

Enhancing the accuracy of polycystic ovary syndrome diagnosis

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, experienced by 1 in 10 women of childbearing age. Its aetiology is multifactorial and complex, and its clinical presentation is heterogeneous with menstrual irregularities, high levels of androgens and the presence of multiple follicles or cysts in the ovaries giving its name to the condition. In addition, PCOS has been linked to reproductive, cardiometabolic, dermatologic and psychological complications making it a significant public health concern.¹ Diagnosing PCOS has always been a challenge with some women remaining undiagnosed hence potentially experiencing delays in their care.² Therefore, optimising PCOS diagnosis accuracy is of crucial importance.

In this issue of the *Annals*, Yong et al. have elegantly attempted to achieve that goal by proposing a simplified set of 3 criteria to define PCOS for an East Asian phenotype.³ In that study, the authors have focused on PCOS diagnosis and provided a detailed summary of the diagnosis evolution, from Stein and Leventhal's first description in 1935 to now. Over time, several groups and societies have attempted to refine PCOS diagnosis according to women's life stage, physical characteristics or ethnic differences. Overall, they all agree that PCOS diagnosis is established if 2 out of the following 3 criteria are met: (1) menstrual irregularities, (2) clinical and/or biochemical signs of hyperandrogenism, and (3) polycystic ovaries, provided that other mimicking disorders have been excluded. However, the complexity of the diagnosis lies in the lack of standardisation in the definition of these 3 main features.

Yong et al. explain the individual criteria and their limitations with an explanation of their proposed simplified option. They commence with menstrual irregularities as it is the main consultation reason for PCOS. For this first criterion, they decided to limit menstrual irregularities to oligomenorrhea or amenorrhea, defined as cycles longer than 35 days. While this is one of the manifestations of oligo or anovulation, it has its limitations because this definition only covers 85–90% of menstrual disorders experienced by PCOS women.⁴ In this

context, 10–15% of adult PCOS patients with normal or shorter menstrual cycles will be missed. Conversely, some adolescents within the first 3 years after menarche, with longer menstrual cycles due to an immature hypothalamus pituitary ovarian axis, might be unnecessarily screened and/or wrongly diagnosed. This is the reason why the 2018 international evidence-based guidelines for assessment and management of PCOS have included in their definition of oligo or anovulation an exhaustive list of menstrual irregularity types that should be considered and assessed for PCOS.⁵ So, while narrowing the first criterion to women with longer cycles could help identify a majority of PCOS patients, a more detailed list of eligible menstrual cycle types should be considered in order to screen all possible PCOS patients.

With regard to the other 2 criteria, Yong et al. adopted a compelling model: they performed a prospective cross-sectional study with 200 healthy East Asian adult women to identify predictive factors of menstrual cycle variability.⁶ The 5 factors strongly associated with menstrual cycle variability were: ovarian volume, AFC (antral follicle count), AMH (anti-Müllerian hormone), serum testosterone and LH (luteinising hormone). Interestingly, these parameters coincide with the factors playing a role in PCOS physiopathology. Among these 5 components, 2 parameters are required: one that would be reflective of androgen excess and the second as a marker of polycystic ovaries. With that in mind, Yong et al. analysed these factors further to select the 2 that would effectively complement oligomenorrhea for PCOS diagnosis.

To define androgen excess, most PCOS guidelines use clinical and/or biochemical measures. Clinically, the modified Ferriman and Gallwey (mFG) score is the tool used to quantify the degree of hirsutism. However, its usefulness is debatable because it is operator-dependant and requires an ethnicity-based interpretation. This is particularly valid in East Asian populations. Chinese patients, for example, tend to have a naturally undetectable mFG score, making mFG score a futile non-discriminant parameter for them. For this reason, Yong et al. chose to exclude the use of the mFG

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score for their patients. On the other hand, serum testosterone is fairly stable across the menstrual cycle and was flagged as a predictive factor of cycles variability. Hence, the authors decided to solely rely on serum testosterone as a marker of hyperandrogenism. While this is practical and legitimate, the type of marker they have selected is arguable. In fact, serum-free testosterone or free androgen index measures would be more coherent as they are reflective of the bio-active form of serum testosterone. Indeed, around 70% of circulating testosterone is bound to serum sex hormone binding globulin (SHBG) and when testosterone is bound, it is inactive. The serum total testosterone is a combination of free testosterone and testosterone bound to SHBG. Obesity and/or insulin resistance, often associated to PCOS, can cause the serum SHBG level to drop and therefore increase the level of bio-available testosterone, which will not be reflected by the serum total testosterone alone.⁷ The total serum testosterone might then underestimate the biochemical hyperandrogenism.

Finally, the last criterion is about polycystic ovaries or polycystic ovary morphology (PCOM), which is a sign of increased number of follicles in the ovary. The assessment of the follicles number can be done directly, via a transvaginal pelvic ultrasound (AFC) or indirectly via a biochemical marker (serum AMH). AMH is secreted by the granulosa cells of the preantral and small antral ovarian follicles and is strongly correlated with AFC; AMH and AFC can therefore be used interchangeably.⁸ Serum AMH is significantly higher in women with PCOS and as mentioned earlier, AFC and AMH were identified by Yong et al. as factors significantly correlated with menstrual variability. Because pelvic ultrasound often poses challenges, Yong et al. recommend to replace AFC with AMH as a marker of polycystic ovaries. The threshold suggested for AMH is 37pmol/L, based on a prospective cross-sectional study performed in Singapore.⁶ This new criterion will be useful and cost-effective for patient assessed for PCOS even though further studies will be required to ensure that population and assay specific cut-offs are used. Furthermore, it is meaningful to mention that in July 2023 the international evidence-based guidelines for assessment and management of PCOS have released their 2023, recommendations where AMH has also been added as an acceptable marker of PCOM as an alternative to AFC.⁹

To summarise, Yong et al. present the use of the following 3 criteria for the diagnosis of PCOS in an East Asian population: (1) menstrual cycles longer than 35 days, (2) raised serum total testosterone, and (3) AMH ≥ 37 pmol/L. These criteria are mainly applicable for adult patients. Studies with a larger sample size would be required to confirm the AMH cut-off, and serum-free testosterone should be considered instead of total testosterone. However, despite these 3 limitations, the authors provide clinicians with a simplified and cost-effective set of PCOS diagnostic criteria for identifying a large proportion of East Asian adult PCOS women.

Declaration

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REFERENCES

1. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Med* 2010;8:41.
2. Gibson-Helm M, Teede H, Dunaif A, et al. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2017;102:604-12.
3. Yong EL, Teoh WS, Huang ZW. Polycystic ovary syndrome v.2023: Simplified diagnostic criteria for an East Asian phenotype. *Ann Acad Med Singap* 2023;52:669-678.
4. Hart R, Hickey M, Franks, S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. *Best Pract Res Clin Obstet Gynaecol* 2004;18:671-83.
5. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril* 2018;110:364-379.
6. Zhu R, Lee BH, Huang Z, et al. Antimüllerian hormone, antral follicle count and ovarian volume predict menstrual cycle length in healthy women. *Clin Endocrinol (Oxf)* 2016;84:870-7.
7. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. *Obes Rev* 2013;14:95-109.
8. Pigny P, Jonard S, Robert Y, et al. Serum anti-Müllerian hormone as a surrogate for antral follicle count for definition of the polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006;91:941-5.
9. Teede HJ, Tay CT, Laven JJE, et al. Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *J Clin Endocrinol Metab* 2023;108:2447-69.