An in-depth discussion with the patient/carer about potential benefits and risks is necessary when making the decision to use a medicine off-label. This is particularly important when the use of a medicine off-label is being considered on the wishes of the patient/carer. In general, the off-label use of a medicine should only be considered when the approved use of a registered medicine does not address the clinical needs of patients [322].
Pharmacological management considerations for Indigenous women

We expect that the above recommendations are applicable to Indigenous women but acknowledge that they may not be applicable in the Indigenous setting due to the limitations in care and service provision in rural and remote locations.

RESEARCH RECOMMENDATION

Further methodologically rigorous trials are important to address the role of aromatase inhibitors in ovulation induction in polycystic ovary syndrome. In particular, the comparison of letrozole and clomiphene citrate in population subgroups according to BMI and prior therapy or not is important to explore. The impact on birth defects should also be investigated.
CHAPTER EIGHT

Surgical management of infertility in PCOS

Surgical therapy can be used to induce ovulation, but as a more intensive second line therapy for ovulation induction in women with PCOS. Risks and benefits should be well considered by the patient and clinician, together.

8.1 Laparoscopic ovarian surgery

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

Clinical need for the question

In 1935 Stein and Leventhal were the first to describe an association between the presence of polycystic ovaries, oligo/anovulation and hirsutism, later known as PCOS [323]. The observation that women with PCOS resumed regular ovulations following ovarian biopsies led to the belief that the condition was primarily ovarian in origin. This also resulted in the development of a surgical treatment for the condition involving a wedge resection of both ovaries via laparotomy [324]. 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% [325].

No alternative treatment was available until the arrival of hormonal preparations such as clomiphene citrate and gonadotrophins. Ovarian wedge resection was then soon abandoned because of the relative cost of the surgical treatment and the risk of post-operative adhesions.

It was not until the introduction of minimally invasive techniques that surgical approaches were revisited. The laparoscopic ovarian drilling procedure was first described by Gjønæss in 1984 [326]. Minor variations of the technique have been reported (electrocautery, laser vaporization, multiple ovarian biopsies and others) but all are characterised by an altered endocrine profile following surgery. It remains poorly understood, however, which mechanisms bring about the hormonal changes and the resumption of ovulation.

The main reason laparoscopic ovarian surgery has found support for the treatment of women with CCR PCOS is the fact that the endoscopic approach is thought 1) to cause fewer adhesions, 2) to be more cost-effective as an outpatient-procedure and 3) to restore regular mono-ovulations, albeit for a limited time in the majority of cases. In contrast, ovulation induction with gonadotrophins is expensive, requires regular monitoring and often results in the development of multiple mature follicles with a potential risk of multiple pregnancies and ovarian hyperstimulation syndrome. It is important to establish the effectiveness of laparoscopic ovarian surgery, particularly in comparison to other treatments, in infertile women with PCOS in light of the potential risks.

Evidence to answer the question

Six articles reporting five studies were identified by our search to answer this question. One high quality systematic review of RCTs (level I) with low risk of bias compared laparoscopic ovarian surgery to gonadotrophins and found that there was no difference between the interventions for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy, but
laparoscopic ovarian surgery was better than gonadotrophins for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] \( I^2 = 0\% \), 4 studies, 303 participants) [327].

One high quality RCT (level II) with a low risk of bias compared laparoscopic ovarian surgery to clomiphene citrate plus metformin and found that clomiphene citrate plus metformin (CC+M) was better than laparoscopic ovarian surgery for ovulation rate per cycle (LOS: 77/107 (72%), CC+M: 52/92 (56.5%), p=0.023), but there was no difference for live birth rate per cycle, pregnancy rate per cycle and miscarriage rate per pregnancy [328].

Two medium quality RCTs (level II) with a moderate risk of bias compared laparoscopic ovarian surgery to metformin and found that there was insufficient evidence to make a recommendation about laparoscopic ovarian surgery compared to metformin for live birth rate per patient, ovulation rate per cycle, pregnancy rate per cycle, pregnancy rate per patient and miscarriage rate per pregnancy [329-331] because the evidence was conflicting. One RCT reported that laparoscopic ovarian surgery was better than metformin for ovulation (OR 2.05; [1.4–2.9] p=0.001) and pregnancy rate (per cycle: OR 2.19 [1.03–4.63] p=0.03; per patient: OR 2.47 [1.05–5.81] p=0.03) [329] and the other study reported that metformin was better than laparoscopic ovarian surgery for live birth rate (metformin: 82.1%, LOS: 64.5%, p<0.05), pregnancy rate per cycle (metformin: 18.6%, LOS: 13.4%, p<0.05), and miscarriage rate (metformin: 15.4%, LOS:29.0%, p<0.05) [330, 331]. Both medium quality single centre studies had a small sample size and moderate risk of bias and therefore need to be interpreted with caution.

One high quality RCT (level II) with a low risk of bias compared laparoscopic ovarian surgery to clomiphene citrate [332] and one high quality systematic review of RCTs (level I) with low risk of bias found that laparoscopic ovarian surgery was better than gonadotrophins for multiple pregnancy rate (OR 0.13 [0.03 to 0.59] \( I^2 = 0\% \), 4 studies, 303 participants) [327]. These studies found that there was no difference between laparoscopic ovarian surgery, clomiphene citrate and gonadotrophins for live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy [327, 332].

There was insufficient evidence to support or refute the use of laparoscopic ovarian surgery over metformin or clomiphene citrate or clomiphene citrate plus metformin for multiple pregnancies [329-332] and there was insufficient evidence to support or refute the use of laparoscopic ovarian surgery over any intervention for adverse effects and QoL.

The evidence obtained from the included studies is generalisable to the patient population in terms of age and BMI. Detail about the study setting was often not reported but studies were conducted in New Zealand, Italy, UK and Egypt. While the studies conducted in Europe and Egypt may not be directly generalisable to the Australian setting, it is possible that the RCT [333] included in the systematic review by Farquar et al. [327], conducted in New Zealand, may address issues of special importance, such as generalisability to Indigenous populations.
## Recommendations

<table>
<thead>
<tr>
<th>EVIDENCE-BASED RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.1a Laparoscopic ovarian surgery should be second line therapy in women with polycystic ovary syndrome who are clomiphene citrate resistant, anovulatory, and infertile, with no other infertility factors.</td>
</tr>
</tbody>
</table>

### CLINICAL PRACTICE POINT

8.1b If undergoing laparoscopic ovarian surgery, the patient should be advised of the risks (see below).

### CLINICAL CONSENSUS RECOMMENDATION

8.1c Where ovulation induction would be considered appropriate, laparoscopic ovarian surgery can be used as first line treatment if laparoscopy is indicated for another reason in infertile women with PCOS.

### CLINICAL PRACTICE POINT

8.1d Where gonadotrophins (see 7.3) or laparoscopic ovarian surgery are to be prescribed, the following should be considered:

- Cost of either intervention for ovulation induction
- Expertise required for the use of either intervention for ovulation induction
- The degree of intensive monitoring that is required for gonadotrophin therapy
- Implications of potential multiple pregnancy for gonadotrophin therapy
- Implications of the potential risk of ovarian hyperstimulation syndrome for gonadotrophin therapy
- Laparoscopic surgery in women who are overweight or obese is associated with both intra-operative and post-operative risks.

