Author’s response to reviews

Title: Adolescent Polycystic Ovary Syndrome according to the International Evidence-Based Guideline

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Author’s response to reviews:

Professor Lin Lee DPhil
Editor in Chief
BMC Medicine

Dear Professor Lee,

Thank you for considering our revised manuscript ‘Adolescent Polycystic Ovary Syndrome (PCOS) according to the International Evidence-Based Guidelines’ (BMED-D-19-01237). We greatly appreciate the useful comments and we have addressed all comments.

Reviewer reports:

Reviewer #1: Corrine Welt
1. The guidelines are improved with the changes made. I would again suggest moving the evidence type to the end of the recommendation because the evidence remains the most prominent portion of the recommendation.
For example, in the following:

"There were no evidence-based recommendations and the Guideline included strong consensus recommendations: The first CCRconsensus recommendation was: A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, which"
"There were two conditional evidence based-recommendations with low GRADE quality that were derived from studies in adult women that reported on the diagnostic accuracy of different hormone markers to detect PCOS. [34-39] One study compared the diagnostic accuracy of different types of assay to detect PCOS but did not include adolescents. [40] These evidence-based recommendations included: 1) High quality assays It takes two to four lines to actually get to the recommendation. If one puts the evidence at the end, it will be available but not distracting.
RESPONSE:
As suggested by the reviewer, we have now moved the evidence type to the end of the each section and started each section with the recommendation it-self. This change was applied to all recommendations starting with the type of recommendation and we would like to highlight to the editor that even though the tracked changes look substantial there is no change in the content just the movement of segments. See Pages 11, 12, 13, 14, 15, 17, 18, 19, 22, 23 and 24.

2. Of note, the responses to this comment below were broken into sections to make the answers to this comment clearer.

a) The second concern I have remains the recommendation that ultrasound not be used until 8 years after menarche. "3. Pelvic ultrasound is not recommended for diagnosis of PCOS within 8 years of menarche." I cannot agree with this recommendation.
RESPONSE:
With respect to this individual reviewer’s right to not agree, this is not an option-based recommendation. We do acknowledge the controversy in the area; however, this recommendation has occurred after 15 months of extensive evidence review and expert panel engagement, as well as consultation with 37 international societies and their special interest groups and refinement of the guidelines taking into account international peer review. This process was detailed in the methods section of the manuscript (See Pages 5, second and third paragraph and Page 8 last paragraph). Additionally we want to point out as stated this was a consensus recommendation not an evidence-based recommendation.

b) In a woman with menarche at age 14, the possibility that one would not be able to use ultrasound as a criteria for PCOS before the age of 22 yrs seems incorrect. Is there any evidence that multifollicular ovaries persist for 8 years after menarche?
RESPONSE:
In evaluating the evidence indeed multi-follicular ovaries do persist 5 to 8 years post menarche as previously reported in the manuscript (Reference 55 - Kristensen SL, Ramlau-Hansen CH, Ernst E, Olsen SF, Bonde JP, Vested A, Toft G: A very large proportion of young Danish women have polycystic ovaries: is a revision of the Rotterdam criteria needed? Human reproduction (Oxford, England) 2010, 25(12):3117-3122). Of note, this study used transvaginal ultrasound that should be avoided in females not yet sexually active.
We have also acknowledged the limited data regarding natural history of follicular ovaries. See Page 14, lines 13-16.

c) One would need to provide longitudinal evidence for this comment because that is a partial reason not to use ultrasound. Several manuscripts examining PCO morphology by ultrasound include women 18 years of age and older. Therefore, there is a basis to use ultrasound criteria for the diagnosis of PCOS in women aged 18 and over.

RESPONSE:
The aggregate data from the studies including women 18 years and older informed the current recommendation. Original data was also accessed when making these recommendations, which provided better detail by age than that available directly from published literature. These data included 15 studies with 2207 women with PCOS and 1172 women without PCOS. Of these, there were only 3 studies in females younger than 18 years that have been reported in the original manuscript. The remaining studies in women older than 18 years (n=12) are included in the technical report of the guidelines (which we referred to in the manuscript) and listed below. These were not included in the manuscript as the manuscript focus was adolescents. Of note, the ranges of average ages reported in these adult women studies were 24.9 -31.2 years.


Additionally, we have data on longitudinal changes from childhood through to early adult hood. (Follow up data of the Australian RAINE study [a large prospective cohort from pregnancy] – manuscript under review). Very importantly where polycystic ovarian morphology (PCOM) was included in the diagnostic criteria in women <8 years post menarche, the diagnosis rate of PCOS was 30%. Where PCOM was not included, the diagnosis rate in adolescence was 15%, akin to the adult rate. Most importantly only those diagnosed not using PCOM < 8 years went on to have clear longer term PCOS.

