If submitting feedback on behalf of an organisation, name of organisation

Guideline recommendation to which feedback is targeted.

Comments

Guideline development group consensus response

19

Department of Health Western Australia

General comment

With regards to the implementation and dissemination of the Guidelines, will there be alignment with or dissemination to commonly used online clinical practice guidelines such as Up To Date and BMJ Best Practice? The implementation program does not specify ensuring of alignment with commonly used clinical practice guidelines.

This was intended and has now been added into the implementation plan.

62

SA Health

General comment

Over all a well presented document. I wonder if the authors considered weight gain as a causative factor of PCOS and the effects of weight loss on the disease and outcomes. For example, ‘Does weight loss improve fertility?’. Another question would be, ‘In some cases, can PCOS be solely due to obesity?’.

The structure of the document would suggest that the weight gain is caused by PCOS and that diet and exercise have little benefit beyond general wellbeing. Given this, it risks normalising obesity and harming obesity treatment in the community.

The question ‘Does weight loss increase fertility?’ was considered under the section on effects of lifestyle and weight loss. Evidence is currently inadequate to demonstrate increased fertility with weight loss. For the question, ‘In some cases, can PCOS be solely due to obesity?’ the guideline does not explore causation which is out of scope, however whilst not covered here directly, there is evidence of so-called secondary PCOS and evidence of resolution after weight loss. This is noted in the section on bariatric surgery.

104

NT Health

General comment

The Key Principle focused on the needs of Indigenous and Torres Strait Islanders as high-risk populations. Aboriginal and Torres Strait Islander people are a high-risk population and within the Northern Territory our largest stakeholder group making up approximately 27% of the population (Northern Territory: Aboriginal and Torres Strait Islander population summary | Australian Bureau of Statistics (abs.gov.au)). A principle focusing on high-risk populations ensures the guideline’s relevance to First Nations’ people with high need and who may be otherwise marginalised.

A strong focus on high-risk population is integrated in the dissemination plan including Indigenous Australians. An Aboriginal and Torres Strait Island advisor has been engaged throughout and will be actively involved with other broader indigenous stakeholders in the national implementation and dissemination plan. Our diverse international partnerships include culturally and linguistically diverse representatives across world regions engaged in all phases of guideline development and will lead dissemination including language translation with their communities globally.

2.6.1 Information needs

Section 2.6 includes a recommendations on information resources, models of care, cultural and linguistic considerations. It is imperative that all people receiving health care are able to understand their treatment in order to provide informed decision making. This recommendation ensures high-risk populations and diverse cultural and linguistic groups are provided with appropriate models of care and information to enable informed decision making.

This is addressed in Chapter 2 of the guidelines. An Aboriginal and Torres Strait Island advisor has been engaged throughout and will be actively involved with other broader indigenous stakeholders in the national implementation and dissemination plan. Our diverse international partnerships include culturally and linguistically diverse representatives across world regions engaged in all phases of guideline development and will lead dissemination including language translation with their communities globally.

The implementation and dissemination plan also incorporates this. Also the strong emphasis on Indigenous engagement in the implementation and translation plan includes coproduction of an array of translation resources with this community.

Other invited Government stakeholders

Consumer health forum. No response.

Department of Health Victoria. No response.

Department of Health Qld. No response.

Department of Health NSW. No response.

Department of Health Tasmania. No response.

Department of Health ACT. No response.

Australian Government Department of Health and Aged Care. No response.
<table>
<thead>
<tr>
<th>ID</th>
<th>Comments</th>
<th>Guideline development group consensus response</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Practical recommendation for PCOS                                                                ệnh</td>
<td>Nil needed</td>
</tr>
<tr>
<td>5</td>
<td>Compiled document showing evidence for each point.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>12</td>
<td>This is a very welcome update to the previous International evidence-based guideline. The authors are to be commended for a rigorous and comprehensive review.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>12</td>
<td>Abstract. Page 1. Process. Suggest “Committees members nominated by collaborating organisations, provided international peer review, and evidence expert reviewed methods and outputs were submitted to NHMRC for independent review” is changed to “Committee members nominated by collaborating organisations provided international peer review, and evidence expert-reviewed methods and outputs were submitted to NHMRC for independent review”</td>
<td>Wording changes made</td>
</tr>
<tr>
<td>12</td>
<td>Recommendations to avoid ultrasound in adolescence (due to poor specificity) and to obviate the need for ultrasound or AMH when the diagnosis is otherwise established are welcome.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>12</td>
<td>We welcome the emphasis on lifelong care and the importance of screening for non-reproductive (psychological, dermatological and cardiometabolic) as well as reproductive sequelae.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>12</td>
<td>Abstract. Page 1. Recommendations. Suggest “Weight bias and stigma should be minimised and healthcare professionals should seek permission weigh women, with explanation of weight related risks” to “Weight bias and stigma should be minimised and healthcare professionals should seek permission to weigh women, with explanation of weight related risks”.</td>
<td>Wording changes made</td>
</tr>
<tr>
<td>12</td>
<td>Abstract. Page 1. We welcome the recognition that inositol may offer little clinical benefit as this is used widely by patients and is a common question at consultation.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>12</td>
<td>Abstract. Page 1. Clarification of the positioning of metformin as a therapy predominantly in metabolically at risk patients rather than for other indications is also helpful.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>12</td>
<td>Abstract. Page 1. We agree that antiandrogens have a limited role. Expectation management is an important part of the counselling around use of these agents as second-line therapy for hirsutism, with modest benefits at best. Should a practice point to this effect be considered later in the guideline?</td>
<td>The GDG considered this feedback but agreed that the point was made in current recommendations.</td>
</tr>
<tr>
<td>12</td>
<td>Abstract. Page 1. The recommendation for laser therapy is new and helpful but access to treatment can be difficult in some healthcare economies, including the UK. The evidence-base is quite limited and we would support a call for more studies on clinical- and cost-effectiveness when added to first-line therapy such as the combined oral contraceptive pill. Patient surveys place a high importance on the need for effective therapies in improving hirsutism.</td>
<td>Added to research priorities</td>
</tr>
<tr>
<td>12</td>
<td>Abstract. Page 1. Whilst we do not dispute the recommendation for letrozole over clomiphene first-line for ovulation induction, the LOCI trial (LOCI trial - University of Birmingham) will clarify this question as well as the potential added benefit of metformin. Would it be helpful to include a reference to this effect later in the guideline, in the expectation that this study will report before the guideline is next updated?</td>
<td>We are unable to refer to all pending studies but this is a living guideline hence if significant studies emerge evidence will be updated and recommendations altered if warranted.</td>
</tr>
<tr>
<td>12</td>
<td>We strongly endorse the call for more funding and research, and welcome the provision of evidence-based resources for consumers, policy makers and healthcare professionals.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>12</td>
<td>General. There is no section commenting on the utility of specific cosmetic measures in the management of hirsutism (such as waxing, shaving, plucking, threading). Should there be a practice point stating that these can be useful, with choice determined according to individual preference, and no evidence of an adverse effect on hair re-growth (which is a common misconception)?</td>
<td>These topics were not prioritised by consumers or health professionals and whilst this appears a reasonable request, evidence around lack of adverse effect on hair regrowth has not been sought. This can be considered in the next guideline.</td>
</tr>
<tr>
<td>12</td>
<td>Should there be an EBR or CR commenting on the usefulness (or not) of topical eflornithine in the management of hirsutism?</td>
<td>This topic was not prioritised by consumers or health professionals hence is not included here.</td>
</tr>
<tr>
<td>16</td>
<td>Congratulations to you all. I have no comments to make</td>
<td>Nil needed</td>
</tr>
<tr>
<td>23</td>
<td>Inclusion and stigma comments page 10</td>
<td>The overwhelming feedback support the statement, as such it was retained. However, the observation that this varies across cultures and ethnicities was added in pg 10.</td>
</tr>
<tr>
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<tr>
<td>As discussed previously this section (if included) should be in chapter 6 where it explains the methods and reasoning behind this wording. As discussed previously, I question the length and necessity of several paragraphs which add little to the document considering the relatively uncontroversial wording of the recommendations. These paragraphs in my view advocate a progressive, culturally contested view of sex and gender which is not needed in these guidelines and is unique in any reproductive guideline published so far. It could be shortened to commence at &quot;To this end, we have applied the following approaches throughout the guideline update:............................................&quot;. In addition if retained it should highlight the observation that not all cultures and ethnicities share the same viewpoint on gender description.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>A 'to' is missing in this sentence in the abstract: professionals should seek permission weigh women</td>
<td>This grammatical error was corrected</td>
</tr>
<tr>
<td>28</td>
<td>Please consider the impacts of PCOS on sexual health, and add point about offering sexual health screening to discussions with patients</td>
<td>This was out of scope for the guidelines as sexual health is relevant to all women and not specifically to those with PCOS.</td>
</tr>
<tr>
<td>30</td>
<td>Overall very comprehensive.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>37</td>
<td>Rigor of Development on the guideline; Justifications for few recommendation are short and with little or no references in that section (for example 3.5.1 and 3.5.2 (AGREE instrument- Question 12)</td>
<td>As noted throughout the guideline, there are thousands of references captured in the 55 systematic reviews here and hence not all referenced in the summary document. All are referenced in the accompanying technical document including the 37 papers in section 3.5.</td>
</tr>
<tr>
<td>38</td>
<td>Page 10 -Inclusiveness and stigma; The last paragraph in this page that starts with &quot;To this end, we have applied...&quot; is redundant since the same statement is repeated in the previous paragraph. Page 15 -Table 1: Categories of the PCOS guideline recommendations; There is an extra blue line under PP and there is no line between CR and PP.</td>
<td>&quot;To this end, we have applied...&quot; has been removed to limit repetition. The issue of resources for those with PCOS is vitally important and these will be released alongside the guidelines and have been codeveloped with consumers. Final formatting of the document will occur once all responses to feedback have been agreed by the GDGs.</td>
</tr>
<tr>
<td>39</td>
<td>Firstly, we would like to thank the PCOS Guideline team for their concerted efforts to produce such a well-researched guideline. We appreciate the amount of work that has fed in to this draft.</td>
<td>Nil needed as specific points are covered with responses below.</td>
</tr>
<tr>
<td>40</td>
<td>Wonderful work, well detailed, easy to read, follow and understand. Thank you very much.</td>
<td>Nil needed</td>
</tr>
<tr>
<td>42</td>
<td>RANZCR would be happy to endorse the draft 2023 guidelines.</td>
<td>We have engaged with RANZCR who are important stakeholders and they have been acknowledged and included.</td>
</tr>
<tr>
<td>As radiologists report the majority of pelvic ultrasounds in Australia and New Zealand, RANZCR respectfully requests that we are cited as being included in the consultation process and would be grateful if the RANZCR logo be included amongst the stakeholders.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>On page 2 under the heading Recommendations summary it begins with table 3, are there any other tables before this? It may also be good to include an introductory paragraph explaining what CR, PP, and EBR mean and a legend for the symbols used under GRADE would be helpful.</td>
<td>This was taken directly from the main guideline document and table order will be rectified in the final published document with explanations of the recommendation types provided.</td>
</tr>
<tr>
<td>46</td>
<td>The Summary needs a formatting review</td>
<td>Final formatting will occur once all feedback has been received.</td>
</tr>
</tbody>
</table>
This version is much more patient friendly to read and engages with the idea of joint ownership of management of the condition.  
2.6.4.2 the patients’ own voice in management seems to be missing from this despite the strength of it in other areas.  
3.1.7 - refers to lifelong conditions but then focuses on fertility  
3.6 - All supporters spoken to felt that their experiences meant that this section needs to be stronger in terms of GPs ‘NEED’ to do things as opposed to should do. The patient experience is that should is not strong enough.  
- still seems a fair bit of ‘lean’ pcos missing and so wording around pcos management for all is needed  
- very positive response to inclusion and presentation of quality of life and this feels stronger then 2018 guidelines  
- the glossary needs extending such as what is male pattern hair loss, what is assay - the document makes assumptions as to patient’s language and level of understanding.  
- numbering consistency between 52 and fifty two - document switches between numbers and words on figures constantly

2.4.6.2 was focused primarily on patients “Healthcare professionals should recognise the importance of being knowledgeable about PCOS, and apply evidence-based practices when sharing news on diagnosis, treatment and health implications, ascertaining and focusing on patient priorities”. This particular recommendation does relate directly to the health professional using evidence based approaches to working with patients.  
3.1.7 this has been extended to other features.  
3.6 In evidence based guideline, “should” is the strongest level of recommendation that can be made. PCOS is used intending to refer to all, and where the evidence is only for higher weight categories this is stated. We have made this clearer in the guideline introduction. Formatting of numbers/words will be completed in the final guideline and the glossary will be extended to consider patient/consumer needs. The assumption is that recommendation include lean and higher weight women unless BMI specific recommendations are made.