### Clinical impact of the recommendations: Slight

Laparoscopic ovarian surgery should be considered a second line treatment indicated for infertile, anovulatory women with CCR PCOS. Laparoscopic ovarian surgery, when compared to other such second line treatments, is equally effective to gonadotrophins but has a lower risk of multiple pregnancy (for comparison see 7.3). However, it is important to note that laparoscopic surgery in women who are overweight or obese is associated with both intra-operative (ie. difficulty with access to abdominal cavity and manipulation of surgical instruments, reduced operative field exposure) and post-operative (ie. bleeding, infection, thromboembolism, pulmonary atelectasis/hypoxemia, and wound complications) risks. Where laparoscopic ovarian surgery is not already second line treatment, indicated for infertile, anovulatory, CCR women with PCOS, there may be resource implications. The guideline development group is not aware of changes to the way care is organised or barriers to implementation of these recommendations. Issues covered in the clinical practice point should be considered when deciding between laparoscopic ovarian surgery and gonadotrophins.
8.2 Bariatric surgery

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

Clinical need for the question

Obesity has been shown to adversely impact on fertility. Weight loss improves fertility and addresses maternal and neonatal complications associated with obesity. It may also increase the safety and effectiveness of ovulation induction. Most studies suggest even modest weight loss improves spontaneous pregnancy rates and this has also been observed following bariatric surgery, however surgical studies are generally poorly designed [334]. Many bariatric procedures require presurgical weight loss and given that major weight loss may not be essential to improve ovulation and pregnancy, differentiating between the impact of presurgical and surgically induced weight loss is difficult [335].

Weight loss or preventing weight gain using established lifestyle interventions should be implemented for all reproductive-aged women with PCOS. More intensive lifestyle interventions should be considered for those overweight women wishing to improve fertility. Women with a BMI ≥35kg/m² and who have tried weight loss methods for at least 1 year without success may consider bariatric surgery. The 2009 American Congress of Obstetricians and Gynecologists clinical practice guidelines does recommend bariatric surgery for fertility treatment [336].

The most recent clinical guidelines for obesity management in the general population [337] recommended consideration of bariatric surgery in patients with a BMI ≥35kg/m² with presence of one or more severe complications, which are expected to improve with weight reduction. Completion of a structured lifestyle intervention, not resulting in significant and sustained weight loss is also required [337]. Obesity surgery can be considered after non-surgical treatment has been attempted unsuccessfully for at least 6 months in adults with a BMI ≥40kg/m² and that obesity surgery can be first line treatment instead of lifestyle interventions or drug treatment in adults with BMI ≥50kg/m² [338].

A Cochrane review on bariatric surgery in general populations noted greater weight loss in obesity (BMI ≥30kg/m²) and associated reductions in complications including DM2 post-surgery. There is limited data on weight loss and relative safety with different procedures although greater weight loss was noted with gastric bypass, isolated sleeved gastrectomy and banded gastric bypass [339]. A recent update and meta-analysis reported an overall weight loss of 38.5 kg or 55.9% excess body weight loss, complete resolution of DM2 in 78.1% of diabetic patients and partial resolution of DM2 in 86.6% of patients [340].

Specifically with regards to PCOS, recent guidelines from the American Association of Clinical Endocrinologist, The Obesity Society and American Society for Metabolic and Bariatric Surgery [341] provided expert opinion based on lack of conclusive clinical evidence that women with PCOS should be advised that their fertility status may be improved postoperatively. Current controversies relevant to PCOS include whether PCOS should be considered an obesity-related condition as BMI cut-offs for bariatric surgery may be reduced in this circumstance (e.g. poorly controlled DM2 with BMI ≥30kg/m²) [342], however evidence is insufficient to recommend bariatric surgery with a BMI ≤35kg/m² [341].

Bariatric methods can result in malabsorptive states, poor food tolerance or psychological issues which may compromise nutritional status, particularly with ongoing vomiting and or disordered eating. Rates of eating disorders are higher in women with PCOS than in the general population (21% vs 4%) [152] and may contribute to a greater nutritional risk which may impact adversely on fertility, maternal and neonatal
complications. Average energy intake is around 1600kcals/day following bariatric surgery [343] and nutrient density therefore becomes an issue affecting nutritional status. Women may be at particular risk of deficiencies in iron, folate and iodine in addition to other nutrients as the recommended daily intake increases in pregnancy. While supplement use is widely recommended following bariatric surgery and for pregnant women, there are reports of poor compliance with supplement use in the general population of pregnant women with only 10% taking adequate folate [344]. This may be further compromised because of poor food tolerance in bariatric patients, particularly of foods fortified with iodine and folate such as bread.

Assisting women with a BMI ≥35kg/m² through standard infertility is not appropriate (see recommendation 6.1c). In severe obesity, lifestyle interventions have very limited efficacy but given the substantial efficacy of bariatric surgery in women who are severely obese, including in women with PCOS, it is important to determine the impact of bariatric surgery on infertility in women with PCOS. The potential benefits also need to be balanced with the risks of bariatric surgery.

Evidence to answer the question

We did not identify any evidence about the effectiveness of bariatric surgery in women with PCOS to inform this recommendation and therefore a clinical consensus recommendation has been made based on the clinical expertise of the multidisciplinary guideline development group, informed by existing evidence-based clinical guidelines for bariatric surgery in the general population. In general populations, bariatric surgery is recommended in those who have a BMI ≥35kg/m² and the presence of co-morbid conditions that are expected to improve significantly with weight reduction [337, 341]. PCOS is a co-morbid condition that improves significantly with weight reduction and is strongly associated with other co-morbidities including DM2, obstructive sleep apnoea, non-alcoholic fatty liver disease and increased CVD risk. Therefore the recommendation reported in the evidence-based guidelines for management of obesity is applicable to this evidence review and patient population.

Recommendations

<table>
<thead>
<tr>
<th>CLINICAL CONSENSUS RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2a Bariatric surgery could be considered second line therapy to improve fertility outcomes in adult women with polycystic ovary syndrome who are anovulatory, have a body mass index ≥35kg/m², and who remain infertile despite undertaking an intensive (frequent multidisciplinary contact) structured lifestyle management program involving reducing dietary energy (caloric) intake, exercise, behavioural and/or drug interventions for a minimum of 6 months.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLINICAL PRACTICE POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2b If bariatric surgery is to be prescribed, the following key issues should be considered:</td>
</tr>
<tr>
<td>- A structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health should continue post-operatively.</td>
</tr>
<tr>
<td>- The patient should be made aware of the risk of pre-and post-operative nutritional deficiencies and should be managed in a specialist interdisciplinary care setting, including a bariatric surgeon, a dietitian and/or other multidisciplinary staff trained to work with patients who have had bariatric surgery.</td>
</tr>
</tbody>
</table>
CLINICAL PRACTICE POINTS

8.2c If bariatric surgery is to be prescribed, the following key issues should be considered:

- Bariatric surgery should not be conducted in patients who are known to be pregnant [24]
- Pregnancy should be avoided during periods of rapid weight loss
- Patients should be counselled to avoid pregnancy for at least 12-18 months after bariatric surgery [24, 25]
- Contraception should be discussed prior to surgery
- If pregnancy occurs, the patient should be made aware of the risk of pre-and post-operative nutritional deficiencies and should ideally be managed in a specialist interdisciplinary care setting which includes an obstetrician, bariatric surgeon and a dietitian and/or other multidisciplinary staff trained to work with patients who have had bariatric surgery to ensure that nutritional deficiencies and complications are avoided
- Fetal growth should be monitored during pregnancy
- A structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health should continue post-operatively.

RESEARCH RECOMMENDATIONS

Further methodologically rigorous trials are important to address the efficacy, safety and role of bariatric surgery in polycystic ovary syndrome including to improve fertility.

