Reviewer’s report

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

Version: 1 Date: 28 Oct 2019

Reviewer: Corrine Welt

Reviewer's report:

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.

2. 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. 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? 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. 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? 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? 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.

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.

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.

Are the methods appropriate and well described? 
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls? 
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Are the conclusions drawn adequately supported by the data shown? 
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