Consider including the following in the Implementation, Translation and Dissemination Plan:  
Collaborate with ASUM to develop and deliver education and Continued Professional Development (CPD) specific content for imaging professionals (e.g., a webinar).  
- Write and submit an ultrasound-focused publication to the Australasian Journal of Ultrasound in Medicine (AJUM) (Note: Monash University have an open access waiver with Wiley). Peer review will strengthen the guideline and dissemination.  
- Submit an abstract to ASUM 2023 to present this work to the ultrasound community. Potential to run a workshop on the implementation or other formats would be welcome. (Abstract submission guidelines and link to submission portal are available here - https://asum.com.au/docs/Events/Call%20for%20Abstracts%20-%20Submission%20-%20Guidelines%20-%20Updated%2020230323.pdf?_zs=MUt1b&_zl=PbcT2)  
- Write a blog (e.g., What’s new in the 2023 PCOS updates) for the new Waveforms Blog on ASUM Connect.  

These disseminations strategies are welcome and we will reach out during dissemination.

Overall, the Guidelines are very well documented and clearly written. They will be very useful to healthcare providers and stakeholders. Congratulations to all!  
Nil needed

Stronger guidance needed on recommendations from should to need or must  
The strongest recommendations allowable in guidelines are "should". Must is avoided as there are always clinical nuances or exceptions in individual circumstances.
We would like to commend the guideline writing committee for acknowledging that women with polycystic ovary syndrome have a higher prevalence of cardiovascular risk factors and subsequently greater risk of cardiovascular disease and potential mortality. It is important that we raise awareness among health professionals and the public to address and reduce the overall and future cardiovascular disease risk.

As stated in the technical report evidence summary there is conflicting and very low/low GRADE certainty of the evidence on cardiovascular disease in women with polycystic ovarian syndrome. We agree that there is a need for more research in this area to strengthen the evidence of the cardiovascular risk (and need for management) in women with polycystic ovary syndrome.

In the technical report on page 740, fourth paragraph, last sentence there is a spelling error. Therefore, the results of the meta-analysis on this topic should be interpreted with cautious, since they have a high degree of heterogeneity in terms of design and quality of included studies. Cautious should be caution.

Thank you for the opportunity to provide feedback on the draft International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2023. We look forward to seeing the final published guideline. Please let us know when the guideline is published, we could assist with promoting the publication through our networks.

The detected spelling error was corrected in the technical report.
Congratulations on a comprehensive guideline and the wide group of stakeholders. Just a few comments to make,
1. the wording of the EB recommendations often use 'should' when the quality of the studies has been graded low or very low.
This is not the wording that GRADE recommends using for wording recommendations e.g. 1.2.1, 1.2.3 etc. Also using should in a PP where presumably there is no evidence seems a stretch. e.g. "Healthcare professionals, adults and adolescents with PCOS and their first-degree relatives, should be aware of the increased risk of diabetes and the need for regular glycaemic assessment." Presumably no evidence for this as not a EBR. Yet this uses strong words such as "should". Setting up for a lifetime of glycaemic assessment (not defined) seems extreme.
2. The ovarian volume calculation should mention that ovulatory follicles should not be included in the measurements.
3. General mention was made of the wide scope of the guideline. Much of the guideline is of limited interest to gynaecologists especially in clinical settings that are resource constrained and where patients with PCOS only come to gynaecologists if they have a gyno problem - such as abnormal bleeding and infertility. GPs Could manage most of the common PCOS skin symptoms and screening for long term diseases.
4. Some concerns about increasing anxiety amongst young women. PCOS is associated with risk factors but there is no attempt in the guideline to reassure young women - for example what is the likelihood of infertility e.g. STIs and endometriosis. Can you try and put PCOS into perspective. It is NOT cancer. it does not necessarily mean they can't have children. How can you stop making them feel anxious. and still encourage safe sexual practices. Many young women with PCOS will assume infertility and not use contraception.
5. The structure of the majority of the recommendation starts with these three words. "Health care professionals should ..." It is rather repetitive. Alternative wording could place the Patient at the beginning of the sentence. e.g. "Women with PCOS who have abnormal bleeding should have an ultrasound to assess the endometrium as EH and EC are more likely to occur" or something similar.

In this recommendation 1.11.1 "Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher risk of developing endometrial hyperplasia and endometrial cancer". Can you clarify if this evidence applies regardless of BMI. Is the word 'markedly' justified when it is very low evidence. we note this sentence in the full document. "Routine screening for endometrial cancer in PCOS is not recommended as absolute risk remains low, despite much higher relative risks in PCOS, hence clinician vigilance and awareness of increased risk." shouldn't this be the recommendation instead of the EBR 1.11.1.

Research recommendations will be added onto the guideline as an appendix and also published separately. All research recommendations emanating from all GDGs will be highlighted to stimulate prioritised research in these areas.
We have also added a general practice point in GDG 2 for funding bodies should prioritise psychological health in PCOS.

GDG1 provided some guidance toward funding bodies regarding the importance of specific research areas in need of support. There is a lack of those types of specific recommendations to funders in GDG2 and I wonder if this is a missed opportunity. Perhaps a CR aimed at funding bodies to recognise the prevalence/higher risk of anxiety and depressive symptoms with diverse aetiology in women with PCOS and the need for greater research support in this area.

Nil needed here, but responses to specific comments are under the Psychological tab.
<table>
<thead>
<tr>
<th>Page</th>
<th>Paragraph</th>
<th>Line</th>
<th>Sentence</th>
<th>Revision / Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>7</td>
<td>4</td>
<td>Sentence needs revision</td>
<td>Page 7 - Plain language summary - Paragraph 4 and line 4 (The guidelines also recommend) - Sentence needs revision</td>
</tr>
<tr>
<td>10</td>
<td>exec summary</td>
<td>The two paragraphs above “Governance” section appear to be repetitive except for the word adolescent.</td>
<td>retain only the later paragraph</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Section 5.5.1</td>
<td>The statement is confusing as the summary clearly states that gonadotropins are second line therapy - Clarity required for using gonadotropins in treatment naive patients</td>
<td>There is no mention of HMG - While considering urinary preparations, use of HMG should be addressed</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>Section 5.7.3.1</td>
<td>There is no mention of HMG</td>
<td>While considering urinary preparations, use of HMG should be addressed</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Section 1.6</td>
<td>Line 2, paragraph 2: a comma is required after European</td>
<td>The sentence should be rephrased as above healthy weight?</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Section 1.11</td>
<td>What should be considered as excessively endometrium?</td>
<td>The last point - the sentence should be rephrased as above healthy weight?</td>
<td></td>
</tr>
<tr>
<td>109</td>
<td>Section 5.6.2</td>
<td>The last point -</td>
<td>The sentence should be rephrased as above healthy weight?</td>
<td></td>
</tr>
</tbody>
</table>

**The most important areas which need clarification are:**
1. Recommending use of gonadotropins as first line therapy in women with PCOS and infertility.
2. Not including urinary HMG in the discussion.
3. Some guidance on BMI beyond which consideration of anti-obesity medications
4. Inclusion of acanthosis nigricans (page 6) and bitemporal hair recession (page 4) on physical assessment.

**Grammatical errors and typos listed were amended in the guideline.**
Regarding the areas needing clarification:
1 and 2) Extensive consideration of the evidence supported gonadotrophin recommendations and no additional evidence has been provided here to support a change.
3) Evidence does not support any specific any BMI cut-off for antiobesity agent and this has been highlighted as an area for more research.
4) Acanthosis nigricans was not prioritised in this guideline and can be considered in the next update.

**To the section on “inclusion and stigma” and the approach in the guideline regarding gender inclusive language, ESHRE would like to applaud the guideline developers for their effort and consideration. ESHRE supports all inclusive purposes and understands that the language used is not intended to isolate, exclude, or diminish any individual’s experience nor to discriminate against any group.**

**nil added**

**While the guideline provides extensive information and recommendations on hyperandrogenism, AMH, and ultrasound. There is no upfront recommendation on the diagnosis of PCOS. The diagnostic criteria for PCOS should be stated at the beginning of the document and they should provide information whether disturbances in hyperandrogenism, AMH, and ultrasound are necessary, or whether a combination of two factors is sufficient for a PCOS diagnosis.**

For clarity a statement on diagnosis is added upfront in the section “context statement on diagnosis”. The algorithm on diagnosis addressed this also.

**Generally, there have been great improvements in the Guidelines since their original publication and they have been well received. There are some points that our Special Interest Group mentioned (some evidence based - others more general but we have included them too in the interest of providing patient experiences). Wording in some sections is a little confusing and people may interpret the sections differently. It should be more clear and easier to understand and follow for both healthcare professionals and patients. The management options for sexual health related concerns should also be touched upon in more detail. The language currently focuses on PCOS being a condition that can only impact women, however, with certain changes, the language can be made more gender inclusive or they could add a section acknowledging the health care needs of those who might be assigned female at birth but don’t identify as women.**

Wording in the extensive consumer translation resources will be tailored with and for consumers using plain language targeted to relevant health literacy levels and in multiple languages. Sexual health was not prioritised in the current guideline hence it is out of scope but can be considered in the next iteration. The language statement upfront seeks to address this issue around gender. On wide consultation across the GDGs, the consensus was that gender inclusive and not gender neutral language was preferred as the vast majority of those of female sex, who are assigned female at birth identify as women and the desire to avoid erasure of that identity guided the consensus to include a gender inclusive statement and several strategies to enhance inclusion without moving to gender neutral language.
<table>
<thead>
<tr>
<th>Line</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>91</td>
<td>We were particularly happy to see more inclusive language that accounts for all patients and how they may identify and the recognition of bias in care, including in addressing weight and gender. A new feature of the updated guideline is introductory material explaining the inclusive use of language and stigma. We appreciate the acknowledgment of gender-diverse individuals with PCOS and the recognition that PCOS occurs in those who identify as cisgender and transgender/nonbinary. The introductory material on inclusive language is a welcomed addition to the guideline; however, the retention of the word ‘woman’ to represent all regardless of how they identify is counter to the focus on inclusion. While we do not want or intend to erase women from the conversation, there are several instances in the guidelines where the word woman could be omitted, and the guideline would retain its meaning. In other instances, the word “woman” can easily be replaced by “person,” and the word “women” can be replaced with “people,” where person or people refers to those who were assigned female at birth to increase inclusion.</td>
</tr>
<tr>
<td>105</td>
<td>There is no mention or discussion regarding the ontogeny of PCOS and the novel notion that PCOS - at least in adolescent girls - may not be a post-menarcheal disorder, but a pre-menarcheal disorder that manifests after menarche. This notion may obviously influence the therapeutic options (doi: 10.1159/000479371; doi: 10.1016/j.tem.2018.09.005; doi: 10.1002/oby.21935). As this is a clinical guideline, genetics and ontogeny are not covered and are considered out of scope. They were also not prioritised by the partners, experts or consumers in this guideline.</td>
</tr>
<tr>
<td>105</td>
<td>Cut-off values should be given for androgen levels and FAI (despite the methodological considerations that have been raised). Methodological considerations for defining ovulatory dysfunction and polycystic ovarian morphology are also discussed and yet the guideline provides detailed descriptions of these additional diagnostic criteria. Evidence was explored on this topic, but was not adequate for a consistent international cut off value. Cut offs are influenced by lab method and assay which is a central issue for all hormonal assays and is not an issue for ovulatory dysfunction and follicle number</td>
</tr>
<tr>
<td>105</td>
<td>A section of acne and its treatment is lacking, despite the fact that it may be a major cause of psychological distress in these women. The guideline was not able to cover all areas of PCOS and areas prioritised by consumers took priority. Acne was stated for consideration in the next guideline update.</td>
</tr>
</tbody>
</table>
Guideline recommendation | Comments | Guideline development group consensus response
---|---|---
1.3.7 PP | Healthcare professionals should: | Consider including statement that overt virilisation is not consistent with a diagnosis of PCOS | This was considered and was added to the background section of the guideline.
1.3.8 CR | All women with PCOS, regardless of age and BMI, should have a fasting lipid profile (cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglyceride level) at diagnosis. | Whilst we support the importance of addressing cardiovascular risk factors, including fasting lipids, at baseline and follow-up, prescription of lipid lowering therapy will need to consider the desire for fertility in addition to lipid levels. | The GDG agrees hence no recommendations on the use of lipid lowering therapy has been made here.
1.3.9 CR | Funding bodies should recognise that PCOS is highly prevalent with multisystem effects including cardiometabolic disease, and should diversify and increase research support accordingly. | Research funding statement is very much welcome | This has already indicated that individual risk factors for diabetes should be taken into account.
1.5 PP | Ovulatory dysfunction can still occur with regular cycles and if amenorrhoea needs to be confirmed serum progesterone levels can be measured. | Should the guideline stipulate the timing of progesterone measurement to confirm or refute ovulation? | As women with PCOS are oligoanovulatory we cannot stipulate this accurately.
1.9.11  EBR  An OGTT should be offered to all women with PCOS and without pre-existing diabetes, when planning pregnancy or seeking fertility treatment, given the high risk of hyperglycaemia and the associated comorbidities in pregnancy. If not performed preconception, an OGTT should be offered at the first prenatal visit and all women with PCOS should be offered the test at 24-28 weeks gestation.