Clinical impact of the recommendations: Very large

Obesity is increased in PCOS with major health implications including adverse impacts on fertility and pregnancy. Bariatric surgery could be considered second line therapy to improve fertility outcomes in women with PCOS. Current practice is unclear, although it is likely that few of these women are currently having bariatric surgery. Implementation of these recommendations is likely to have resource implications including the cost of bariatric surgery and specialist care, which may be offset by less use of assisted reproductive technologies and fewer complications in pregnancy and beyond. Indications to date regarding bariatric surgery have primarily addressed Caucasian populations. It is well known that there are ethnic differences in adiposity, weight distribution and disease risk, such that BMI and cut-off points for clinical intervention may be adjusted for ethnicity. Women with PCOS who become pregnant after bariatric surgery could be considered as a high risk pregnancy, as are women in the general population who are obese and pregnant.

Surgical management considerations for Indigenous women

We expect that the above recommendations are applicable to Indigenous women but acknowledge that they may not be applicable in the Indigenous setting due to the limitations in care and service provision in rural and remote locations. There may be cultural factors and potential issues around acceptability of bariatric surgery, given that most of the evidence is in Caucasian populations.
Summary of the impacts of implementation of the recommendations

Impacts of implementation of recommendations, including costs, have been considered throughout the guideline by the guideline development groups. Recommendations on challenges in diagnostic assessment of PCOS impact primarily through increased investigations. Metabolic tests on CVD risk factors and glycaemic status would be expected to increase in response to guideline implementation, with cost implications, whereas more limited androgen testing and less usage of ultrasounds in adolescents may reduce costs.

In assessment of emotional wellbeing, screening may increase consultation time, however initial screening time can be minimised by the use of the devised general emotional wellbeing screening tool developed with this guideline (Appendix V) that can be completed outside consultation times and has been trialled and used in clinical practice. The primary challenges here are the cost implications when psychological dysfunction is detected, potentially requiring additional consultation time and referral to other health professionals and utilisation of care plans may be required.

Likewise, in lifestyle management of PCOS, recommendations may increase consultation times, utilisation of care plans and referral to allied health professionals and as such, higher associated healthcare costs. However long term benefits of lifestyle change are anticipated to reduce the health and economic burden of PCOS. Whilst in the overall management of infertility, lifestyle intervention and bariatric surgery have cost implications, which may be offset by reduced medical intervention to induce fertility, overall the fertility recommendations are not expected to have major resource implications.
Summary of recommendations for research

Further methodologically rigorous trials in women with PCOS are important to address:

- Age-appropriate normal ranges for sonographic features of polycystic ovaries and for clinical and biochemical features of PCOS in adolescents (<18 years)
- Accuracy of ovarian volume to diagnose PCOS in adolescents (<18 years)
- Implementation and evaluation of an interdisciplinary model of care in PCOS, where an evaluation strategy for a service model needs to be designed from the outset of the interdisciplinary service. Evaluation of health service models requires resources
- Absolute risk of CVD in women with polycystic ovary syndrome across age ranges
- The most appropriate way of identifying those with PCOS at highest risk of developing DM2 and the value of utilising existing scores such as the AUSDiab risk score
- The most effective method to prevent the development of DM2
- Further methodologically rigorous trials in women with PCOS are important to determine the most effective tool to assess and optimal approaches to manage:
  - depression and/or anxiety
  - psychosexual dysfunction
  - eating disorders and disordered eating
  - negative body image
  - overall health related quality of life
- This body of research should consider emotional wellbeing across the different cultural and age groups affected by PCOS.
- The extent of the benefits of lifestyle management compared to no or minimal treatment for all clinically relevant outcomes
- Comparing efficacy of different types of lifestyle management (diet alone, exercise alone, behavioural modification alone, or combinations of the three)
- The effect of lifestyle management in prevention of weight gain/weight maintenance compared to weight loss
- The effect of lifestyle management for women who are both overweight and not overweight and specific reproductive outcomes such as menstrual regularity, ovulation and fertility and the relative efficacy of lifestyle management either compared to or in combination with pharmacological therapy
- A range of diet compositions including low GI for both prevention of weight gain/weight maintenance and weight loss in women who are overweight and in women who are lean
- Monitoring of safety and harms of diets and longer follow-up
- Increasing engagement and compliance with intervention studies
- The types of diet delivery methods and diet support and tools that are effective - an initial study would be to have diet compositions the same and vary the delivery method or support tools between the groups
- Comparison of the delivery methods for lifestyle interventions including comparing settings and providers
- The types, intensities and delivery methods of exercise strategies that are optimal for lean and overweight women for improved clinical outcomes
• The impact of lifestyle improvement on fertility outcomes including live birth
• Optimal translation strategies (implementation research to inform consumers, health professionals and policy makers) on optimal care of women with PCOS and infertility
• Whether the addition of metformin to clomiphene citrate improves live birth rate in women with PCOS who are anovulatory and infertile with no other infertility factors
• Whether there is a difference in effectiveness between clomiphene citrate and metformin in women with PCOS who are anovulatory, infertile and have BMI ≤30kg/m² to improve fertility outcomes
• The role of gonadotrophins in ovulation induction in PCOS
• The role of aromatase inhibitors in ovulation induction in PCOS; in particular, the comparison of letrozole and clomiphene citrate in population subgroups according to BMI and prior therapy or not is important to explore.
• The impact of different ovulation induction agents in PCOS subgroups including those based on BMI
• The efficacy, safety and role of bariatric surgery in PCOS including to improve fertility.
Limitations of the guideline

Given the enormity of the condition of PCOS and its associated complications, it was beyond the resources, time frame and scope of this guideline to address all possible clinical questions. It is important to note that there is a paucity of evidence and the evidence that is available is of poor quality.

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 to the patient’s clinical profile and personal preferences. It is recommended that the reader consults the Therapeutic Guidelines (www.tg.com.au) and the National Prescribing Service (www.nps.org.au) for detailed prescribing information including:

- indications
- drug dosage
- method and route of administration
- contraindications
- supervision and monitoring
- product characteristics
- adverse effects.

This guideline does not include a formal analysis of cost effectiveness of recommended practice compared to current/established practice, nor does it cover economic feasibility of the recommendations. Consideration of cost did occur in guideline development group meetings and did impact on recommendations. These considerations are discussed in the clinical impact of the recommendation sections in each chapter.

The guideline is based on the best evidence available up to November 2010. Evidence published after this date has not been reviewed for the guideline. Development of technology and pharmacological intervention progresses rapidly and so the guideline may become outdated. However steps are in place to ensure that the guideline is updated in a timely manner, such as upon publication of new evidence that has any bearing on the safety of the recommendations or if there are changes in the indications registered by the Therapeutic Goods Administration for any drug included in the guideline. For more information about scheduled review and update, see Scheduled review and update of the guideline.

All recommendations are limited by their applicability to a particular population and setting, therefore use of the recommendations need to be guided by clinical judgement. For example, high risk populations where cardiometabolic and DM2 risk is increased, the impact of weight gain appears to be more significant than in Caucasian populations and this needs to be considered when assessing and managing women with PCOS.

Finally, a guideline is only useful if it has been translated and implemented into practice appropriately. In doing so, cultural barriers may be experienced.
Translation and implementation

Jean Hailes for Women’s Health will be leading the translation of the evidence-based guidelines for assessment and management of PCOS as a not-for-profit, government funded national women’s health organisation. The Alliance will be actively involved and will provide guidance and expertise to facilitate the translation process. Jean Hailes for Women’s Health has a successful 18-year history of delivering positive health outcomes to Australian women through an innovative mix of research, education and clinical care. It has an innovative, three-fold approach to health and wellbeing: the integration of education for the community and healthcare professionals with clinical practice and focused research with broad translation strategies. It engages with consumers, communities, health professionals and peak bodies to encourage a model of informed preventive health.

