Does the ratio of anterior anogenital distance to posterior anogenital distance fit the novel biomarker for women with polycystic ovary syndrome?

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Polycystic ovary syndrome (PCOS), common endocrine disorders in women, presenting with various kinds of symptoms, signs or both, resulting in a range of phenotypes (a multifaceted condition with characteristics of oligomenorrhea/amenorrhea, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology) and contributing to the diagnosis based on criteria (the 2018 international evidence-based guidelines, including the National Institutes of Health criteria; Rotterdam criteria; and Androgen Excess and PCOS criteria).\textsuperscript{1-4} In the diagnosis of PCOS, at least three tools are needed as follows: (1) one is history taking and physical examination; (2) the other is laboratory examination; and (3) the final is ultrasound examination. The detection of multiple small cysts on the peripheral side of enlarged ovaries needs ultrasound, which is a well-documented technology widely used in the many fields.\textsuperscript{5,7} The diagnosis of biochemical hyperandrogenism or other hormones needs blood test.\textsuperscript{8,9} In fact, history taking and physical examination (clinical hyperandrogenism) might be one of most cost-effective tools for diagnosis of women with PCOS. We are happy to introduce the study by Simsir et al\textsuperscript{10}, published in the October issue of the \textit{Journal of the Chinese Medical Association}, on the investigation of the relationship between the anterior/posterior ratio of anogenital distance (AGD\textsubscript{ant}/AGD\textsubscript{post}) and women with diagnosis of PCOS.

The authors performed a prospective cohort study to compare the difference of demographic, clinical, laboratory, and ultrasound findings between women with and without PCOS, and found that women with PCOS had significant differences of evaluated items compared to women without PCOS, such as body weight, body mass index, waist circumference, hip circumference, ratio of AGD\textsubscript{ant} (the distance between anterior clitoral surface and the upper verge of the anus) and AGD\textsubscript{post} (the distance from the posterior fourchette to the upper verge of the anus), serum level of luteinizing hormone, sex hormone-binding globulin, hyperandrogenism phenotype, oligomenorrhea, acne vagaries, and alopecia.\textsuperscript{10} The further evaluation showed that ratio of AGD\textsubscript{ant} and AGD\textsubscript{post} was statistically significantly positively correlated with waist circumference, but negatively correlated with free androgen index.\textsuperscript{10} Therefore, the authors concluded that both AGD\textsubscript{ant} and AGD\textsubscript{post} were longer in women with PCOS than those in women without.\textsuperscript{10} Of most importance, the authors found that the ratio of AGD\textsubscript{ant} and AGD\textsubscript{post} was statistically significant smaller in women with PCOS than that in women without, suggesting that this ratio can be used as a novel biomarker for PCOS.\textsuperscript{7} This study is interesting and worthy of discussion.

We totally agree with uncertain etiopathogenesis of PCOS, as shown by authors.\textsuperscript{10} We also agree with strong positive correlation between androgen levels and the observation of PCOS traits.\textsuperscript{10} Androgen excess is a key trait and the most frequent common feature, as hyperandrogenism as a diagnostic criteria in three out of the four PCOS phenotypes (A-D) endorsed by the 2018 international evidence-based guidelines.\textsuperscript{1} In the animal study, prenatal exposure to testosterone or early postnatal exposure to dihydrotestosterone have been reported to generate the closest overall PCOS-like phenotype in rodents, sheep, and non-human primates.\textsuperscript{11} However, differences in the timing of exposure of androgen excess may lead to variations in the expression of phenotypes of PCOS.\textsuperscript{1} Although the timing of exposure of importance, one hypothesis favors a fetal origin might be the main pathogenesis of PCOS.\textsuperscript{1} As shown by authors, males (or boys) have 50%-100% longer AGD than females (girls) do.\textsuperscript{10} Therefore, it is rational to suppose that women with PCOS may have longer AGD than women without PCOS since it is believed that excessive androgen exposure might prolong the length of AGD. In fact, prenatal ultrasound tried to detect the fetal sex in the early pregnancy. One study using 3D virtual reality ultrasound still concluded that accurate determination of the
fetal sex in the first trimester of pregnancy is still not possible, even using an advanced 3D ultrasound technique. In the study by Simsir et al., women with PCOS seemed to have a longer AGD_{ant} and AGD_{post} than women without (10.1 ± 1.2 cm vs 9.8 ± 1.7 cm for AGD_{ant} and 2.3 ± 0.6 cm vs 2.1 ± 0.5 cm for AGD_{post}, respectively); however, this difference is still failed to reach the statistical significance, although the authors claimed that the use of ratio seemed to be valuable in the relation to the diagnosis of PCOS, based on a statistically significant smaller ratio of AGD_{ant} and AGD_{post} in women with PCOS compared to women without (4.4 ± 1.0 vs 4.9 ± 1.0; p = 0.003). Contributing to the enthusiasm of the authors conclusion to highlight the value of this finding. The conclusion might be overestimated. In fact, the difference of distance the authors measured is indeed very smaller (10.1 vs 9.8 and 2.3 vs 2.1), and of most importance, we have a good reason to say that the intra-observer’s and inter-observer’s reproducibility might be lower. Why is it? The authors’ measurable area is not smooth and covered by many skin appendages and fatty tissues, such as hair or others, which are the factors contributing to the inaccurate measurement. In addition, vulvar size and morphology might be significantly varied in every subject. It is absent of agreement of morphology or size of the vulva is related to any single factor. Although the authors have introduced the distance they measured, they did not mention whether the vulva part, such as labial major or labial minor is included or not. It is difficult to guess how to measure it. Therefore, if reproducibility of measurement is supposed to be low, the results might not be believable.

Second, the authors claimed that it is a prospective study. We are wondering why this study needed the prospective design? If this measurement of AGD can be performed before adolescence, and these subjects can be followed up when the diagnosis of PCOS is made, the value of this biomarker may be high. Basically, clinical/biochemical hyperandrogenism parameters do not include the waist circumference or body weight, or body mass index. Androgen is believed to be associated with many physiological changes, including body image, muscular distribution, and fatty tissue distribution. All of them are candidate to be reflective as the phenotype of androgen exposure.

Third, what is the role of this biomarker, which is for the purpose of diagnosis or prediction or prognosis? The biomarker should be informative, predictable, and cost-effectiveness. Does this ratio of AGD_{ant} and AGD_{post} predict any worse or better outcome of the patients with PCOS? For diagnosis, criteria have been established. Therefore, it should be considered as the prognostic factor.

Fourth, the authors found that ratio of AGD_{ant} and AGD_{post} was statistically positively correlated with waist circumference, suggesting that this biomarker might lose its prediction rate or correlation if the women are overweight since the authors found that women with PCOS have a lower ratio of AGD_{ant} and AGD_{post} than women without do. Women with higher waist circumference have a higher ratio of AGD_{ant} and AGD_{post} which might tend to reach the ratio of AGD_{ant} and AGD_{post} in women without PCOS. However, it is well known that PCOS women tend to have overweight. This conflicted presentation needs our attention.

Finally, the current study emphasizes again the importance of the detection of phenotypes of diseases, including physical examination. When we initially approach one subject with a suspicion of specific diseases, besides a series of expensive examination, history taking, or physical examination, such as characteristics of the body, they can provide us much more information before attempting the next-step evaluation. Based on this consideration, there is no doubt of value of the current study by Simsir et al., published in the October issue of the Journal of the Chinese Medical Association.

REFERENCES


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