Typographical error. Change "without pre-existing diabetes" to "without pre-existing diabetes"

This typographical error was corrected

1.10.3 PP  Simple obstructive sleep apnea screening questionnaires (such as the Berlin questionnaire, validated in the general population) can assist in identifying obstructive sleep apnea in women with PCOS.

Recommend including a statement that referral for formal sleep studies is advised based on cut offs in screening assessment “sleep scores in isolation cannot diagnose sleep apnea”

Wordings of the recommendation are changed

1.3.6  CR  The prevalence of hirsutism is similar across ethnicities, yet the severity of hirsutism varies by ethnicity.

The translation tools developed for the consumer will clearly explain the difference between relative and absolute risk for consumers.

1.1.6 CR  The prevalence of hirsutism is similar across ethnicities, yet the severity of hirsutism varies by ethnicity.

The risk of NAFLD is not discussed. Was this considered? We accept that formal screening for NAFLD may not be justified in the absence of specific therapies and in line with other recommendations (e.g, NICE). However, should clinicians have a heightened awareness of an increased risk of NAFLD in PCOS, and if so, detected/suspected refer accordingly?

NAFL was not prioritised in the guideline and as such is out of scope. The reasons for this in part relate to the factors raised by the reviewer, that this is a manifestation of obesity and that there are no specific therapies that are effective above recommended weight loss.

1.11.1  EBR  Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher-risk of developing endometrial hyperplasia and endometrial cancer. We agree that the relative risk of endometrial cancer may be higher but the absolute risk is still low in a premenopausal population and are pleased to see that practice point 1.11.2 recognises this. The benefits of addressing risk factors (obesity, amenorrhoea) and introducing preventative strategies (cyclical progestogens, progesterone-releasing IUD, COPCs) needs to be balanced against the potential to increase health anxiety if this difference between relative and absolute risk isn’t appreciated.

The substitution of ultrasound for biochemical markers is no different to the current scenario where women may be diagnosed based on non clinical parameters. Either PCOM or AMH alone result in similar rates of disease detection. The interpretation of this new testing guideline or disease definition will need to be reviewed with care.

1.3.6 OR  The prevalence of hirsutism is similar across ethnicities, yet the severity of hirsutism varies by ethnicity.

The narrative review details that polycystic ovary morphology (PCOM) alone is not diagnostic for PCOS. Given the risk of over diagnosis, in addition to this PP 1.4.9, a recommendation for clinicians on the implication of PCOM noted on ultrasound would be very helpful (e.g. PCOM on ultrasound should prompt serum androgen assessment etc).

This typographical error was corrected

1.1.6 OR  The prevalence of hirsutism is similar across ethnicities, yet the severity of hirsutism varies by ethnicity.

The substitution of ultrasound for biochemical markers is no different to the current scenario where women may be diagnosed based on non clinical parameters. Either PCOM or AMH alone result in similar rates of disease detection. The interpretation of this new testing guideline or disease definition will need to be reviewed with care.

1.4.9  PP  mFG scores vary significantly between various ethnic groups. Data from various collaboration centres including China, Italy, USA, Nigeria, Russia, South Korea, Turkey and Iran show that mFG varies significantly between ethnic groups from these countries. These findings are pending confirmation after accounting for inter-observer variation.

The substitution of ultrasound for biochemical markers is no different to the current scenario where women may be diagnosed based on non clinical parameters. Either PCOM or AMH alone result in similar rates of disease detection. The interpretation of this new testing guideline or disease definition will need to be reviewed with care.

1.8.1 CR  AMH as one of the diagnostic criteria

Not all laboratories have standardised methods for AMH. This might lead to fake diagnosis (most likely over diagnosis) if only two laboratory markers are positive e.g. hyperandrogenism and AMH, it will make a diagnosis of PCOS. Having diagnosis based on only biochemical parameters (without lab/ USG) might overdiagnose PCOS.

The substitution of ultrasound for biochemical markers is no different to the current scenario where women may be diagnosed based on non clinical parameters. Either PCOM or AMH alone result in similar rates of disease detection. The interpretation of this new testing guideline or disease definition will need to be reviewed with care.

1.11.2 CR  Healthcare professionals should be aware that premenopausal women with PCOS have markedly higher-risk of developing endometrial hyperplasia and endometrial cancer.

There was a lot of concern is that these guidelines expand the definition of PCOS. Six editors agreed with this concern. This will inevitably lead to more women being diagnosed with a disease that potentially has serious short and long term health consequences. https://pubmed.ncbi.nlm.nih.gov/28814550/; Tessa Copp has done a lot of work in this area, and I understand that 16% of reproductive age women will meet the new diagnostic criteria for PCOS if this guidance is implemented. This has the potential to do harm. Concerningly, women newly diagnosed with PCOS were 3.4x more likely to stop using contraception! https://pubmed.ncbi.nlm.nih.gov/32014257/

The translation tools developed for the consumer will clearly explain the difference between relative and absolute risk for consumers.

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The substitution of ultrasound for biochemical markers is no different to the current scenario where women may be diagnosed based on non clinical parameters. Either PCOM or AMH alone result in similar rates of disease detection. The interpretation of this new testing guideline or disease definition will need to be reviewed with care.

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Concerningly, women newly diagnosed with PCOS were 3.4x more likely to stop using contraception! https://pubmed.ncbi.nlm.nih.gov/32014257/

The key problems with overdiagnosis occurs with the use of ultrasound in adolescents (now not recommended in the guideline) and to a lesser extent in adults. Ultrasound is now not recommended routinely in diagnosis in adolescents and collaborations with the Ultrasound Society of Australia will lead to implementation of reporting requirements to limit inappropriate over diagnosis, should an ultrasound occur. Phenotypes captured under Rotterdam criteria have very significant long term health implications as clearly outlined in the guideline. Indeed the long term natural history especially in terms of infertility and pregnancy complications indicates the significant need to avoid both over and underdiagnoses.

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PCOS is a diagnosis of exclusion, hence having two features of PCOS criteria in FHA does not allow a diagnosis of PCOS. These can be difficult to differentiate however evidence is inadequate currently on the optimal way to differentiate these. Detailed recommendations on differentiation from FHA, Cushing’s and other differentials was outside of scope in the current guideline.

Wordings of the recommendations in 1.4 are also amended now.

The GDG reviewed the additional evidence added to the guideline systematic review after contacting authors and the background section of 1.6 have been updated. Wordings of the recommendation are amended accordingly.

Wordings of the recommendation are changed.

Nil needed

Wordings of the recommendation are amended now.

The narrative review details that PCOM alone is not diagnostic for PCOS and this requires correlation with serum androgen assessment etc).

Wordings of the recommendations in 1.4 are also amended now.

The GDG members have updated the guideline draft to reflect the new evidence. These updates have been reviewed by the GDG and the draft is now ready for final approval by the GDG and the publication phase.

Given the risk of over diagnosis from this, in addition to this PP 1.4.9, a recommendation for clinicians on the implication of PCOM noted on ultrasound would be very helpful (e.g. PCOM on ultrasound should prompt serum androgen assessment etc).

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No additional evidence is required. Your review has covered this evidence well. I would just consider adding this specifically as it's own recommendation.

No additional evidence was provided for the GDG members to assess. Insulin is a well established driver of hyperandrogsomism, however as per prior responses: insulin resistance cannot yet be accurately assessed in clinical practice and is not recommended.

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Wordings of the recommendation are changed.
One aspect that is not mentioned in Chapter 1 is an estimate of the current delay for PCOS diagnosis. Indeed, healthcare professionals should use total testosterone, free testosterone or calculated FAI. Delay in diagnosis is reported in many papers but opportunities for improving gaps are not provided. Early predictors are not addressed in available items.

The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation wordings in 1.5.5 regarding BMI is retained.

Concerning the second point, AMH variations according to the menstrual cycle, this is very disputed and with very modest variations of circulating AMH documented in the literature. I personally would not include this sentence at all.

Veno-occlusive disease was not prioritised for inclusion in this guideline update by consumers or health professionals however it is a relevant consideration and will be considered for inclusion in the next guideline update. Risk of CVD is covered in 1.8.

E2R: Serum AMH could be used for assessing antral follicle excess in adults.

This is well made and the algorithm for diagnosis clarifies this. Wordings of the recommendation are also changed now.

PCOS is associated with both CVD and venous thromboembolism (VTE). However, this aspect has not been mentioned in this chapter. A recent meta-analysis found an odds ratio of 1.44 (1.13-1.84) for coronary heart disease in women with PCOS vs non-PCOS and a cohort study, which included 87,000 participants, found a 5.5-fold higher risk for VTE in women with PCOS than in controls. In general, cardiovascular events are rare in premenopausal women, which is why markers of low-grade inflammation and endothelial dysfunction could be included as measures of CVD risk in PCOS. If space allows, this could be discussed in the introductory paragraph.

This statement is a little bit peremptory and is not supported by the recent literature. No study has shown that specific thresholds should be used for non-obese/obese patients. Frazzini A, Robin G, Pépy P, Lefebvre T, Cattaneo-Jonard S, Dewailly D. Use of the serum anti-Müllerian hormone assay as a surrogate for polycystic ovarian morphology: impact on diagnosis and phenotypic classification of polycystic ovary syndrome. Hum Reprod. 2017 Aug 1;32(8):1716-1725.

Defining PCOS by using either PCOM or AMH as one of the three Rotterdam items does not change significantly the prevalence of PCOS. Using both markers (PCOM and/or increased AMH level), the prevalence is significantly increased.

Other measures have not proven superiority compared to all other tests. However, it is not reflected in the recommendation.

The sentence is well made and the algorithm for diagnosis clarifies this. Wordings of the recommendation are also changed now.

As above this has now been clarified in the recommendations.

The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation wordings in 1.5.5 regarding BMI is retained.
1.8.3 CR All women with PCOS, regardless of age and BMI, should have a fasting lipid profile
This wording is based on the use of the non-fasting state to detect abnormalities in lipid metabolism in TG, apoD, and non-HDL-C (as markers of atherogenic remnant cholesterol). This recommendation is based on international cardiovascular risk and dyslipidaemia guidelines including 2021 Canadian Cardiovascular Society (CCS). [Can J Cardiol. 2021 Aug;37(8):1329-1350. doi: 10.1016/j.cjca.2021.03.016; Aplaku 2021 Mar 29, Table 2], and Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz445. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (5.4.3 fasting or non-fasting).A traditional, blood sampling for lipid analyses has been recommended in the fasting state. Recent systematic studies comparing fasting and non-fasting samples have suggested that the difference is small for most lipid parameters. Non-fasting sampling has been used in large population-based studies. In most studies, non-fasting samples display a higher TG level. On average, and for most individuals, this increment will be of no clinical significance. Indeed, a number of guidelines recommend non-fasting sampling. It is also easier for patients to do non-fasting samples.