The implications of using PCOM in women less than 8 years post-menarche are considerable as there will be a high rate of over diagnosis of PCOS, which the guidelines are aiming to reduce.

d) The difficulty of the recommendation is illustrated by the following example. If a girl has irregular cycles after menarche at age 13 that persist to age 18 yrs and has a testosterone at the upper limit of normal but not elevated and went to see a GYN as a new patient, she could not be diagnosed with PCOS. It is likely that the GYN would do an ultrasound if the patient was sexually active to make the PCOS diagnosis. Would you say that it was not a true diagnosis?

RESPONSE:
This example provided does not take into account clinical hyperandrogenism, which is an important part of the diagnosis of PCOS. If there was no clinical hyperandrogenism and free androgen index or free testosterone were not elevated this is correct - but here she would be deemed to be at risk and later review recommended as per guidelines. Of note, reviewer stated the patient was sexually active not all are and able to have a transvaginal ultrasound anyway.

e) If you make this recommendation, you are obligated to provide data that age based ultrasound criteria after the age of 18 years are not correct. Your own guidelines state that, "A small study of healthy adolescents 2 to 4 years post menarche suggests polycystic ovarian morphology is common and not associated with reproductive dysfunction. [56]" Why would one not suggest that 2-4 years be the time frame to avoid using ultrasound criteria?

RESPONSE:
We cannot suggest 2-4 be the time frame to avoid using ultrasound criteria as multi-follicular ovaries persist and overlap with controls for around 8 years post menarche and there will be a high risk of over diagnosing PCOS during this time.

See also response to comments above b and c.
f) The argument that "A gynaecological age of < 8 years or < 8 years post menarche as cut off was in part chosen based on normative models suggesting the maximum ovarian volume is reached at age 20. [57]" does not describe longitudinal multifollicular ovary status, which is the argument that the guidelines present.

If ovaries are large at 18 years and get larger, the PCO morphology criteria would be met. The references quoted in your guidelines all suggest ovarian volumes for normal adolescents that are well under the 10 cc cutoff.

RESPONSE:
We disagree with reviewer as there were more arguments in deciding the cut off already described over the 2 pages.

The arguments for using the gynaecological age of < 8 years or < 8 years post menarche as cut off as described in submitted previous manuscript Pages 9 and 10 are as follows:

1) Aggregate data from 15 studies that reported on diagnostic accuracy of different ovarian morphology parameters to diagnose PCOS and highlighted the high incidence of multi-follicular ovaries in adolescence and early adulthood. These studies were selected after systematic review of the literature to answer this clinical question: What is the most effective ultrasound criteria to diagnose PCOS? (See also response to comment c).

2) Physiological maturation of the hypothalamic-pituitary ovarian axis.

3) The inconsistent correlation and overlap between ovarian morphology (ovarian size and follicles numbers) and menstrual function in adolescence and early adulthood.

4) The evolution of ultrasound technology that increases sensitivity to detect a much higher follicle counts causing over diagnosing of PCOS in the younger age groups.

3. In the following section: For symptomatic treatment, combined oral contraceptive pill and/or metformin may be beneficial. Please add norethindrone to the lower risk COCPs as that is a common progestin.
RESPONSE:
Norethisterone is also known as norethindrone and we had Norethisterone already in the lower risk COCP. We have added norethindrone in brackets after norethisterone. See Page 23, lines 11-12.

4. I do not agree with the concept of secondary PCOS due to obesity. Genetic studies have demonstrated that obesity is a causal factor for PCOS using Mendelian Randomization approaches. Therefore, it is difficult to suggest that obesity may be causing a different diagnosis when all of the criteria for PCOS are met.

RESPONSE:
We do agree with this reviewer; however the subsequent reviewer was very firm in their opinion that this should at least be noted as a possibility. We are happy to remove this from the manuscript at the editor’s discretion.

See Page 20, lines 2-12.
Reviewer #2: Renato Pasquali
The authors adequately replied to all my comments, although they disagreed on some perspective (i.e. the concept of secondary PCOS to obesity).

RESPONSE:
Thanks for reviewing our responses.

Editorial comments:

1.) Please note that the declaration 'Consent for declaration' refers to consent from participants (not authors) when identifiable data are included in a manuscript. Please edit this accordingly. For further details, see: https://www.biomedcentral.com/getpublished/editorial-policies#consent+for+publication

RESPONSE:
Thanks for clarification, the consent for declaration has been updated to non-applicable. See Page 30.

2.) Regarding the declaration 'Competing interests', please clarify if the pharmaceutical firms listed played a role in this study (e.g. the design).

RESPONSE:
Pharmaceutical firms listed did not played a role in these guidelines. This has been added to competing interests section. See Page 30.

3.) Please update the citation details for citations [64] (Teede et al.) and [86] (Thong et al.).

RESPONSE:
Thanks for pointing reference 64 out as this reference was a duplicate (102 reference) and not accurate. See Page 36. Reference 86 now 85 is an epub ahead of print - doi details have been added. See Page 37.

All references have been crosschecked again and are accurate and correct. The only other reference that required revision was Reference 63 that was previously listed as 57.

Thank-you for reviewing updated version of our manuscript, which used track changes on a clean copy from last revision to facilitate review.

Yours sincerely,
Alexia Pena