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 appreciate the useful comments and we have addressed all comments.

Editorial comments:

Reviewer 1’s previous point 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."
Your 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."

Note, you deleted the relevant text. We think it should be retained, as it had been adequately tempered, so please do feel free to add it back in.

RESPONSE:
Deleted text has been added back in. See Page 19, lines 31-41.

Reviewer report:
Reviewer #1: Corrine Welt

1. The authors have discussed their reasoning. There are still some small changes needed for the PCO Morphology section. Please note that the fact that I cannot agree with the recommendation relates to the issue that the arguments in the section, the references provided and the available data do not support the comment that ultrasound should not be used for up to 8 years after menarche as a criteria for PCOS. The 8 year post menarche cutoff remains poorly justified. At minimum, the paragraph needs more detail as the references are not supportive of 8 years. 8 years does not have any bearing to age 20 years as the age at which ovaries are largest, the 2-4 years of expected irregular menses post menarche or the age of the HPG axis maturation. It appears to be tied most strongly to, as yet, unpublished data. Therefore, the guidelines should include the data or wait for the publication so that readers can understand the reasoning. If these data are part of the technical information, the technical information should be provided as the link is not working.

RESPONSE:
We acknowledged the point of the reviewer in relation to lack of robust and specific data on the 8 years cut off. This was based on a consensus recommendation with the top experts in the field and on direct and specific interrogation of individual data sets (authors of prior publications were members of the guideline group and re-reviewed their data from past publications). It was also based on data on maturity of the hypothalamic pituitary ovarian axis, patterns of menstrual cycles and anovulation around puberty and on a series of published data (References included in manuscript 2, 24, 26, 31, 32, 53-60).

See further clarification on Page 13, lines 47- 54.

It is clearly stated in the paper that it is not an evidence-based recommendation. The detailed process of deliberation and the individual and detailed responses to feedback from the 37 endorsing organisations are included at the link provided (https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline under Technical report and Public consultation comments and developers responses).

In the absence of adequate evidence from the reviewer of data that supports any other cut off we would recommend that the guideline recommendation stands with the caveats included and the recognition that this is a consensus recommendation that now cannot be altered based on opinion alone but that needs considerable further research.

Whilst we acknowledged we cannot add unpublished data in the current manuscript from the abstract below that has been accepted as oral presentation at USA Endo Annual Meeting 2020 (Abstract number
the data supported the recommendation made by the Guideline and we felt it was important to share emerging data from a population study in our response.

Of note, additional data from the abstract below is not in the technical report. We are unsure about the issues regarding access to technical report – the link provided was tested multiple times and it worked. The link takes you to either open or save file depending on the browser. There is also an option to view the report by clicking on Technical report after viewing general website https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline

Abstract number 3328 – USA Endo Annual Meeting San Francisco 2020
NEW ADOLESCENT DIAGNOSTIC CRITERIA FOR POLYCYSTIC OVARY SYNDROME: IMPACT ON PREVALENCE AND LONGITUDINAL BODY MASS INDEX TRAJECTORIES
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The Rotterdam criteria defines polycystic ovary syndrome (PCOS) as the presence of two out of three clinical features: oligo-anovulation (OA), hyperandrogenism (HA) and polycystic ovary morphology (PCO), after the exclusion of other causes. Diagnosis is more challenging in adolescents as normal pubertal changes including PCO can overlap with pathology in PCOS in this age-group. The 2018 International Evidence-based PCOS Guideline endorsed across 38 societies, updated adolescent Rotterdam diagnostic criteria to needing both OA and HA, omitting PCO, until 8 years post menarche. Here, we aimed to i) examine the impact of the updated Rotterdam adolescent diagnostic criteria on PCOS prevalence in a population-based female adolescent cohort and ii) explore the association between updated criteria and diagnostic phenotypes with long-term adverse health outcomes (longitudinal body mass index (BMI) trajectories). Overall, 227 adolescents in the Western Australian Pregnancy Cohort (Raine) Study undertook detailed PCOS assessment at the mean age of 15.2 years (mean age of menarche 12.4 years). Detailed anthropometric measurements were collected from birth until age 22 years. T-test was used for group BMI comparisons and longitudinal BMI was analysed using Generalised Estimating Equations with PCOS by time and PCOS phenotypes by time as interaction terms. Rotterdam criteria identified 66 (29.1%) with PCOS and updated adolescent criteria identified 37 (16.3%), similar to prevalence in adults. On updated adolescent PCOS criteria, those with PCOS had higher mean group BMI than participants without PCOS from 5 years of age onwards. Significant interaction was detected between PCOS and time (Wald test p&lt;0.001) on longitudinal BMI gain, where higher BMI gain was observed in participants with PCOS from age 14 years onwards. Only the updated adolescent criteria or phenotype with OA and HA, was significantly associated with
long-term BMI gain. Other PCOS phenotypes had similar BMI trajectories as participants without PCOS (Wald test p<0.001). Our findings validate updated PCOS guideline recommendation on narrower diagnostic criteria in adolescents which have the potential to improve diagnostic accuracy and limit over-diagnosis in adolescents as well as identifying those at risk of long-term weight gain, where targeted lifestyle prevention is most relevant. We also show that BMI trajectories in those with and without PCOS divert in childhood, supporting PCOS manifestations in the pre-pubertal period. (Supported by NHMRC PCOS CRE and Australian Research Training Program Scholarship).