1.8.4 CCR Cardiovascular general population guidelines should consider the inclusion of PCOS as a risk factor for CVD. The technical report only investigates CVD outcomes in PCOS not the usefulness of assessment of primary risk factors such as atherogenic dyslipidaemia, blood pressure, ACVD in those at different ages with PCOS: adolescents, young women, menopausal women. There is new recommendations and new and revised concept for on cardiovascular imaging for patients with dyslipidaemia. [Fort Health J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz445. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk]. This should be highlighted clearly once overall results suggest that FPG or HbA1C cannot replace OGTT. A consensus recommendation, but should be better aligned with the overall population guidelines and the associated comorbidities.

1.8.6 CCR Cardiovascular general population guidelines should consider the inclusion of PCOS as a risk factor for CVD. The risk of hypertension in women with PCOS who are premenopausal remains low. Blood pressure in women with PCOS should be done according to the CVD risk guidelines and in consideration of all potential risk factors. This is a consensus recommendation, but should be better aligned with the overall population guidelines and the associated comorbidities.

1.9.9 EBR Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glycaemic status in PCOS. This important point will be picked up in the translation resources. The heading of 1.5 is also changed to indicate the recommendations are regarding PCOS diagnosis. The clinical impact of the increased direct-to-consumer sales of AMH tests, should there be a caution to inform patients that this test cannot predict current or future fertility and that this can be affected by PCOS?

1.5 Anti-Mullerian Hormone (AMH)
In light of the increased online direct-to-consumer sales of AMH tests, there should be a caution to inform women that this test cannot predict current or future fertility and that this can be affected by PCOS. [Douglas J, Vandik PD, Gassier A, Mustafah RA, Horvath AR, Francen, A, Al-Arany L, Bossuyt P, Ward RL, Kopp I, Gollogly L, Schunemann H, Glasziou P; Guidelines International Network (G-I-N) Preventing Overdiagnosis Working Group. Guidance for Modifying the Definition of Diseases: A Checklist. JAMA Intern Med. 2017 Jul 1;177(7):1020-1025. doi: 10.1001/jamainternmed.2017.1302. PMID: 28505266. This recommendation would also increase the number of women diagnosed with PCOS: Bell RJ, Islam RM, Skiba MA, Herbert D, Martinez Garcia A, Davis SR. This  should be highlighted clearly since overall results suggest that FPG or HbA1C cannot replace OGTT. A consensus recommendation, but should be better aligned with the overall population guidelines and the associated comorbidities.

1.5.1 EBR Serum AMH could be used for assessing antral follicle excess in adults. This was considered and the GDG has reworded the recommendation.

44 1.5.1 EBR Serum AMH could be used for assessing antral follicle excess in adults. AMH should not be used as an alternative to PCOS. This review has examined measures of diagnostic accuracy comparing the sensitivity and specificity of AMH against the reference standard of polycystic ovary morphology. However, this is not the appropriate method to determine if a test should be incorporated into the definition of a disease. The test should be examined to determine that it is able to group patients with similar progress or response to treatment. See Dutt J, Yandik PD, Gassier A, Mustafah RA, Horvath AR, Francen, A, Al-Arany L, Bossuyt P, Ward RL, Kopp I, Gollogly L, Schunemann H, Glasziou P; Guidelines International Network (G-I-N) Preventing Overdiagnosis Working Group. Guidance for Modifying the Definition of Diseases: A Checklist. JAMA Intern Med. 2017 Jul 1;177(7):1020-1025. doi: 10.1001/jamainternmed.2017.1302. PMID: 28505266. This recommendation would also increase the number of women diagnosed with PCOS: Bell RJ, Islam RM, Skiba MA, Herbert D, Martinez Garcia A, Davis SR. Substituting serum anti-Mullerian hormone for polycystic ovary morphology increases the number of women diagnosed with polycystic ovary syndrome: a community-based cross-sectional study. Hum Reprod. 2021 Dec 27;37(1):109-118. doi: 10.1093/humrep/deab232. PMID: 34741176.

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In light of the increased online direct-to-consumer sales of AMH tests, there should be a caution to inform women that this test cannot predict current or future fertility and that this can be affected by PCOS?

45 1.7.1 CR Healthcare professionals should be aware that a diagnosis of PCOS should be considered as enduring / lifelong. The uncertainty of this statement needs to be included in the recommendation. The evidence here supports that the risk of features of PCOS including diabetes, CVD and non-fertility related issues is increased and as such this genetic condition which is recognised to manifest beyond reproductive features, is considered to be enduring.

45 1.8.4 CR All women with PCOS should have blood pressure measured annually and when planning pregnancy or seeking fertility treatment, given the high risk of hypertension disorders in pregnancy and the associated comorbidities. The evidence here supports that the risk of features of PCOS including diabetes, CVD and non-fertility related issues is increased and as such this genetic condition which is recognised to manifest beyond reproductive features, is considered to be enduring.

45 1.8.6 CR Cardiovascular general population guidelines should consider the inclusion of PCOS as a risk factor for CVD. The evidence here supports that the risk of features of PCOS including diabetes, CVD and non-fertility related issues is increased and as such this genetic condition which is recognised to manifest beyond reproductive features, is considered to be enduring.

45 1.8.8 CR All women with PCOS should have a fasting lipid profile taken at diagnosis. Thereafter, frequency of measurement should be based on the presence of hyperlipidaemia and additional risk factors or global cardiovascular risk.

45 1.8.3 CR All women with PCOS, regardless of age and BMI, should have a fasting lipid profile
This wording is based on the use of the non-fasting state to detect abnormalities in lipid metabolism in TG, apoD, and non-HDL-C (as markers of atherogenic remnant cholesterol). This recommendation is based on international cardiovascular risk and dyslipidaemia guidelines including 2021 Canadian Cardiovascular Society (CCS). [Can J Cardiol. 2021 Aug;37(8):1329-1350. doi: 10.1016/j.cjca.2021.03.016; Aplaku 2021 Mar 29, Table 2], and Eur Heart J. 2020 Jan 1;41(1):111-188. doi: 10.1093/eurheartj/ehz445. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (5.4.3 fasting or non-fasting).A traditional, blood sampling for lipid analyses has been recommended in the fasting state. Recent systematic studies comparing fasting and non-fasting samples have suggested that the difference is small for most lipid parameters. Non-fasting sampling has been used in large population-based studies. In most studies, non-fasting samples display a higher TG level. On average, and for most individuals, this increment will be of no clinical significance. Indeed, a number of guidelines recommend non-fasting sampling. It is also easier for patients to do non-fasting samples.
EBR Healthcare professionals and women with PCOS should recommend the 75-g oral glucose tolerance test (OGTT) as the most accurate test to assess glucose status in PCOS. The guidelines recommend a different test for testing type 2 diabetes in women with PCOS than in the general population. This recommendation should be changed. It is now recommended that HbA1c be used to diagnose type 2 DM. This is on the basis that HbA1c is able to predict microvascular and macrovascular complications of type 2 DM at all as well as the OGTT and has better biochemical predictability. The review has used the OGTT as a reference standard in determining the diagnostic accuracy of HbA1c. This will artificially make it appear as though HbA1c is an inferior test, whereas it is more likely to be a superior test.

The awareness of increased risk did not extend to routine screening which should rely on the composite of risk factors present. A note to this effect was added to the guideline justification to focus on composite-risk. Magnitude of increased risk is captured in the guideline main text.

The use of and/or in the 2018 guidelines created confusion as to whether one of the features was sufficient or both follicle number per ovary (FNPO) and increased ovarian volume were necessary. The wording on this 2023 update is greatly improved from the previous guideline. However, further clarity will remove any ambiguity.

The usual caveats about population screening should apply to this recommendation. Also the magnitude of the increased risk should be highlighted. Although there is an increased risk of the risk factors described above, from the papers included here the risk is primarily mediated through BMI.

The results of the extensive studies reviewed here support the lack of accuracy of HbA1c in this population. The use of and or in the 2018 guidelines created confusion as to whether one of the features was sufficient or both follicle number per ovary (FNPO) and increased ovarian volume were necessary. The wording on this 2023 update is greatly improved from the previous guideline. However, further clarity will remove any ambiguity.

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1.5.1 EBR Serum AMH could be used for assessing antral follicle excess in adults.

I would add: it may be used as a surrogate for excess FNPO, providing the use of a sensitive and specific cut-off that must be defined-in-house since there is no international consensus for the moment.

Unfortunately, data is lacking to include an age-specific recommendation for the cut-off of AMH as a predictor for PCOS in PCOM.

It is unclear as yet whether international applicable cut offs can be developed and hence no specific cut-off is mentioned in the guideline.

Androgen cut-offs are very assay and lab influenced and specific cut-offs were not deemed evidence based or appropriate.

1.2.9 PP If androgen levels are markedly above laboratory reference ranges, causes of hyperandrogenaemia other than PCOS, including ovarian and adrenal neoplastic growths, congenital adrenal hyperplasia, Cushing’s syndrome, ovarian hyperthecosis (after menopause), iatrogenic causes, and syndromes of severe insulin resistance, should be considered. However, some androgen-secreting neoplasms are associated with only mild to moderate increases in androgen levels. The clinical history of time of onset and/or rapid progression of symptoms is critical in assessing for an androgen-secreting tumour.

Note that there are no universally accepted visual instruments for assessing the presence of acne. There is good evidence on assessing the presence of acne. If we can modify our statement that we do not have any reference scoring in PCOS then the sentence might sound acceptable.

https://jamiatmekongjournals.com/journals/jamalodentology/fullarticle/2759750

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5023602


https://pubmed.ncbi.nlm.nih.gov/9785319-32885-1.96

1.3.7 PP Healthcare professionals should:

- Be aware that standardised visual scales are preferred when assessing hirsutism, such as the nongal scale in combination with a photographic atlas.
- Be aware of the Ludwig or Olsen visual scales for assessing female pattern hair loss.
- Be aware that there are no universally accepted visual instruments for assessing the presence of acne.
- Recognise that women commonly treat clinical hyperandrogenism cosmetically, diminishing their apparent clinical severity.
- Appreciate that self-assessment of unwanted excess hair growth, and possibly acne and female pattern hair loss, has a high degree of validity and merits close evaluation, even if overt clinical signs of hyperandrogenism are not readily evident on examination.
- Be aware that terminal hairs need to be considered in defining hirsutism, and these can reach >5 mm if untreated, vary in shape and texture and are generally pigmented.
- Note that new-onset severe or worsening hyperandrogenism, including hirsutism, requires further investigation to rule out androgen-secreting tumours and ovarian hyperthecosis.
- Monitor clinical signs of hyperandrogenism, including hirsutism, acne and female pattern hair loss, for improvement or treatment adjustment during therapy.

Note that there are no universally accepted visual instruments for assessing the presence of acne.

There is good evidence on assessing the presence of acne. If we can modify our statement that we do not have any reference scoring in PCOS then the sentence might sound acceptable.

https://jamiatmekongjournals.com/journals/jamalodentology/fullarticle/2759750

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5023602


https://pubmed.ncbi.nlm.nih.gov/9785319-32885-1.96

1.4.3 CR PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (DV).

CR: PCOM criteria should be based on either follicle excess (FNPO, FNPS) and/or ovarian enlargement (DV).

Would add: Other measures have not proven superior.

This is well discussed in the review evidence. No need to add further references.

This will be addressed in each guideline update every 5 years.

1.4.1 PP Follicle number per ovary (FNPO) should be considered the most effective ultrasound marker to detect polycystic ovarian morphology (PCOS) in adults.

Thresholds for PCOS should be increased regularly with advancing ultrasound technology.

