Reviewer’s report

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

Version: 0 Date: 19 Sep 2019

Reviewer: Renato Pasquali

Reviewer's report:

This manuscript is an extension paper of a previous Guidelines on the diagnosis and treatment of PCOS in adult women by the same scientific Australian group. The following are my specific comments:

1. The concept of "adolescence" , as reported in these Guidelines is rather large and does not consider the the Tanner stages.

2. The definition of PCOS should consider that different phenotypes exist, which may have different pathophysiological aspects and probably should require different therapeutic strategies

3. Among the exclusion criteria to define PCOS, the authors did not address the potential role of obesity. There is convincing evidence that obesity "per se" may be characterized by a hyperandrogenic state (increased total and free T levels, etc) (McCartney CR, 2007; Burt Solorzano CM 2010, etc). In addition, it has been proposed that a "secondary PCOS to obesity" may exist and that, particularly in adolescents, the main goal is to reduce body weight.

4. I suggest that the impact of obesity in adolescents should be much more emphasized. There are well-done studies supporting that testosterone excess is largely dependent on BMI. These pathophysiological aspects should be considered for either diagnosis and treatment

5. Why not to discuss the treatment of infertility according to the Tanner stage? Undoubtedly, treatment of infertility should/could have some relevance in the late adolescent girls, who may have sexual relations.

6. Δ4Androstenedione (Δ4A) has been proved to highly correlate with testosterone blood levels, therefore I should include it in the hormonal panel of androgens used to define PCOS. In addition, it is well demonstrated that Δ4A levels strongly correlate with metabolic disorders

7. I believe that the Ferriman & Galwey score is rather inadequate to define hirsutism in adolescents, even because normative data in adolescents are unavailable
8. AMH is not included in the panel of hormones in adolescents as well as in adult PCOS women. Moreover, the role of AMH on the HPG axis: this has been demonstrated in both animal models and adult women (Cimino I et al, Nature Comm 2016; Tata B, Nature Med 2018). Moreover, it has been reported that elevated prenatal anti-Müllerian hormone reprograms the fetus and induces PCOS polycystic ovary in adulthood. Accordingly, it has been reported that most women with PCOS exhibit higher levels of circulating luteinizing hormone, suggestive of heightened gonadotropin-releasing hormone (GnRH) release and AMH) as compared to healthy women and that excess AMH in utero may affect the development of the female fetus (Tata B, Nature Med 2018). This implies that AMH is not simply a biomarker of ovarian morphology, rather it is a potential factor in the development of PCOS.

1. Exclusion of other conditions: I understand that in adults many disorders may mimic PCOS and therefore should be excluded to define PCOS itself. On the other hand, it should also be considered that many of them are extremely rare in adolescent. This should be clearly defined.

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Yes

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