2. The rebuttal also raises issues around overlap with adult guidelines. "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." Are you saying that women older than 18 years are not adolescents? Therefore, when your guidelines cross age 18 and reach into the adult guidelines, I believe you need to note that these guidelines will conflict with adult guidelines.

RESPONSE:
We disagree with the reviewer the Guideline will not be in conflict with adult guidelines. On the contrary and most importantly the Guideline have clarified PCOS diagnosis around this challenging time which is transition age with specific cut offs definitions according to time post menarche for menstrual irregularity and the use of pelvic ultrasound.
The 12 studies mentioned in adult women have average ages between 24.9 and 31.2 years. These are clearly not adolescents.
Age of adult women in these studies has been added to text (See Page 14, lines 4-6).

3. The sentence in the second paragraph, "Furthermore, the correlation between ovarian morphology (ovarian size and follicle numbers) and menstrual function is inconsistent in adolescence and early adulthood. [55]" does not recognize that the manuscript used older criteria for PCOM and that even then, 40% of the subjects met polycystic ovary syndrome criteria based on irregular menses and hyperandrogenism. Therefore, the sentence is misleading, as is the response to the comment. Please revise. In other words, when stating that, "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):31173122).", the comment does not take into consideration that this is not a study of multifollicular ovaries and is not longitudinal. As above, the manuscript used older criteria for PCOM and even then, 40% of the subjects met polycystic ovary syndrome criteria based on irregular menses and hyperandrogenism. Therefore, it is not supportive of the concept that multifollicular ovaries persist post menarche.

RESPONSE:
The concept that multifollicular ovaries persist post menarche and is not associated with reproductive dysfunction is supported by Codner. This is the only longitudinal study, which was already in the manuscript in the sentence that followed the one mentioned by the reviewer. This was also part of our previous comment (Reference 56: Codner E et al: Polycystic ovarian morphology in postmenarchal adolescents. Fertility and Sterility 2011, 95(2):702-706.e701-702).
The word “longitudinal” was added to this study in the manuscript (See Page 14, line 22).

Whilst we acknowledged that Kristensen study is not a longitudinal study, it is a population study that carefully assessed ovarian follicles/PCOM according to Rotterdam criteria that were in place in 2010 and identified 68% of young women with PCOM without clinical features of PCOS. The quoted 40% of women with PCOS (defined as menstrual irregularity and hyperandrogenism) as per reviewer was
from women who demonstrated PCOM by this definition. It is recognized that PCOM definition is changing based on progress of technology and additional studies are needed, however these data are consistent with the idea that a large proportion of young adult women without other reproductive abnormality demonstrate multifollicular ovaries.

Clarification details of Kristensen study have been added. See Page 14, lines 13-18.

4. Importantly, please consider this rebuttal. "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." These as yet unpublished data sound as if they influenced the 8 year mark extensively. Therefore, it is very difficult for the reader to have any concept of the longitudinal ovarian morphology results without those data available. The technical report is not accessible from the link. If the technical report is critical for understanding, please send it for review.

RESPONSE:
See response to comment 1.

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