Follicle number per ovary are the most effective marker of PCOS then changes in USG machine as a criteria to rule the threshold might not be a great option to revise.

Moreover, how regularly the criteria should be revised if machines changes very often or do not change. This could be considered, even if the reviewers consider the evidence for this section is well discussed.

This was not added.

1.6.5 PP Healthcare professionals need to be aware of factors that influence AMH including:

1. Age: Serum AMH generally peaks between the age of 20-25 years.
2. Obesity: Serum AMH is lower in those with higher BMI. See response above about AMH and BMI.
3. GnRH: Serum AMH can be suppressed by current or recent COCP use.
4. Menstrual cycle day: Serum AMH may vary across the menstrual cycle.
5. Ethnicity: Serum AMH may be influenced by ethnicity.
6. Ovarian (UCM) and endometrial thickness may be assessed by current or recent COCP use.
7. Ovarian: Serum AMH may vary across the menstrual cycle.

The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation words in 1.5.5 regarding BMI is retained.

The GDG have considered the comment but this is out of the scope of the guideline and other endometrial hyperplasia and endometrial cancer guidelines are available.

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This was not included as no new references were added.

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This was not included as no new references were added.
Healthcare professionals need to be aware of factors that influence AMH including:

- Body mass index (BMI): Serum AMH is lower in those with higher BMI.
- Ethnicity: Serum AMH may be influenced by ethnicity.
- Contraception use (COCP): Serum AMH may be suppressed by current or recent COCP use.

Body mass index (BMI): Serum AMH is lower in those with higher BMI. Change to: Body mass index (BMI): Serum AMH is lower in those with higher BMI.

Ethnicity: Serum AMH may be influenced by ethnicity.

COCP: Serum AMH may be suppressed by current or recent COCP use.

This is beyond the scope of the current guideline.

Healthcare professionals should be aware of the high prevalence of PCOS among adults. Global prevalence is quoted as 6-20% depending on the diagnostic guideline used (Escobar., 2018).

Endometrial cancer.

Healthcare professionals should be aware that a diagnosis of PCOS can impact someone throughout their life.

There is evidence that different ethnic groups have different serum AMH concentrations, however, these studies are small and there are no conclusive findings.

Change to: Global prevalence is quoted as 6-20% depending on the diagnostic guideline used (Escobar., 2018).

As glycaemic abnormalities require regular screening and need prevention, women should be aware of these issues.

Wordings are changed.

The GDG agreed that the data for ethnicity is still inconclusive and has deleted the sentence from 1.5.5.

Healthcare professionals should be aware that both clinical and biochemical hyperandrogenism can persist in the postmenopause for women with PCOS.

Wordings of the recommendation are changed.

The wording on this recommendation was endorsed by all GDG members, went out to public consultation and has not raised concerns. It also aligns to evidence and hence wording has not been changed here.

The recommendation wordings has been modified.

The majority of studies show an influence of BMI. The evidence were reviewed by the GDG and the recommendation wordings in 1.5.5 regarding BMI is retained.

The recommendation wordings in 1.5.5 regarding BMI is retained.

The GDG has considered this comment and confirmed evidence that AMH variation across the cycle is dependent on the assay and the recommendation wordings are retained. Also as most individuals PCOS is a lifelong condition it is not clinically recommended.

The GDG has considered this comment and confirmed evidence that AMH variation across the cycle is dependent on the assay and the recommendation wordings are retained. Also as most individuals PCOS is a lifelong condition it is not clinically recommended.

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1.3.6 CR: The prevalence of hirsutism is similar across ethnicities, yet the severity of hirsutism varies by ethnicity. While this is true, I have personally felt dismissed about the severity of my symptoms due to my ethnicity. It is important for HCPs to recognize the difference between idiopathic hair growth and male pattern terminal hairs, and not simply put it down to ethnicity. This was considered by the GDG and we agreed that the potential negative psychosocial impact of clinical hyperandrogenism is high. This is covered in CR 1.3.4

1.6: Ethnic variation

There is some evidence to suggest rates are higher in South Asian and Black women; however, this is not conclusive in the highest (1,2,6) is however important for HCPs to consider the pre existing higher rates of hirsutism and risk of cardiovascular complications in BAME individuals and pay more attention to monitoring and management in these populations. (3)

106 I didn’t see anything about NAFLD. The prevalence in women with PCOS is actually quite high—at an earlier age and seems to be more advanced seems-like screening with ALT is fairly inexpensive

Aim: alcohols fatty liver disease (NAFLD) and non alcoholic steatohepatitis (NASH) were not prioritized for the update. Whilst NAFL is prevalent (24% US population has NAF based on 5% of liver fatty infiltration), NASH is uncommon (1-5% of NAFL) and cirrhosis extremely uncommon and most with NAFL dies of CVD and not liver disease itself. We understand that both NAFL and NASH are prevalent in PCOS because their main risk factor is obesity. However, the only treatment available now is weight loss and weight management is already highlighted in the guideline. The guideline development group feels that 1) separating the diagnosis of NAFLD/NASH is difficult and expensive; and 2) the benefit of widespread screening for NASH/NAFLD in women with PCOS, over obesity, remains unclear at this time. They may be prioritized in the next guideline update when more is known.

1.5 Anti-Müllerian Hormone (AMH)

In light of the increased online direct-to-consumer sales of AMH tests, should there be a caution to inform women that this test cannot predict current or future fertility and that levels can be affected by PCOS? This was not the scope of the PICO. 1.5 subject heading is changed to reflect the use of AMH in the diagnosis of PCOS

13 Abstract: Page 1

While it is important to acknowledge a relatively increased risk of endometrial cancer (and to prevent further evidence on ethnic differences has since emerged, sparked by the guideline questions. This section and recommendations have been updated.

21 Page 14, prelude to the guideline: “Further evaluation recommended in those with amenorrhoea and more severe clinical features including consideration of hypogonadotropic hypogonadism, Cushing’s disease, or suspected androgen producing tumours.” We understand that both NASH and NAFLD are prevalent in PCOS because their main risk factor is obesity. However, the only treatment available now is weight loss and weight management is already highlighted in the guideline. The guideline development group feels that 1) separating the diagnosis of NAFLD/NASH is difficult and expensive; and 2) the benefit of widespread screening for NASH/NAFLD in women with PCOS, over obesity, remains unclear at this time. They may be prioritized in the next guideline update when more is known.

22 Justification:

Another reviewer stated I would add “in case of amenorrhoea in a context of recent weight loss and/or psychological distress and/or eating disorder, a Functional Hypothalamic Amenorrhea should be ruled out even in the presence of polycystic ovaries on ultrasound. This can be confirmed by a low serum LH level.”

Identification: Unrecognition of FHA may lead to inappropriate care. Those patients should be treated as “regular” FHA, in particular for ovulation induction. It has been effectively reported that pulsatile GnRH therapy is a more successful and safer treatment for ovulation induction than gonadotropins (1,2).

1. Subkel et al; Freylin T, Devalle L, Barriere P. Prospective randomized comparison between pulsatile GnRH therapy and combined gonadotropin FSH+LH treatment for ovulation induction in women with hypothalamic amenorrhoea and underlying polycystic ovary syndrome. Eur J Obstet Gynecol reprod Biol. 2015;186:45-8


The order of steps in Formulate guidance and Disseminate, implement, update is reader difficult to follow if we can 11-15 and 16-22 PCOS is a frequent finding in FHA (see Makolk et al for review). Its significance is unclear but this association is confusing since it includes 2 out of the 3 items of the Rotterdam classification. Those patients must therefore be differentiated from PCOS phenotype D. Patient’s history and assays of serum testosterone, SHBG and LH may help. Unrecognition of FHA may lead to inappropriate care of patients who need psychological/nutritional support. Those patients should be treated as “regular” FHA, in particular for ovulation induction. It has been effectively reported that they most often respond to pulsatile GnRH therapy (1,2).


105 1.1 Irregular cycles and ovulatory dysfunction

The first and second year after menarche is too early to consider menstrual irregularities as a PCOS feature. It may result in overdiagnosis, and certainly in overtreatment. Menstrual irregularities & anovulatory cycles are not uncommon up to 3-5 yr post menarche (Din: AJSRE/FPSR/CGO). Accordingly, the definition of “irregular menstrual cycles” for the diagnosis of PCOS should not be considered before at least 2 yr post-menarche at any age. This recommendation is retained from 2018, where it was endorsed by all 40 collaborating societies. It has since been validated in one of the longest running cohort studies on PCOS from in utero to the early 30s (Tay et al 2021). The only reference provided here is a consensus based guideline from 8 years ago, with superseding research that confirms the 2018 recommendations and as such the GDG recommendations were not altered. The duration of normal cycles is varied by gynaecological age, based on direct evidence on menstrual cycle length in the general population as per the 2018 guidelines.

125 1.1 Irregular cycles and ovulatory dysfunction

Please define in detail what is considered to be a girl “at risk”.

The concept of “at risk” is clarified in the guideline as referring to an adolescent with either hyperandrogenism or irregular cycles who then warrants later evaluation to avoid both ovariodenoma and a potential missed diagnosis. This was prioritised strongly by consumer groups with many women / studies highlighting the challenges of missed and delayed diagnosis.
<table>
<thead>
<tr>
<th>Line</th>
<th>Paragraph</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2.2 EBR</td>
<td>If testosterone or free testosterone is not elevated, healthcare professionals could consider measuring androstenedione and dehydroepiandrosterone sulfate (DHEAS), noting their poorer specificity and the greater age associated decrease in DHEAS.</td>
<td>Explain the rationale for considering androstenedione and DHEAS measurements as a substitute of testosterone for PCOS diagnosis when the latter happens to be within normal limits. The evidence is very low. GDG1</td>
</tr>
<tr>
<td>1.2.8 PP</td>
<td>In most adolescents, androgen levels reach adult ranges at the age of 12-15 years.</td>
<td>The statement that in most adolescents, androgen levels reach adult ranges at the age of 12-15 yrs should take into consideration gynaecological age, not chronological age. GDG1 PAEDS</td>
</tr>
<tr>
<td>1.3</td>
<td>Clinical hyperandrogenism</td>
<td>The definition for female pattern hair loss was added to the glossary</td>
</tr>
<tr>
<td>1.9</td>
<td>Impaired glucose tolerance and type 2 diabetes risk</td>
<td>Gestational diabetes is dealt with in the section on pregnancy risk in GDG4.</td>
</tr>
<tr>
<td>1.10.1 EBR</td>
<td>Healthcare professionals should be aware that women with PCOS have significantly higher prevalence of obstructive sleep apnea compared to women without PCOS. It should state whether this is independent from the co-presence of obesity (as mentioned for eating disorders).</td>
<td>Thank you for this comment, the evidence supports an increased risk of sleep apnoea independent of obesity and hence this change has been made to note this is “independent of BMI”.</td>
</tr>
</tbody>
</table>
Guideline development group consensus response

2.2.2 EBR Healthcare professionals should be aware of the high prevalence of moderate to severe anxiety symptoms and anxiety disorders in adults and should screen for anxiety in all adults with PCOS, using regionally validated screening tools.

2.4 Body image


2.6.1 Information needs

As an international guideline, we acknowledge that this issue of greater relevance to some cultures. This is noted in the background of the information section and will require local application for some cultures, and in 2.4.1.4 we recommend considering the diversity of the population they serve when adapting practice paradigms.

2.1.1 EBR Healthcare professionals and women should recognise the adverse impact of PCOS and/or PCOS features on quality of life in adults.

2.6.1.1 EBR Healthcare professionals should provide tailored information, education and resources that are high-quality, culturally appropriate and inclusive to all with PCOS.

2.2.2 EBR Healthcare professionals should be aware of the high prevalence of severe anxiety symptoms and anxiety disorders in adults and should screen for severe anxiety symptoms and anxiety disorders in adults and adolescents who screen for anxiety in PCOS patients, using regionally validated screening tools.