A key strength of Jean Hailes for Women’s Health is its ability to take research findings and translate them using a broad range of strategies, including the development of evidence-based guidelines, into educational resources and programs for health professionals and women, and target marginalised groups including CALD and Indigenous groups at a national level. We do this in a number of diverse ways including:

- training health professionals in diagnosis and treatment of specific conditions and diseases
- producing multi-media presentations that health services and agencies can use to educate their staff and clients
- maintaining a sophisticated, data-rich website with health education resources for women and health professionals on a variety of topics relating to women, in multiple languages and for all regions of Australia
- responding to requests for information from all sectors by phone, as well as through face-to-face seminars, presentations and briefings for women and health professionals throughout Australia
- extending health promotion messages through the media.

A deliverable of the funding for this guideline is a comprehensive 18 month translation program, commenced as of February 2011. This program includes dissemination of the guideline and translation of the guideline into a range of practice enhancement and education tools (e.g. algorithms, facts sheets), targeting a diverse range of end-users. A comprehensive evaluation of the translation tools is integrated into the dissemination and translation program. The evaluation is also ongoing through the funded PCOS Service of Excellence at Jean Hailes for Women’s Health which is underpinned by this guideline.

Translation of the updated Section 7.4 Aromatase inhibitors will be facilitated through Jean Hailes for Women’s Health channels, through the fertility-related networks of Alliance and guideline development group members and through publication of the updated evidence review.

Below are the proposed resources to be developed and translation activities to be undertaken.
<table>
<thead>
<tr>
<th>Resources</th>
<th>Date</th>
<th>Dissemination/use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Printed copies of the Guidelines (for general distribution and use in educational activities)</td>
<td>To begin November 2011 (ongoing)</td>
<td>• Dissemination via publication in a medical journal and through targeted education programs delivered by the Jean Hailes for Women’s Health Electronic copies available via Jean Hailes for Women’s Health website (promotion and links through relevant college, medical institutions, university, POSAA and PCOS Alliance (members) websites. • Promotion through relevant professional colleges, appropriate government departments and via PCOS Alliance/Strategic Advisory Group members • National media campaign to promote Guidelines, supplementary resources &amp; education programs</td>
</tr>
<tr>
<td>Summary document of recommendations contained within the Guidelines</td>
<td>November 2011 (ongoing)</td>
<td>As above</td>
</tr>
<tr>
<td>Algorithms and stepped care processes (as developed within the Guidelines) as stand-alone resources</td>
<td>November 2011 (ongoing)</td>
<td>• Dissemination via targeted education programs delivered by Jean Hailes for Women’s Health and through relevant health professional conference exhibitions. • Electronic copies available through the health professional section of the Jean Hailes for Women’s Health website</td>
</tr>
<tr>
<td>Consumer Resource (which includes information about PCOS and tools such as types of HPs to consult, ability to record test results, food/mood/physical activity diary, etc)</td>
<td>April 2011</td>
<td>• Promotion and dissemination to patients attending the JH PCOS Clinic • Promotion via <a href="http://www.managingpcos.org.au">www.managingpcos.org.au</a> and through POSAA • Dissemination via targeted education programs (for consumers and health professionals) delivered by Jean Hailes for Women’s Health</td>
</tr>
<tr>
<td>Education Programs/Activities</td>
<td>Date</td>
<td>Comments/Further Detail</td>
</tr>
<tr>
<td>-------------------------------------------------------------------</td>
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<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Face-to-face health professional educational sessions             | Feb – Nov 2012     | At least 1 education session to be delivered in each capital city (in Australia). Sessions to be delivered in partnership with local general practice networks and with the support of members from the  
  • Guideline Development Groups  
  • Strategic Advisory Group  
  • PCOS Alliance |
| Website content (separate pages for consumers and health professionals) for [www.managingpcos.org.au](http://www.managingpcos.org.au) | All new content to be completed by December 31, 2011 |                                                                                                                                                                                                                       |
| National Videoconference for health professionals                 | June 2012          |                                                                                                                                                                                                                       |
| How-to-treat PCOS supplement in Australian Doctor (National magazine/newspaper) | By Nov 2012        | Participation of PCOS Alliance members in specialty (Fertility Society, Endocrine Society) conferences (by invitation).                                                                                                                                                           |
| Conference presentation & panel discussion                        | Aug 2011- ongoing  | Updates to be made and guidelines incorporated into Jean Hailes for Women’s Health RACGP-accredited category 1 activity which is available online at [http://education.jeanhailes.org.au](http://education.jeanhailes.org.au) |
| Diagnosis & Management of PCOS – an online Active Learning Module (ALM) | By Feb 2012        | Updates to be made and guidelines incorporated into Jean Hailes for Women’s Health RACGP-accredited category 1 activity which is available online at [http://education.jeanhailes.org.au](http://education.jeanhailes.org.au) |
| Public seminars                                                   | Feb – Nov 2012     | At least 1 public seminar to be delivered in each capital city (in Australia). Ideally these seminars should be delivered in each state in conjunction with the health professional seminars. Public Seminars to be delivered in partnership with POSAA. |


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### Appendix I: Membership of PCOS Australian Alliance

Membership at April 2011

<table>
<thead>
<tr>
<th>Title</th>
<th>First name</th>
<th>Last name</th>
<th>Profession</th>
<th>Organisation/ State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>Jacqueline</td>
<td>Boyle</td>
<td>Obstetrician/Gynaecologist</td>
<td>Jean Hailes for Women’s Health, Victoria</td>
</tr>
<tr>
<td>Doctor</td>
<td>Leah</td>
<td>Brennan</td>
<td>Clinical and Health Psychologist and Senior Research Fellow</td>
<td>Centre for Obesity Research and Education, Monash University, Victoria</td>
</tr>
<tr>
<td>Doctor</td>
<td>Grant</td>
<td>Brinkworth</td>
<td>Research Scientist</td>
<td>Commonwealth Scientific and Industrial Research Organisation, South Australia</td>
</tr>
<tr>
<td>Associate Professor</td>
<td>Wendy</td>
<td>Brown</td>
<td>General Surgeon</td>
<td>Centre for Obesity Research and Education, Victoria</td>
</tr>
<tr>
<td>Professor</td>
<td>Henry</td>
<td>Burger</td>
<td>Endocrinologist</td>
<td>Jean Hailes for Women’s Health, Victoria</td>
</tr>
<tr>
<td>Professor</td>
<td>Iain</td>
<td>Clarke</td>
<td>Academic</td>
<td>Monash University, Victoria</td>
</tr>
<tr>
<td>Doctor</td>
<td>Anne</td>
<td>Corbould</td>
<td>Endocrinologist</td>
<td>Prince Henry’s Institute, Victoria</td>
</tr>
<tr>
<td>Doctor</td>
<td>Michael</td>
<td>Costello</td>
<td>Obstetrician/Gynaecologist Reproductive Endocrinologist</td>
<td>University of New South Wales, Royal Hospital for Women and IVF Australia, New South Wales</td>
</tr>
<tr>
<td>Doctor</td>
<td>Andrea</td>
<td>Cussons</td>
<td>Endocrinologist</td>
<td>Royal Perth Hospital, Western Australia</td>
</tr>
<tr>
<td>Associate Professor</td>
<td>Michael</td>
<td>Davies</td>
<td>Epidemiologist</td>
<td>The University of Adelaide, South Australia</td>
</tr>
<tr>
<td>Doctor</td>
<td>Amanda</td>
<td>Deeks</td>
<td>Psychologist</td>
<td>Jean Hailes for Women’s Health, Victoria</td>
</tr>
<tr>
<td>Associate Professor</td>
<td>John</td>
<td>Eden</td>
<td>Obstetrician/Gynaecologist Reproductive Endocrinologist</td>
<td>University of New South Wales, New South Wales</td>
</tr>
<tr>
<td>Doctor</td>
<td>Meredith</td>
<td>Frearson</td>
<td>General Practitioner</td>
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<td>Manny Noakes</td>
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<td>Robert Norman</td>
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<tr>
<td>Professor</td>
<td>Deborah Sloboda</td>
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<td>Jennifer Wong</td>
<td>Endocrinologist</td>
<td>Monash Health, Victoria</td>
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Appendix II: Membership of guideline development committees