2.4 Body image

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As an international guideline, we acknowledge that this issue of greater relevance to some cultures. This is noted in the background of the information section and will require local application for some cultures, and in 2.4.1.4 we recommend considering the diversity of the population they serve when adapting practice paradigms.
2.3 Psychosexual function
Healthcare professionals should be aware of the multiple factors that can influence psychosexual function in PCOS including infertility, higher weight, hirsutism, mood disorders and PCOS medications. It would be better to rearrange this list as the focus appears to be only on infertility, whereas people could be facing issues much before they are trying to conceive.

The order was considered by the GDG and we have now immersed infertility as one of the factors but not listed it first.

2.3 Psychosexual function
They should refer patients or reassess treatment options depending on the trigger.

Our guiding principles include person centred care which is relevant here. There is inadequate evidence for psychosexual dysfunction in PCOS which limits recommendations to screen or refer and above the general population.

2.4 Body Image
Specify what aspects might be affecting patients. Ask the patient and refer based on the cause of concern.

This is addressed under recommendations to ascertain and address patient concerns. Our guiding principles include person centred care which is relevant here. See 2.6.4

2.6.1 Information needs
People might have differing views about the best types and sources of information. Some research has indicated people might prefer digital sources. Health care professionals should refer to up-to-date, scientifically accurate and culturally appropriate information sources.

Evidence on information needs has informed the dissemination strategies.

2.6.1 Information needs
Information provided should be tailored based on the patients concerns and life stage.

This is dealt with in some of the recommendations (2.6.1) and will be covered in the dissemination section and added to the justification section of the guideline. This also is covered under patient centred care.

2.6.3 Support to manage PCOS
Information regarding PCOS should be provided during menstrual health education to improve awareness and support.

This is encompassed in the reproductive lifeplan recommendation and can be addressed in regional adaptation.

2.6 Psychological therapy
Section 2.8 on psychological therapy should come before 2.7 or combine it into one section.

We have reordered the sections as suggested.

2.8.2 Women with PCOS with disordered eating, body image distress, low self-esteem, problems with fitting with social norms, or psychosexual dysfunction should be offered evidence-based treatments (e.g., cognitive behaviour therapy) where appropriate.

Problems with feminine identity can be a controversial statement; I would avoid this to be gender inclusive.

Feminine identity is irrespective of sex and gender. This relates to social and cultural norms and hence we have altered the terminology around feminine identity to social and cultural norms.

2.3 Health related Quality of Life
These are much welcomed interventions. There must be a much higher focus on quality of life from HCPs. However, given funding cuts and long waiting times for psychotherapy I am not sure how well this will play out in practice. The first HCP a patient meets is generally a GP, and patients do not feel that their GP is adequately informed about the psychosocial complications of PCOS. Referral to charities and CBT resources may be a first step for women suffering with psychological symptoms unable to get therapy on the NHS.

Psychosocial concerns vary by ethnicity. For example, this study concluded that Non-white women and women born in India reported higher emotional and sexual dysfunction, whereas white women and women born in the UK reported higher body image concerns and weight stigma. Ethnicity and birthplace need to be considered for tailored, multidisciplinary care (4).

CBT based education and strategies will be included in the PCOS resources. Ethnicity is also being considered in the translation tools and in the provision of resources, which also consider lack of access.
3.1.10. PP Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care. 

**Guideline recommendation to which feedback is targeted.**

Guideline development group consensus response: We have kept the practice point in Chapter 3 as well as now adding it to Chapter 1.

3.1.9. PP In those who are not overweight, in the adolescent and at key life points, the focus should be on healthy lifestyle and the prevention of excess weight gain. 

**Comments**

- Many physicians and the public are unfamiliar with healthy eating guidelines. It may be more helpful to include descriptions of a healthy diet which can lower insulin resistance and strengthen the gut microbiome such as a plant forward, whole food diet, decreased heavily processed foods, decreased sugary foods and beverages, and decreased red and processed meats.

- The working in the recommendation is focused separately for healthy lifestyle AND prevention of weight gain as two separate points here. Lifestyle is not instituted to directly target insulin resistance which cannot be reliably measured in clinical practice. There is also no evidence-based approach to optimising insulin levels through diet. Hence the GDG after considering this feedback did not alter the recommendations. Also detailed reference to specific diets is managed in the translation tools.

3.1.10. PP Insulin resistance is a pathophysiological factor in PCOS, however, clinically available insulin assays are of limited clinical relevance and should not be used in routine care.

**Comments**

- Insulin Assays are of good clinical relevance, especially for those who do not present with signs of insulin resistance e.g. hip to waist ratio, and HbA1c is normal.
- Can provide further critical data on the patient and their insulin status to better inform practitioners for personalised treatment.

**Guideline recommendation to which feedback is targeted.**

Insulin resistance is key to pathophysiology on PCOS however there are no accurate assays as opposed to clamp studies that can be applied in clinical practice in diabetes or PCOS. No evidence was provided in the feedback for the GDG to review the current recommendations.

3.2.2. PP Behavioural support could include: goal setting, problem solving, self-monitoring and reviewing, or SMART goals (Specific, Measurable, Achievable, Realistic and Timely)

**Comments**

- We have found that SMART goals need to be based on behaviour/habit change rather than an outcome. Outcomes can be out of the patient’s control e.g. the amount of weight they want to lose. The goal should be linked to the behaviour change rather than the outcome which is within control of the patient.
- Based on clinical observations and experience.

**Guideline recommendation to which feedback is targeted.**

The PP does not specify either behaviour or health outcomes, rather the point is for behavioural support.

3.2.3. CR Any diet composition consistent with population guidelines for healthy eating will have health benefits, and within this, healthcare professionals should advise sustainable healthy eating tailored to individual’s preferences and goals.

**Comments**

- Population guidelines include 4-6 servings of carbohydrates and grains. May need to be tailored to the patient.
- RDI for nutrients are not PCOS specific. Cannot guarantee health benefits just by following population guidelines. E.g. following guidelines does not mean a patient may achieve weight loss or the goals of the patient.

**Guideline recommendation to which feedback is targeted.**

Please refer to the PP above regarding diet plans for cardiovascular disease and diabetes population. There is no additional evidence provided to alter the GDG recommendations.

3.3.3. PP Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals and avoiding unhealthy restrictive and nutritionally unbalanced diets, are important, as per general population guidelines.

**Comments**

- Coloring of dietary changes to food preference and clinical markers of the individual.
- PP: personal carbohydrate tolerances differ within individuals hence it is critical to find what is the best for the particular patient.

**Guideline recommendation to which feedback is targeted.**

We have already recommended that diet advice should be provided based on personal preferences and goals in 3.3.2 and 3.3.3.

3.4.3. CR Healthcare professionals should encourage and advise the following in concordance with general population physical activity guidelines: 

- Adults should undertake physical activity as doing some physical activity is better than none.
- Adults should limit the amount of time spent being sedentary (e.g. sitting, screen time) as replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits. 
- For the prevention of weight gain and maintenance of health, adults (18-64 years) should aim for a minimum of 150 to 300 minutes of moderate-intensity activities or 75 to 150 minutes per week of vigorous intensity aerobic activity or an equivalent combination of both spread throughout the week, plus muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week.
- For promotion of greater health benefits including modest weight loss and prevention of weight regain, adults (18-64 years) should aim for a minimum of 250 mins/week of moderate intensity activities or 105 mins/week of vigorous intensity or an equivalent combination of both, plus muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week.
- Adolescents should aim for at least 60 minutes of moderate- to vigorous-intensity physical activity per day including activities that strengthen muscle and bone, at least three times per week.

**Comments**

- Strength training on consecutive days: It might suit the routine and lifestyle of the patient to do 2 days back to back to strength training. Adequate time for recovery with 2 strength based exercise sessions on consecutive days.

**Guideline recommendation to which feedback is targeted.**

We have adopted the WHO guidelines which recommended 2 non-consecutive days due to research showing 44 hours of recovery post muscle strengthening exercise. However, we have now amended the wording in 3.4.3 to reflect that muscle strengthening activities (e.g. resistance/flexibility) on two non-consecutive days per week is ideal but not compulsory.

3.6.4. PP Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes. In PCOS this includes: 

- Tailoring of dietary changes to food preferences, allowing for a flexible, individual and co-developed approach to achieving nutritional goals and avoiding unhealthy restrictive and nutritionally unbalanced diets, are important, as per general population guidelines.

**Comments**

- Higher weight is a risk factor for PCOS - wording indicates that PCOS has been developed from weight

**Guideline recommendation to which feedback is targeted.**

As outlined in the technical report, the evidence supports that the relationship between weight and PCOS is bidirectional. In susceptible individual, higher weight increases the risk of PCOS and symptom severity, and PCOS increases propensity to weight gain, whilst weight loss reduces PCOS features. No evidence was provided for GDG consideration to alter this recommendation.

### Additional Comments

- Adherence to physical activity and dietary guidelines can be improved by tailoring advice to individual preferences and goals.
- The use of insulin resistance measurement in clinical practice is limited, and further research is needed.
- The role of lifestyle modification alone in the management of PCOS remains uncertain, with more research needed to determine its effectiveness.
- The focus on weight loss in the management of PCOS is not supported by evidence, and alternative strategies should be considered.
- The importance of insulin resistance as a key factor in the pathophysiology of PCOS has been highlighted, but further research is needed to develop effective interventions for its management.
Healthcare professionals should be aware of weight-inclusive practices which promote acceptance of and respect for body size diversity and focus on improvement of health behaviours and health outcomes for people of all sizes. In PCOS, this includes:

- Acknowledging that whilst higher weight is a risk factor for PCOS and its complications, it is only one indicator of health and broader factors should be assessed.
- Making permission to discuss and measure weight and using strategies to minimise discomfort (e.g. blind weighting).
- Recognising that the terms "overweight" and "obese" can be stigmatising with suggested alternatives including "higher weight".
- Weighing, explaining how weight information will be used to inform risks, prevention and treatment and how not knowing may impact on recommendations.
- Ensuring appropriate equipment is available for women of all sizes.
- Offering options of weight-centric care (promoting intentional weight loss) or weight-inclusive care (promoting healthy lifestyle change without focusing on intentional weight loss) tailored to individual goals and preferences.
- Offering all women best-practice assessment, treatment and support regardless of weight, acknowledging that weight may be a non-modifiable risk factor when using lifestyle modification alone.

Practitioners should query if weight really needs to be known and would change the treatment plan for the patient. Would body composition be a better measure to take over body weight? Progress can be tracked via clothes feel, how the patient feeling, body comp measurements etc. rather than body weight.

Where is the value in knowing body weight? Does this alter the treatment plan for the patient (e.g. may be needed for medication dose, if not, then is weight relevant?). No need to cause unnecessary stress to the patient.

The guideline group agrees and it is already stated in 3.6.3 that health policy makers, managers and educators should all promote and invest in weight stigma education and minimisation strategies.

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4.7 Inositol (P5R) in guideline.  

- The sentence is proposed that hyperinsulinaemia in PCOS enhances MI to DCI conversion and impacts the ratio which is 100:1 generally but in PCOS may be 0.2:1 needs some clarifications, as it is misleading.  
- The sentence “MI may also enhance androgen production is false. No publication has ever reported this information, least of all the reference indicated in the text.  
- The sentence “there is considerable reinformation on efficacy” is quite outdated.  
- Under insulin stimulation, epimerase enzyme converts myo-inositol (myo-Ins) into its stereoisomer D-chiro-insitol (D-chiro-Ins). This unidirectional reaction allows each organ and tissue to benefit from a specific and proper balance between myo-Ins and D-chiro-Ins content, ensuring the correct metabolite functions and consequent physiological status.  
- In some pathological conditions, the decreased insulin sensitivity in many tissues leads to reduced epimerase activity and lower D-chiro-Ins production [1]. However, ovaries can maintain normal insulin sensitivity, despite the presence of insulin resistance. Indeed, according to the so-called ‘ovarian paradox’ ovaries never become insulin resistant, and therefore, the compensatory hyperinsulinaemia overstimulates the ovarian epimerase, causing excessive D-chiro-Ins synthesis at the expense of myo-Ins concentration [2]. So, while healthy women’s ovaries show higher myo-Ins levels and lower concentrations of D-chiro-Ins, with a ratio around 100:1; on the contrary, ovaries in PCOS patients proved to have marked myo-Ins depletion and increased D-chiro-Ins content, with a ratio dropping to 0.2:1 [3]. The resultant impaired ovarian myo-Ins to D-chiro-Ins ratio may account for PCOS pathogenesis in insulin resistant patients. In fact, the increase in D-chiro-Ins concentration promotes androgen synthesis, meanwhile myo-Ins depletion worsens FSH signalling and reduces ovulatory cycles. The ovarian paradox hypothesis may help to explain why supplementation with D-chiro-Ins alone, especially at high dose and for a prolonged time, cannot be considered an effective approach to manage PCOS. In contrast, several lines of evidence proved myo-Ins efficacy and safety in managing PCOS symptoms and improving outcomes [4] with the most promising clinical results observed in obese, insulin-resistant women with PCOS, when combining myo-Ins and D-chiro-Ins in a 40:1 ratio. The 40:1 ratio which may appear arbitrary, actually, is similar to the plasma ratio reported in healthy women [5], thus supporting its supplementation to restore the physiological concentrations of myo-Ins and D-chiro-Ins. In this case, the small quantity of D-chiro-Ins reduces systemic insulin levels, leading to an increase in intracellular myo-Ins, which improves FSH sensitivity and restored ovulation.  
- It is well known that research on inositols demonstrated that D-chiro-Ins, and not myo-Ins, stimulates the ovarian production of androgens by theca cell [6].