Terms of reference for each committee can be provided upon request ([jhf.diabetes@monash.edu](mailto:jhf.diabetes@monash.edu)).

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Discipline</th>
<th>Organisational affiliation</th>
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<tr>
<td>Technical team</td>
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</tr>
<tr>
<td>Project Director</td>
<td>Professor Helena Teede</td>
<td>Endocrinologist</td>
<td>Director of Research, Jean Hailes for Women’s Health; Head of Diabetes, Monash Health; Professor of Women’s Health and Monash Site Director, School of Public Health, Monash University</td>
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<tr>
<td>Project Manager</td>
<td>Ms Linda Downes</td>
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<tr>
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</tr>
<tr>
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<td>Chief Executive Officer, Jean Hailes for Women’s Health</td>
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<tr>
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</tr>
<tr>
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<td>Professor Helena Teede</td>
<td>Endocrinologist</td>
<td>Director of Research, Jean Hailes for Women’s Health; Head of Diabetes, Monash Health; Professor of Women’s Health and Monash Site Director, School of Public Health, Monash University</td>
</tr>
<tr>
<td></td>
<td>Professor Rob Norman</td>
<td>Reproductive Endocrinologist</td>
<td>Director, The Robinson Institute, University of Adelaide</td>
</tr>
<tr>
<td></td>
<td>Mrs Veryan McAllister</td>
<td>Consumer</td>
<td>President, Polycystic Ovary Syndrome Association Australia (the peak consumer organisation in PCOS)</td>
</tr>
<tr>
<td>PCOS Australian Alliance Strategic Advisory Group</td>
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<tr>
<td><strong>Chair</strong></td>
<td><strong>Professor Rob Norman</strong></td>
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<td><strong>Director, The Robinson Institute, University of Adelaide</strong></td>
</tr>
<tr>
<td><strong>Ms Irene Apostolopolous</strong></td>
<td><strong>Consumer</strong></td>
<td><strong>Polycystic Ovary Syndrome Association Australia</strong></td>
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</tr>
<tr>
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<td><strong>Director of Research, Jean Hailes for Women's Health; Head of Diabetes, Monash Health; Professor of Women’s Health and Monash Site Director, School of Public Health, Monash University</strong></td>
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<tr>
<td><strong>Ms Angela Melder</strong></td>
<td><strong>Evidence Service Manager</strong></td>
<td><strong>Centre for Clinical Effectiveness, Monash Health</strong></td>
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<tr>
<td><strong>Dr Sarah Jane McEwan</strong></td>
<td><strong>General Practitioner</strong></td>
<td><strong>Queen Street Medical Centre, NSW Australian Indigenous Doctors Association</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Professor Ian Clarke</strong></td>
<td><strong>Principal Research Fellow</strong></td>
<td><strong>Chairman, Department of Physiology, Monash University</strong></td>
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<tr>
<td><strong>Dr Michael Costello</strong></td>
<td><strong>Obstetrician Gynaecologist Reproductive Endocrinologist</strong></td>
<td><strong>Consultant, IVF Australia; Senior Lecturer, Obstetrics and Gynaecology, University of NSW; Clinical Academic, Department of Reproductive Medicine, the Royal Hospital for Women</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Associate Professor Michael Davies</strong></td>
<td><strong>Epidemiologist</strong></td>
<td><strong>School of Paediatrics and Reproductive Health, University of Adelaide</strong></td>
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</tr>
<tr>
<td><strong>Associate Professor John Eden</strong></td>
<td><strong>Obstetrician Gynaecologist</strong></td>
<td><strong>Director, Barbara Gross Research Unit Director Sydney Menopause Centre, Royal Hospital for Women Director, Women’s Health and Research Unit of Australia</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Associate Professor Manny Noakes</strong></td>
<td><strong>Senior Research Scientist</strong></td>
<td><strong>CSIRO Food and Nutritional Sciences</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Professor Bronwyn Stuckey</strong></td>
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<td><strong>Director, Keogh Institute for Medical Research, Sir Charles Gairdner Hospital</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Professor Roger Hart</strong></td>
<td><strong>Reproductive Endocrinologist</strong></td>
<td><strong>Medical Director, Fertility Specialists of WA Professor of Reproductive Medicine, School of Women’s and Infant’s Health, University of Western Australia</strong></td>
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<tr>
<td><strong>Dr Meredith Frearson</strong></td>
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## Emotional wellbeing guideline development group

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<tr>
<th>Chair</th>
<th>Dr Amanda Deeks</th>
<th>Clinical and Research Psychologist</th>
<th>Manager, Translation Services, Jean Hailes for Women’s Health</th>
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<td>Endocrinologist</td>
<td>Director of Research, Jean Hailes for Women’s Health; Head of Diabetes, Monash Health; Professor of Women’s Health and Monash Site Director, School of Public Health, Monash University</td>
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<td>Clinical Professor Bronwyn Stuckey</td>
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<td>Director, Keogh Institute for Medical Research, Sir Charles Gairdner Hospital</td>
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<tr>
<td></td>
<td>Professor David Clarke</td>
<td>Psychiatrist</td>
<td>School of Psychiatry, Psychology and Psychological Medicine, Monash University</td>
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<td>Dr Jennifer Wong</td>
<td>Endocrinologist</td>
<td>Deputy Head of Diabetes, Monash Health</td>
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<tr>
<td></td>
<td>Dr Leah Brennan</td>
<td>Clinical and Health Psychologist</td>
<td>Psychological Medicine, Monash University</td>
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<tr>
<td></td>
<td>Dr Cate Lombard</td>
<td>Dietitian, Senior Research Fellow</td>
<td>Head, National Lifestyle Program, Jean Hailes for Women’s Health</td>
</tr>
<tr>
<td>Evidence team</td>
<td>Ms Angela Melder</td>
<td>Evidence Service Manager</td>
<td>Centre for Clinical Effectiveness, Monash Health</td>
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<td>Ms Marie Garrubba</td>
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## Lifestyle guideline development group

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<td>Dr Kate Marsh</td>
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<td></td>
<td>Dr Mac Talbot</td>
<td>Obstetrician</td>
<td>Monash IVF</td>
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### Appendix II: Membership of guideline development committees

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<td>Professor Helena Teede</td>
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<td>Director of Research, Jean Hailes for Women’s Health; Head of Diabetes, Monash Health; Professor of Women’s Health and Monash Site Director, School of Public Health, Monash University</td>
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<td>Dr Ee Mun Lim</td>
<td>Chemical Pathologist</td>
<td>Head Clinical Biochemistry, PathWest Laboratory Medicine</td>
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<td></td>
<td>Gynaecologist</td>
<td>Director Sydney Menopause Centre, Royal Hospital for Women</td>
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<td>Director, Women’s Health and Research Unit of Australia</td>
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<tr>
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<td>Dr Elizabeth Davis</td>
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<td>Deputy Head, Diabetes &amp; Endocrinology, Princess Margaret Hospital for Children</td>
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<td>Evidence Service Manager</td>
<td>Centre for Clinical Effectiveness, Monash Health</td>
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<td>Dr Marie Misso</td>
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<td>Jean Hailes for Women’s Health Research Unit</td>
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<td><strong>Therapy for infertility guideline development group</strong></td>
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## Members

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<tr>
<th>Name</th>
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<th>Institution/Position</th>
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<tbody>
<tr>
<td>Professor Helena Teede</td>
<td>Endocrinologist, Reproductive Endocrinologist</td>
<td>Director of Research, Jean Hailes for Women’s Health; Head of Diabetes, Monash Health; Professor of Women’s Health and Monash Site Director, School of Public Health, Monash University</td>
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<td>Professor Roger Hart</td>
<td>Obstetrician, Gynaecologist, Reproductive Endocrinologist</td>
<td>Medical Director, Fertility Specialists of WA; Professor of Reproductive Medicine, School of Women’s and Infant’s Health, University of Western Australia</td>
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<td>Dr Jennifer Wong</td>
<td>Endocrinologist</td>
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<tr>
<td>Dr Luk Rombauts</td>
<td>Obstetrician, Gynaecologist</td>
<td>Women’s Health Program, Monash Health; Monash IVF, Monash University</td>
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<tr>
<td>Ms Narelle Thredgold</td>
<td>Consumer</td>
<td>Polycystic Ovary Syndrome Association Australia</td>
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<tr>
<td>Associate Professor John Moss</td>
<td>Health Economist</td>
<td>Head of Discipline, School of Population Health &amp; Clinical Practice, The University of Adelaide.</td>
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<tr>
<td>Ms Kelly Allen</td>
<td>Independent consumer</td>
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## Evidence team

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<thead>
<tr>
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<th>Institution/Position</th>
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<tbody>
<tr>
<td>Ms Angela Melder</td>
<td>Evidence Service Manager</td>
<td>Centre for Clinical Effectiveness, Monash Health</td>
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<tr>
<td>Dr Marie Misso</td>
<td>Senior Evidence Officer</td>
<td>Jean Hailes for Women’s Health Research Unit</td>
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**Additional co-opted expertise (to assist with formulation of draft recommendations and practice points for clinical question 'In women with PCOS, what is the effectiveness of lifestyle interventions compared to bariatric surgery for improving fertility, quality of life and adverse outcomes?').** Note: Some members from the Lifestyle guideline development group were also co-opted to assist with recommendations for this clinical question.

<table>
<thead>
<tr>
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<tr>
<td>Associate Professor John Dixon</td>
<td>Researcher</td>
<td>Head of Obesity Research Unit, Department of General Practice, Monash University</td>
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<tr>
<td>Dr Cate Lombard</td>
<td>Dietitian</td>
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<td>Dietitian and Research Fellow</td>
<td>The Robinson Institute, Discipline of Obstetrics and Gynaecology, University of Adelaide and Jean Hailes for Women’s Health</td>
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<tr>
<td>Dr Nigel Stepto</td>
<td>Exercise Physiologist</td>
<td>Centre for Ageing, Rehabilitation, Exercise and Sport Science, Victoria University, Vic</td>
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<tr>
<td>Dr Amanda Vincent</td>
<td>Endocrinologist</td>
<td>Jean Hailes for Women’s Health Research Unit</td>
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### Appendix III: NHMRC Evidence Statement template

#### Question:

1. **Evidence base** (number of studies, level of evidence and risk of bias in the included studies)

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<tr>
<td>B</td>
<td>One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td>
</tr>
<tr>
<td>C</td>
<td>One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias</td>
</tr>
<tr>
<td>D</td>
<td>Level IV studies or Level I to III studies/SRs with a high risk of bias</td>
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2. **Consistency** (if only one study was available, rank this component as 'not applicable')

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</tr>
<tr>
<td>B</td>
<td>Most studies consistent and inconsistency can be explained</td>
</tr>
<tr>
<td>C</td>
<td>Some inconsistency, reflecting genuine uncertainty around question</td>
</tr>
<tr>
<td>D</td>
<td>Evidence is inconsistent</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable (one study only)</td>
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</table>

3. **Clinical impact** (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

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</tr>
<tr>
<td>B</td>
<td>Moderate</td>
</tr>
<tr>
<td>C</td>
<td>Slight</td>
</tr>
<tr>
<td>D</td>
<td>Restricted</td>
</tr>
</tbody>
</table>

4. **Generalisability** (How well does the body of evidence match the population and clinical settings being targeted by the Guideline?)

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Evidence directly generalisable to target population</td>
</tr>
<tr>
<td>B</td>
<td>Evidence directly generalisable to target population with some caveats</td>
</tr>
<tr>
<td>C</td>
<td>Evidence not directly generalisable to the target population but could be sensibly applied</td>
</tr>
<tr>
<td>D</td>
<td>Evidence not directly generalisable to target population and hard to judge whether it</td>
</tr>
</tbody>
</table>

---

*Appendix III: NHMRC Evidence Statement template*  
142
### 5. Applicability

(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Evidence directly applicable to Australian healthcare context</td>
</tr>
<tr>
<td>B</td>
<td>Evidence applicable to Australian healthcare context with few caveats</td>
</tr>
<tr>
<td>C</td>
<td>Evidence probably applicable to Australian healthcare context with some caveats</td>
</tr>
<tr>
<td>D</td>
<td>Evidence not applicable to Australian healthcare context</td>
</tr>
</tbody>
</table>

### Evidence Statement Matrix

Please summarise the development group’s synthesis of the evidence relating to the key question, taking all the above factors into account. Please indicate any dissenting opinions.

<table>
<thead>
<tr>
<th>Component</th>
<th>Descriptor</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consistency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalisability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Applicability</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Other Factors

(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation))

### Recommendations

What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.

The overall grade is the summation of the grades for individual components. A recommendation cannot be graded A or B unless the volume and consistency of evidence are both A or B.

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
</tr>
</thead>
</table>

### Unresolved Issues

(If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.)

### Implementation of Recommendation

Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.
<table>
<thead>
<tr>
<th>Question</th>
<th>YES/NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will this recommendation result in changes in usual care?</td>
<td></td>
</tr>
<tr>
<td>Are there any resource implications associated with implementing this recommendation?</td>
<td></td>
</tr>
<tr>
<td>Will the implementation of this recommendation require changes in the way care is currently organised?</td>
<td></td>
</tr>
<tr>
<td>Are the guideline development group aware of any barriers to the implementation of this recommendation?</td>
<td></td>
</tr>
</tbody>
</table>
Appendix IV: PCOS referral resource

Polycystic Ovary Syndrome and Assessment of Emotional Health

Practitioner’s Information Sheet

Your client has recently attended the Jean Hailes Polycystic Ovary Syndrome Service. This service provides multi-disciplinary management of Polycystic Ovary Syndrome (PCOS), with referral linkages to other health professionals as required in each individual patient’s circumstances. PCOS now affects between 12-18% of Australian women.