4.2 Combined Oral Contraceptive Pills (COCP)  

- It is surprising that there is not as strong statement on the risk of COCP prescription in those with BMI >35, particularly given presence of obesity in this condition.
- We were not inferring regular cycles, but were referring to cycle regulation. No change required.

4.11.1 EBR Metformin should not be routinely used in pregnant women with PCOS as it has not been shown to be effective and which not? Should anti-androgens be avoided when barrier methods alone are in use?  

- We have amended the sections:  
  1) It is proposed that hyperinsulinaemia in PCOS enhances ovarian epimerase activity which enhances D-Chiro-insitol synthesis at the expense of myo-insitol concentration. In women without PCOS, the ratio of MI to DCI is 100:1 in follicular fluid whereas in women with PCOS, this ratio drops to 0.2:1. (Order 2014)  
  2) MI is also postulated to enhance aromatase synthesis in granulosa cells and therefore reducing androgen production

4.8.6 PP Policy makers should consider funding this evidence-based effective therapy for women with PCOS to improve their psychological health.

- For women without PCOS, the ratio of MI to DCI is 100:1 in follicular fluid whereas in women with PCOS, this ratio drops to 0.2:1. (Order 2014)  
- MI is also postulated to enhance aromatase synthesis in granulosa cells and therefore reducing androgen production  
- However, there are concerns about misinformation and potential conflict of interest and these supplements come at high cost, with a priority to ensure evidence-based information on inositol
4.2.7 PP When prescribing COCPs in adults and adolescents with PCOS, and adolescents at risk of PCOS:

- It is important to address main presenting symptoms and consider other treatments such as cosmetic therapies.
- Shared decision-making (including accurate information and reassurance on the efficacy and safety of COCPs) is recommended and likely to improve adherence.
- Natural estrogen preparations and the lowest effective estrogen doses (such as 20-30 micrograms of ethinyl estradiol or equivalent), need consideration, balancing efficacy, metabolic risk profile, side effects, cost and availability.
- The relatively limited evidence on COCPs specifically in PCOS needs to be appreciated with practice informed by general population guidelines.
- The relative and absolute contraindications and side effects of COCPs need to be considered and be the subject of individualised discussion.
- PCOS specific features such as higher weight and cardiovascular risk factors, need to be considered.

Reassurance can be pressure, rather than consent.

4.7 Inositol

- Several false statements, some data out of date and some recommendations to amend.
- This sentence needs some clarifications.
- Under insulin stimulation, epimerase enzyme converts myo-inositol (myo-Ins) into its stereoisomer D-chiro-inositol (D-chiro-Ins). This unidirectional reaction allows each organ and tissue to benefit from a specific and proper balance between myo-Ins and D-chiro-Ins content, ensuring the correct metabolic functions and consequent physiological status.
- In some pathological conditions, the decreased insulin sensitivity in many tissues leads to reduced epimerase activity and lower D-chiro-Ins production [1]. However, ovaries can maintain normal insulin sensitivity, despite the presence of insulin resistance. Indeed, according to the so-called ovarian paradox, ovaries never become insulin resistant, and therefore, the compensatory hyperinsulinaemia overstimulates the ovarian epimerase, causing excessive D-chiro-Ins synthesis at the expense of myo-Ins concentration [2].
- So, while healthy women’s ovaries show higher myo-Ins levels and lower concentrations of D-chiro-Ins, with a ratio around 100:1; on the contrary, ovaries in PCOS patients proved to have marked myo-Ins depletion and increased D-chiro-Ins content, with a ratio dropping to 0.2:1 [3].
- The resultant impaired ovarian myo-Ins to D-chiro-Ins ratio may account for PCOS pathogenesis in insulin resistant patients. In fact, the increase in D-chiro-Ins concentration promotes androgen synthesis, meanwhile myo-Ins depletion worsens FSH signalling and ovocyte quality.
- The ovarian paradox hypothesis may help to explain why supplementation with D-chiro-Ins alone, especially at high doses and for a prolonged time, cannot be considered an effective approach to manage PCOS. In contrast, several lines of evidence proved myo-Ins efficacy and safety in managing PCOS symptoms and improving outcomes [4], with the most promising clinical results observed in obese, insulin-resistant PCOS women, when combining myo-Ins and D-chiro-Ins in a 40:1 ratio.
- The 40:1 ratio that may appear arbitrary, actually is similar to the plasma ratio reported in healthy women [5], thus supporting its supplementation to restore the physiological concentrations of myo-Ins and D-chiro-Ins. In this case, the small quantity of D-chiro-Ins reduces systemic insulin levels, leading to an increase in intraovarian myo-Ins, which improved FSH sensitivity and restored ovulation.
- Page 90
- MI may also enhance androgen production.
- This sentence is false. No publication has ever reported this information, least of all the reference indicated in the text.
- Actually, it is well known that research on inositol demonstrated that D-chiro-Ins, and not myo-Ins, stimulate the ovarian production of androgens by thecal cells [6].

Alternative therapies were not identified as a key priority by women or health professionals and hence are out of scope. Evidence for most alternative therapies is very limited. The guidelines do include recommendations for inositol.

4.7 Inositol

- The background section of inositol has been reviewed and amended.

4.7 Inositol

- The physiological MI:DCI ratio is 40:1, not 100:1.
- There are lots of alternative therapies targeted for PCOS management and it might be beneficial to include a section on alternative therapies with current evidence.
- Please see the following international Position Statement summarising the available pieces of evidence:

Alternative therapies were not identified as a key priority by women or health professionals and hence are out of scope. Evidence for most alternative therapies is very limited. The guidelines do include recommendations for inositol.

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4.7 Inositol

- The background section of inositol has been reviewed and amended.
Inositol

Several false statements, some data out of date and some recommendations to amend (see my suggestions below).

Please see the argument below that has been posted by Dr Simona Dinicola on the CREWHIRL site.

I fully agree with this argument.

Comments on Sections 4.7 and 5.8 about Inositols of the International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023.

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It is proposed that hyperinsulinemia in PCOS enhances MI to DCI conversion and impacts the ratio which is 100:1 generally but in PCOS may be 0.2:1.

This sentence needs some clarifications.

Under insulin stimulation, epimerase enzyme converts myo-inositol (myo-Ins) into its stereoisomer D-chiro-inositol (D-chiro-Ins). This unidirectional reaction allows each organ and tissue to benefit from a specific and proper balance between myo-Ins and D-chiro-Ins content, ensuring the correct metabolic functions and consequent physiological status.

In some pathological conditions, the decreased insulin sensitivity in many tissues leads to reduced epimerase activity and lower D-chiro-Ins production [1]. However, ovaries can maintain normal insulin sensitivity, despite the presence of insulin resistance. Indeed, according to the so-called “ovarian paradox” ovaries never become insulin resistant, and therefore, the compensatory hyperinsulinemia overstimulates the ovarian epimerase, causing excessive D-chiro-Ins synthesis at the expense of myo-Ins concentration [2].

So, while healthy women’s ovaries show higher myo-Ins levels and lower concentrations of D-chiro-Ins, with a ratio around 100:1, on the contrary, ovaries in PCOS patients proved to have marked myo-Ins depletion and increased D-chiro-Ins content, with a ratio dropping to 0.2:1 [3].

The resultant impaired ovarian myo-Ins to D-chiro-Ins ratio may account for PCOS pathogenesis in insulin resistant patients. In fact, the increase in D-chiro-Ins concentration promotes androgen synthesis, meanwhile myo-Ins depletion worsens FSH signalling and oocyte quality.

The “ovarian paradox hypothesis” may help to explain why supplementation with D-chiro-Ins alone, especially at high doses and for a prolonged time, cannot be considered an effective approach to manage PCOS.

In contrast, several lines of evidence proved myo-Ins efficacy and safety in managing PCOS symptoms and reproving outcomes [4], with the most promising clinical results observed in obese, insulin-resistant PCOS women, when combining myo-Ins and D-chiro-Ins in a 40:1 ratio.

The 40:1 ratio that may appear arbitrary, actually is similar to the plasma ratio reported in healthy women [5].

The background section of inositol has been reviewed and amended.

Section 4. Management of non-fertility features

Sexual health and mental health needs should be addressed in this section.

This has been covered in Chapter 2 in detail.

4.2.1 EB The COCP should be recommended in reproductive age adults with PCOS for management of hirsutism and/ or irregular menstrual cycles.

While COCP in effective, HCP should explain properly. Women have expressed frustration with the use of long term medication without other forms of support [6]. I remember feeling that I was being ignored and sent away with a one size fits all solution, when if the HCP had explained the mechanism of action to me, I would have walked away satisfied.

Working in partnership with patients and shared decision making have been discussed in detail elsewhere in the guideline.

4.3.1 EB Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric, and metabolic outcomes including insulin resistance, glucose, lipid profiles and androgen levels.

There is growing evidence that metformin risk varies across different ethnicities and hence the current practice for ethnicity based cut-off for treatment recommendation.

Metformin is not an anti-obesity medication. There is insufficient evidence for metformin for different ethnic BMI cut-offs to provide ethnicity specific recommendations.

4.7.4 PP Specific types, doses or combinations of inositol cannot currently be recommended in adults and adolescents with PCOS, due to a lack of quality evidence.

While this is generic, I wonder if there is merit to address the combination of metformin and inositol which appear to be common practice these days.

The comparison was considered in the evidence synthesis and covered in the background section of inositol.

4.8.1 EB Mechanical laser and light therapies should be considered for reducing facial hirsutism and for related depression, anxiety and quality of life in women with PCOS.

This is extremely welcome, but again I wonder how much it will be prescribed in practice.

No response required.
4.7 Inositol

Our group consensus is that this section is written in such a definitive and negative way towards inositol, especially when compared to other sections of this guideline where recommendations are made with low evidence (for example, section 5.4) without the same tone. Inositol is widely used as an alternative to metformin for those who desire an option with fewer GI side-effects, and this document should encourage additional research. The outline gives a negative narrative of inositol. This may dissuade doctors from being open-minded to their patients taking inositol.

There are many studies to consider which may not have been reviewed in consideration of drafting Section 4.7. The following is an outline of studies from 2007-2023:


We agree that these are important as part of shared decision making. Reference to sections in guideline, e.g. metformin adverse effects. See above regarding inositol. 4.7.6

4.3.2 EBB Metformin alone could be considered in adolescents at risk of or with PCOS for cycle regulation, acknowledging limited evidence.

The evidence for metformin is stronger. Progesterone therapy was not prioritised as a clinical question and the guidance is a potential medical therapy for endometrial protection.

GDG considered that adherence might be a factor to consider also. We acknowledge that cyclical progesterone is a potential medical therapy for endometrial protection.