Living with a chronic condition such as PCOS can negatively impact on emotional health. Symptoms of PCOS including excess hair growth, acne, weight changes and fertility problems may negatively affect mood, sexual function, self esteem, body image and perceptions of femininity. The physical and emotional symptoms of PCOS may also make some women more prone to disordered eating.

Anxiety and depression are commonly experienced by women with PCOS, but are often overlooked and therefore left untreated. Approximately 34 per cent of women with PCOS have depression compared to 7 per cent of women in the general population and around 45 per cent have anxiety, compared to only 18 per cent of the general population.

It is important to address anxiety and depression in women with PCOS as this will assist with self-management of PCOS as a chronic disease and in improving quality of life for women suffering this common condition.

This information sheet contains some questions that may be helpful to provide further information and detail on your client’s emotional wellbeing. The questions we have used include those listed below; however, you may have your own questions you would prefer to use.

Depression/Anxiety

1. During the last month, have you often been bothered by feeling down, depressed, or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?
3. During the last month, have you been bothered by feeling excessively worried or concerned?

Body Image

1. Do you worry a lot about the way you look and wish you could think about it less?
2. On a typical day, do you spend more than 1 hour a day worrying about your appearance? (More than 1 hour a day is considered excessive)
3. What specific concerns do you have about your appearance?
4. What effect does it have on your life?
5. Does it make it hard to do your work or be with your friends and family?
Disordered Eating

1. Do you worry you have lost control over your eating?
2. Do you ever feel disgusted, depressed, or guilty about eating?
3. Have you tried fasting or skipping meals in an attempt to lose weight?
4. Have you tried vomiting, laxatives or diuretics in an attempt to lose weight?
5. Have you had significant (e.g. >5-7%), recurrent fluctuation in body weight?

Psychosexual Dysfunction

1. During the last few months, have you often been bothered by problems with your sex life such as reduced satisfaction, desire, pain, or any other problems?
2. Do you feel that PCOS affects your sex life?
3. Do sexual problems affect your current relationship and/or have sexual problems affected your past relationships?

If you require any additional information regarding PCOS and emotional health please contact the Jean Hailes PCOS Service on 03 9562 7555 and ask to speak with the PCOS Service Coordinator.

You can also visit the Jean Hailes for Women’s Health website www.jeanhailes.org.au and the www.managingpcos.org.au website, which contain professional development webcasts and extensive information on PCOS and other women’s health conditions.

Dr Mandy Deeks
Psychologist
Chair
Emotional wellbeing in PCOS
Guideline development group

Professor Helena Teede MBBS, FRACP, PhD
Endocrinologist
Project Director
PCOS evidence-based guidelines project
# Appendix V: Emotional health screening questionnaire

**Assessment of emotional health in patients with polycystic ovary syndrome**

### Screening questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Maybe</th>
</tr>
</thead>
<tbody>
<tr>
<td>During the last month, have you often been bothered by feeling down, depressed, anxious or hopeless?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the last month, have you often been bothered by having little interest or pleasure in doing things?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the last month, have you often been bothered by feeling excessively worried or concerned?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you worry a lot about the way you look and wish you could think about it less?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On a typical day, do you spend more than 1 hour day worrying about your appearance? (More than 1 hour a day is considered excessive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What specific concerns do you have about your appearance?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What effect does it have on your life?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does it make it hard to do your work or be with your friends and family?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you worry you have lost control over your eating?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you ever feel disgusted, depressed, or guilty about eating?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you tried fasting or skipping meals in an attempt to lose weight?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you tried vomiting, laxatives or diuretics in an attempt to lose weight?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had significant (e.g. &gt;5-7%), recurrent fluctuation in body weight?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the last few months, have you often been bothered by problems with your sex life such as reduced satisfaction, desire, pain, or any other problems?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you feel that PCOS affects your sex life?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do sexual problems affect your current relationship and/or have sexual problems affected your past relationships?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix VI: Emotional wellbeing tools

**Kessler Psychological Distress Scale 10 (K-10)**

<table>
<thead>
<tr>
<th></th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>In the past 4 weeks, about how often did you feel tired out for no good reason?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>2.</td>
<td>In the past 4 weeks, about how often did you feel nervous?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>3.</td>
<td>In the past 4 weeks, about how often did you feel so nervous that nothing could calm you down?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>4.</td>
<td>In the past 4 weeks, about how often did you feel hopeless?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>5.</td>
<td>In the past 4 weeks, about how often did you feel restless or fidgety?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>6.</td>
<td>In the past 4 weeks, about how often did you feel so restless you could not sit still?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>7.</td>
<td>In the past 4 weeks, about how often did you feel depressed?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>8.</td>
<td>In the past 4 weeks, about how often did you feel that everything was an effort?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>9.</td>
<td>In the past 4 weeks, about how often did you feel so sad that nothing could cheer you up?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
<tr>
<td>10.</td>
<td>In the past 4 weeks, about how often did you feel worthless?</td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
<td><img src="#" alt="Circle" /></td>
</tr>
</tbody>
</table>


For more information about its use in Australia, visit: [http://www.abs.gov.au/ausstats/abs@.nsf/mf/4817.0.55.001](http://www.abs.gov.au/ausstats/abs@.nsf/mf/4817.0.55.001)
## Depression Anxiety Stress Scale (DASS-21)


<table>
<thead>
<tr>
<th>DASS21</th>
<th>Name:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement. The rating scale is as follows:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0  Did not apply to me at all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1  Applied to me to some degree, or some of the time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2  Applied to me to a considerable degree, or a good part of time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3  Applied to me very much, or most of the time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1  I found it hard to wind down</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2  I was aware of dryness of my mouth</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3  I couldn't seem to experience any positive feeling at all</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>4  I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>5  I found it difficult to work up the initiative to do things</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6  I tended to over-react to situations</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>7  I experienced trembling (e.g. in the hands)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>8  I felt that I was using a lot of nervous energy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>9  I was worried about situations in which I might panic and make a fool of myself</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>10 I felt that I had nothing to look forward to</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>11 I found myself getting agitated</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>12 I found it difficult to relax</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13 I felt down-hearted and blue</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14 I was intolerant of anything that kept me from getting on with what I was doing</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>15 I felt I was close to panic</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>16 I was unable to become enthusiastic about anything</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>17 I felt I wasn't worth much as a person</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>18 I felt that I was rather touchy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>19 I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>Response Options</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>20</td>
<td>I felt scared without any good reason</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>21</td>
<td>I felt that life was meaningless</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

Remember when using the DASS21 to multiply the obtained scale scores by 2, so that they can be compared to the DASS normative data and to other published DASS data.
### Patient Health Questionnaire (PHQ9)

**NAME:**

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use “✓” to indicate your answer)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>5</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>6</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**DATE:**

**TOTAL:**

---

**10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?**

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

---

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Spitzer at rls@vanderbilt.edu. Use of the PHQ-9 may only be made in accordance with the Terms of Use available at [http://www.pfizer.com](http://www.pfizer.com). Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.
Appendix VI: Emotional wellbeing tools

PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment on accompanying tear-off pad.

2. If there are at least 4 √s in the blue highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

3. **Consider Major Depressive Disorder**
   —if there are at least 5 √s in the blue highlighted section (one of which corresponds to Question #1 or #2)

   **Consider Other Depressive Disorder**
   —if there are 2 to 4 √s in the blue highlighted section (one of which corresponds to Question #1 or #2)

   **Note:** Since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.

2. Add up √s by column. For every √: Several days = 1 More than half the days = 2 Nearly every day = 3

3. Add together column scores to get a TOTAL score.

4. Refer to the accompanying PHQ-9 Scoring Card to interpret the TOTAL score.

5. Results may be included in patients’ files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION

for healthcare professional use only

**Scoring**—add up all checked boxes on PHQ-9

For every √: Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3

<table>
<thead>
<tr>
<th>Interpretation of Total Score</th>
<th>Total Score</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0-4</td>
<td>Depression Severity</td>
</tr>
<tr>
<td>Mild depression</td>
<td>5-9</td>
<td></td>
</tr>
<tr>
<td>Moderate depression</td>
<td>10-14</td>
<td></td>
</tr>
<tr>
<td>Moderately severe depression</td>
<td>15-19</td>
<td></td>
</tr>
<tr>
<td>Severe depression</td>
<td>20-27</td>
<td></td>
</tr>
</tbody>
</table>

Appendix VI: Emotional wellbeing tools  152
### Generalised Anxiety Disorder 7 item scale (GAD7)


<table>
<thead>
<tr>
<th>Over the last 2 weeks, how often have you been bothered by the following problems?</th>
<th>Not at all sure</th>
<th>Several days</th>
<th>Over half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious, or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it's hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

*Add the score for each column + + +*

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all
- Somewhat difficult
- Very difficult
- Extremely difficult

GAD-7 total score for the seven items ranges from 0 to 21.

Scores represent:
- 0-5 mild
- 6-10 moderate
- 11-15 moderately severe anxiety
- 15-21 severe anxiety.
Eating Attitudes Test (EAT-26)

Instructions: This is a screening measure to help you determine whether you might have an eating disorder that needs professional attention. This screening measure is not designed to make a diagnosis of an eating disorder or take the place of a professional consultation. Please fill out the form below as accurately, honestly and completely as possible. There are no right or wrong answers. All of your responses are confidential.

Part A: Complete the following questions:
1) Birth Date: [Month] [Day] [Year]
2) Gender: Male | Female
3) Height: [Feet] [Inches]
4) Current Weight (lbs.): 
5) Highest Weight (excluding pregnancy): 
6) Lowest Adult Weight: 
7) Ideal Weight: 

Part B: Check a response for each of the following statements:

Always: | Usually: | Often: | Some Times: | Rarely: | Never: 
--- | --- | --- | --- | --- | --- 
1. Am terrified about being overweight. 
2. Avoid eating when I am hungry. 
3. Find myself preoccupied with food. 
4. Have gone on eating binges where I feel that I may not be able to stop. 
5. Cut my food into small pieces. 
6. Aware of the calorie content of foods that I eat. 
7. Particularly avoid foods with a high carbohydrate content (i.e. bread, rice, potatoes, etc.) 
8. Feel that others would prefer if I ate more. 
9. Vomit after I have eaten. 
10. Feel extremely guilty after eating. 
11. Am occupied with a desire to be thinner. 
12. Think about burning up calories when I exercise. 
13. Other people think that I am too thin. 
14. Am preoccupied with the thought of having fat on my body. 
15. Take longer than others to eat my meals. 
16. Avoid foods with sugar in them. 
17. Eat diet foods. 
18. Feel that food controls my life. 
19. Display self-control around food. 
20. Feel that others pressure me to eat. 
21. Give too much time and thought to food. 
22. Feel uncomfortable after eating sweets. 
23. Engage in dieting behavior. 
24. Like my stomach to be empty. 
25. Have the impulse to vomit after meals. 
### Part C: Behavioral Questions:
**In the past 6 months have you:**

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Once a month or less</th>
<th>2-3 times a month</th>
<th>Once a week</th>
<th>2-6 times a week</th>
<th>Once a day or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Gone on eating binges where you feel that you may not be able to stop?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>B. Ever made yourself sick (vomited) to control your weight or shape?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>C. Ever used laxatives, diet pills or diuretics (water pills) to control your weight or shape?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>D. Exercised more than 60 minutes a day to lose or to control your weight?</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>E. Lost 20 pounds or more in the past 6 months</td>
<td>YES ☐</td>
<td>NO ☐</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Defined as eating much more than most people would under the same circumstances and feeling that eating is out of control.*
**Appendix VII: Abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>Area under the receiver operating characteristic curve (analysis)</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CCR</td>
<td>Clomiphene citrate resistant</td>
</tr>
<tr>
<td>Dietitian</td>
<td>Accredited Practising Dietitian</td>
</tr>
<tr>
<td>DM2</td>
<td>Type 2 diabetes mellitus</td>
</tr>
<tr>
<td>FBG</td>
<td>Fasting blood glucose</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>HDL-C</td>
<td>High density lipoprotein cholesterol</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>Homeostasis model of assessment-insulin resistance</td>
</tr>
<tr>
<td>IR</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>LDL-C</td>
<td>Low density lipoprotein cholesterol</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>Non-CCR</td>
<td>Non-clomiphene citrate resistant</td>
</tr>
<tr>
<td>OCP</td>
<td>Oral contraceptive pill</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral glucose tolerance test</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCO</td>
<td>Polycystic ovary</td>
</tr>
<tr>
<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>PICO</td>
<td>Participants/Population, Intervention/Exposure, Comparison/Control, Outcome</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>POSAA</td>
<td>Polycystic Ovary Syndrome Association Australia</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SHBG</td>
<td>Sex hormone-binding globulin</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration (Australian Government)</td>
</tr>
<tr>
<td>P-value</td>
<td>Measure of statistical precision</td>
</tr>
</tbody>
</table>
### Appendix VIII: Glossary


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

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

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

Type 2 diabetes results from a combination of genetic and environmental factors and risk is greatly increased when associated with lifestyle factors such as high blood pressure, overweight or obesity, insufficient physical activity, poor diet and the classic ‘apple shape’ body where extra weight is carried around the waist.
Appendix IX: Evidence-based guideline development pathway

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

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

Considered by NHMRC (using assessment criteria)

Is NHMRC involvement appropriate?

Yes

Advice referred to CEO for consideration

CEO gives ‘in-principle’ approval

Which type of advice is most appropriate?

Information paper or other product

Guidelines

Process depends on type of product

Guidelines developed according to NHMRC requirements and standards

Final draft subject to independent review and resubmitted as necessary

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

CEO agrees to approve guidelines

Dissemination and implementation

CEO declines to approve guidelines

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

CEO responds to originator with reasons for decision and alternative suggestions

NHMRC standards and procedures for externally developed guidelines
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Diagram 2: Flow chart of the NHMRC’s development process for evidence based guidelines

1. Define topic/issue
   - Assess need for guidelines, eg: is issue related to clinical decision making? are there suitable existing guidelines?
2. Lodge proposal with NHMRC to consider approval of proposed guidelines
3. Convene multi-disciplinary committee to develop guidelines
4. Develop health care questions appropriate for intended guidelines
5. Identify (or commission) systematic reviews of the scientific literature relating to these health care questions
6. Identify, appraise and collate evidence of the impact of socioeconomic position (SEP) in relation to condition of interest
7. Assess evidence for: strength, quality, size of effect, relevance
8. Compare costs and benefits of health care interventions
9. Apply evidence to clinical/health care situation to determine benefits/harms
10. Apply evidence to clinical/health care situation to determine cost-effectiveness and feasibility
11. Develop evidence-based guidelines or update existing guidelines
12. Consultation, then submit guidelines to NHMRC for approval
13. Disseminate and implement guidelines
14. Develop publication(s) to target other stakeholders, eg consumers, general practitioners, allied health
15. Maintain, evaluate and update guidelines

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