4.3.4 FP Where metformin is prescribed the following need to be considered:

- The authors could mention that measuring kaliemia is not necessary when prescribing spironolactone in young women.
- The authors mention spironolactone acid (CPA) at a high dose > 10 mg. A high dose of CPA is usually higher than 50 mg. The duration of treatment is a major issue.

No action required

4.6.5 PP When prescribing anti-androgens, based on general population recommendations, healthcare professionals should consider that:

- Flutamide and bicalutamide have an increased risk of severe liver toxicity.
- Spironolactone at 25-100mg / day appears to have lower risks of adverse effects.
- Some studies indicate that 50 mg. The duration of treatment is a major issue.

No action required
4.5 Anti-obesity pharmacological agents

The authors should at least mention the existence of novel treatment options in adolescent girls addressed at reducing ectopic fat excess and not at masquerading the symptoms. There is insufficient evidence at present to recommend phentermine/topiramate in women with PCOS. We acknowledge that there is some evidence in the general population for use of these medications in the management of obesity.

4.6.3 PP Whenever pregnancy is possible, healthcare professionals must educate and counsel women and adolescents, parents/c or guardians, regarding the risks of incomplete development of external genital structures of male fetuses (under/development) when anti-androgens are used. To prevent this, women who can get pregnant should be strongly counseled to use effective contraception (e.g. intrauterine device or COCPs).

Important principles

Metformin: Mild adverse effects, including gastrointestinal side-effects are generally dose dependent and self-limiting, but can be decreased by changing to extended release formulations. Metformin intolerance is not insignificant. Switching to the sustained release formulation is often needed, and this option should be made clear to the practitioner. SR is also dose once a day, rather than twice a day, which can improve adherence.

In the original diabetes prevention program study, 16% of adults in the metformin group did not reach the full dose of 1700 mg a day due to side-effects/intolerance, and rather were treated with 850 mg once a day.

Only agents approved for use by multiple regulatory agencies in weight management were the subject of recommendations here including exenatide, liraglutide, semaglutide and orlistat. The question of the novel treatments was not addressed in the guideline as they were not prioritised by the GDG experts or consumers. Furthermore, the evidence provided here was two small pilot trials in a single centre and would not have been adequate evidence to inform recommendations here.

The wording in the guideline does not recommend universal use of COCP, rather it is recommended as first line treatment for PCOS. Given the very low evidence for this recommendation, it makes little sense in many other guidelines regarding obesity, and is a very effective therapy- twice the efficacy of liraglutide.

There is insufficient evidence at present to recommend phentermine/topiramate in women with PCOS. We acknowledge that there is some evidence in the general population for use of these medications in the management of obesity.
Combined Oral Contraceptive Pills (COCP)

The COCP should be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles. Regarding this statement, there is no evidence in the technical report supporting that COCPs should be used in adolescents at risk for PCOS. Additionally, although the recommendation grade became "very low quality" instead of "low quality", the authors state that COCP "should be considered in adolescents at risk"; however, in the 2018 guideline, their statement read: "COCP could be considered in adolescents who are deemed "at risk". This makes no sense. What is the rationale for such a recommendation?

Metformin alone could be considered in adolescents at risk or with a clear diagnosis of PCOS for management of hirsutism and/or irregular menstrual cycles. This is an important point and has now been explained in the guideline justification section. The evidence is of lower quality than the 16 comparisons covered in the 2018 guidelines, however since then many more comparisons have been trialed (32) and these new comparisons have lower level evidence. However, convention dictates that the lowest evidence rating needs to be reported and hence adding in new comparisons results in a lower evidence certainty, despite the original evidence remaining the same since 2018. We have now clarified this overall: under the section on certainty of evidence and the justification section of the individual relevant clinical questions in the guideline where relevant. Furthermore, recommendation for use is informed by use in the general population and effects on hyperandrogenism and same control.

We also added to the Interpreting the recommendations section in p15. Aligned to Cochrane methods, certainty of evidence varies significantly across outcomes for each clinical question. In this guideline, the recorded evidence certainty reflects the lowest certainty for the top three critical outcomes for each question, hence evidence was often stronger for the most critical outcome and often high-quality RCT addressed an individual question, but multiple additional low-quality studies may have resulted in low certainty evidence overall. These nuances in the evidence were considered for every clinical question and are outlined in the technical report and GRADE tables. Hence, an apparent discrepancy may be observed between the strength of the recommendation and the certainty of the evidence. Where this occurs, a justification is added to the guideline under the relevant clinical question.

The underlined text does not align well with other parts in the guideline, such as: OC is preferred for hirsutism treatment (4.2.1). When OC may not be given for hirsutism, other interventions (not metformin) are suggested (4.4.5). The androgen levels section was deleted.

The underlined text is not defined and is therefore unclear. Moreover, this sentence is consistent with the previous guideline version although the recommendation grade became "very low quality" instead of "low quality". On the other hand, the recommendation in adolescents focuses solely on cycle regulation, but not on BMI and metabolic outcomes as in adults. Indeed, the data regarding the effect of metformin on BMI in adolescents is limited. In contrast, in the draft guideline of 172 pages, it is stated that: "There was inadequate evidence to make a recommendation about the use of metformin for irregular menstrual cycles". So, the persistence of this recommendation (4.3.2) exclusively for irregular cycles is, in the best of cases, debatable. In addition, the use of metformin for irregular menstrual cycles, in case the COCPs are contraindicated or not recommended, evidence was often stronger for the most critical outcome and often high-quality RCT addressed an individual question, but multiple additional low-quality studies may have resulted in low certainty evidence overall. These nuances in the evidence were considered for every clinical question and are outlined in the technical report and GRADE tables. Hence, an apparent discrepancy may be observed between the strength of the recommendation and the certainty of the evidence. Where this occurs, a justification is added to the guideline under the relevant clinical question.

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<table>
<thead>
<tr>
<th>ID</th>
<th>Guideline recommendation to which feedback is targeted</th>
<th>Comments</th>
<th>Guideline development group consensus response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General comment</td>
<td></td>
<td>The GDG considered the comment but unfortunately was unclear of the key recommendations this comment was on. As such the GDG decided to stay onto our original workings.</td>
</tr>
<tr>
<td>12</td>
<td>5.2.1 CR in women with PCOS and infertility due to anovulation alone with normal women analysis, the risks, benefits, costs and timing and techniques of tubal patency testing in relation to the cost and complexity of the treatment, should be discussed on an individual basis, depending on personal history and population prevalence, prior to starting ovulation induction with timed intercourse or intrauterine insemination.</td>
<td>In PCOS, FTS under Ou-stimulation could be used both urinary and recombinant gonadotropin as well metformin to reduce eventually OHSS risk that however reduce by antagonist. Asking you evidence in the LETROZOL, use to reduce OHSS risk. Off label use confirmation by if you possible.</td>
<td>Specific adverse effects of all therapies are not listed in the guideline.</td>
</tr>
<tr>
<td>14</td>
<td>5.3.1 EBR Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naive women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.</td>
<td>It is the recommendation that gonadotrophins be first line agents for ovulation induction? This appears to be the conclusion of the statement above. Can this be clarified?</td>
<td>This is a very legitimate point and was considered by the GDG.</td>
</tr>
<tr>
<td>15</td>
<td>5.5.6 PP Where gonadotrophins are to be prescribed, the following should be considered:</td>
<td>Should this be stated a “low dose step up gonadotropin protocol”? Most of the provided literature utilize a step up protocol.</td>
<td>5.5.2 The GDG considered and have amended the PP to “A low dose step up gonadotropin protocol should be used…”</td>
</tr>
<tr>
<td>16</td>
<td>5.4.3.1 Clomiphene citrate vs metformin</td>
<td>For Clomiphene Citrate, what about mentioning the potential risk of many repeated cycles?</td>
<td>This is a very legitimate point and was considered by the GDG.</td>
</tr>
<tr>
<td>17</td>
<td>5.3.1 EBR Clomiphene citrate combined with letrozole is the default first line choice.</td>
<td>Have modified PP 5.4.2.2 to “The risk of multiple pregnancy increases with clomiphene citrate use (alone or in combination with metformin) and therefore clomiphene citrate will require ultrasound monitoring.”</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>5.5.1 EBR Gonadotrophins alone could be considered rather than clomiphene citrate in therapy naive women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, clinical pregnancy and live birth rates.</td>
<td>It is stated in 5.3.1 that letrozole is first line for ovulation induction in PCOS. In 5.5.1 gonadotrophins can be used in preference to clomiphene citrate in therapy naive women with PCOS according to the recommendation. The algorithm will clarify this.</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>5.5.2 PP Prenatal vitamins supplementation should be commenced with ovulation induction therapy aligned to routine prenatal care.</td>
<td>Should prenatal care be changed to pre-conception care, as folic acid needs to be started before conception.</td>
<td>The points of consideration of cost and expertise is covered in PP 5.5.6.</td>
</tr>
</tbody>
</table>
There should be ongoing monitoring of patients for adverse effects and infants for congenital anomalies in all studies conducted with ovulation induction agents and these should be reported in any published papers. The wordings are deliberately broad to cover all types of adverse effects and not just multiple birth/pregnancies.

5.1.2 CR Consistent with routine preconception care, in women with PCOS planning pregnancy, weight, blood pressure, smoking, alcohol, nutritional status, exercise, sleep and mental, emotional and sexual health should be considered and optimised to improve reproductive and pregnancy outcomes and overall health.

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

5.3 Tissue factor expression is increased in women with PCOS and infertility. Consideration should be given to the risk of cardiovascular disease and multiple pregnancy in these women.

5.3.1 EBR Letrozole should be considered the first line pharmacological treatment for ovulation induction in infertility anovulatory women with PCOS, with no other infertility factors. This is already taken into account in the recommendation. No wordings are changed.

5.5 Gonadotrophins

5.5.1 EBR Clomiphene citrate is still commonly used as a first line treatment for ovulation induction in infertility anovulatory women with PCOS, with no other infertility factors. There is evidence that metformin reduces the risk of early miscarriage, as well as other benefits. (Ref Zhao Gynecol Endocrinol 2022;38:7, 558-568) which might support its use during pregnancy

5.5.2 EBR Letrozole is considered the superior oral ovulation induction agent, yet there are a lot more subheadings for clomiphene citrate. Extensive evidence synthesis as outlined in the guideline and technical report, overall did not support the general use of metformin in pregnancy and is covered in GDG4.

5.5.3 Gonadotrophins

5.5.4 This is a critical section of the guideline and very important for best practice. It is a short section and could be expanded. Considered by the GDG and no change made.

5.6 Antidiabetes agents

5.6.1 EBR Metformin should be used alone, in women with PCOS with anovulatory infertility and no other infertility factors, to improve clinical pregnancy and live birth rates, although women should be informed that there are more effective ovulation agents.

5.7 Gonadotrophins

5.7.1 EBR Letrozole should be considered the first line pharmacological treatment for ovulation induction in infertility anovulatory women with PCOS, with no other infertility factors. This is already taken into account in the recommendation. No wordings are changed.

5.7.2 CR This section is not concise enough and not in the correct order. Please consider adding in a comment guiding ‘optimally managed’ diabetes. For example, HbA1c < 6.0% may be taken as a target for optimally managed diabetes.

5.8 Gonadotrophins

5.8.1 EBR Clomiphene citrate is still commonly used as a first line treatment for ovulation induction in infertility anovulatory women with PCOS, with no other infertility factors. There is evidence that metformin reduces the risk of early miscarriage, as well as other benefits. (Ref Zhao Gynecol Endocrinol 2022;38:7, 558-568) which might support its use during pregnancy

5.8.2 CR When using gonadotrophins, best clinical practice is to avoid multiple pregnancy. Considerations here include cancelling cycles when there is more than a total of two follicles greater than 14mm in diameter and advising avoidance of unprotected intercourse.

5.8.3 CR Considered by the GDG and no change made.

5.9 Anti-obesity pharmacological agents

5.9.1 EBR Tissue factor expression is increased in women with PCOS and infertility. Consideration should be given to the risk of cardiovascular disease and multiple pregnancy in these women.

5.9.2 CR Chronic conditions such as diabetes, high blood pressure, anxiety, depression and other mental health conditions, should be optimally managed and women should be counselled regarding the risk of adverse pregnancy outcomes.

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