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Polycystic Ovary Syndrome: An Apparently Simple yet Challenging Diagnosis

Fahimeh Ramezani Tehrani [1,*]

[1]Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Fahimeh Ramezani Tehrani, Reproductive Endocrinology Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122432500, E-mail: ramezani@endocrine.ac.ir

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Polycystic Ovary Syndrome (PCOS), also known as Stein-Leventhal syndrome, had first been described in 1935 as amenorrhea associated with bilateral polycystic ovaries (PCO). Since that moment, its definition has been changed several times. In 1990, according to the National Institutes of Health criteria, PCOS was diagnosed when both ovulatory dysfunction and clinical hyperandrogenism and/or hyperandrogenemia were present, after excluding other endocrinologic disorders, such as non-classic adrenal hyperplasia, androgen secreting tumors, hyperprolactinemia and thyroid disorder. However, these criteria were revised at the Rotterdam ESHRE/ASRM Consensus Conference, in 2003. According to the new definition, any woman with two of the following three manifestations was diagnosed as PCOS, after exclusion of any of the above mentioned disorders: 1) oligoovulation, 2) clinical biochemical signs of hyperandrogenism, 3) PCO. The new criteria extend PCOS definition, by adding two more phenotypes, oligoovulation + PCO and hyperandrogenism + PCO. These phenotypes were challenging, as several studies demonstrated that the reproductive and metabolic consequences of these new phenotypes, oligoovulation + PCO in particular, were closer to healthy subjects than the original PCOS (1, 2). This debate resulted in new diagnostic criteria being specified by the Androgen Excess Society (3) and PCOS was defined as hyperandrogenism + ovarian dysfunction and exclusion of other related disorders. Hence, considering the changes in criteria for PCOS definition, the estimated prevalence changed two to three times (4, 5).

However, it seems that the narrative of the of development of criteria for diagnosis of PCOS is not over yet, as, according to the position statement of the European Society of Endocrinology (6), PCOS criteria must to be revised and even the name needs to be changed, as it is misleading and does not accurately describe the actual picture of this syndrome. This is not limited to just the definition; there is no clear and contemporaneous recognition of each criterion. Hirsutism, as the main clinical manifestation of hyperandrogenism, is measured by the Ferriman-Gallwey score (7), although there is no consensus on its cut-off value and inclusion of body area variation base on race and ethnicity.

East Asians are typically less hairy than Euro-Americans, which may be explained by low levels of 5α-reductase activity, in their skin. It seems that we need to develop race-specific normative ranges, before categorizing just any women having an excessive amount of body hair. There are more challenges, regarding acne and hair loss, since there is no universal scoring system for the assessment of acne, its prevalence varying with ethnicity and age: 20% in mid-teens, 15% in early 20s, 10% in 30s and 5% in the 40s age group (8). As a result, it is unclear whether the prevalence of acne in PCOS women is greater than that observed in the general population. Hair loss has been influenced by several environmental, nutritional and genetic factors; its correlation with biochemical hyperandrogenemia is also poor, and considering that alopecia, as a sore clinical manifestation of hyperandrogenism, in the absence of hirsutism is controversial (9).

There is even more debate for more precise identification of hyperandrogenemia. It appears that assessments of free testosterone levels are much more sensitive than the measurement of total testosterone; however, its measurement by direct radioimmunoassay (RIA) is highly inaccurate and equilibrium dialysis not widely available, technically complex and costly (10). The other main challenging issue is the method used for establishment of normal ranges for androgens (11). While there are studies that suggest identifying the cut-off value according to measuring androgens in a large population of normal women, others recommended this is general population. The main concern is that, if we assess general population, the percentile cut-off value should be used, when the prevalence of PCOS is greater than the fraction allowed to be abnormal under cut-off values, using the 95th percentile.

The objective definition of oligoanovulation is also challenging; while a predictable menstrual cycle, with a 21 - 40 days interval, has been considered normal, several researchers consider vaginal bleeding episodes ≤ 25 days and ≥ 35 days as oligomenorrhea and polymenorrhea, respectively (9). The prevalence of menstrual dysfunction varies by age, which is a common feature among adolescents, in which, even by the third year after menarche, 59% of cycles remain anovulatory. Furthermore, regular menstrual cycles may not exclude oligoanovulation, and about 6% of eumenorrheic women had subclinical oligoanovulation identified by measuring a mid-luteal progesterone level (12).

The PCO has been introduced as one of three manifestations of PCOS, by the Rotterdam definition; this has been defined as the presence of ≥ 12 follicles per ovary (FNPO) measuring 2 to 9 mm, and increased ovarian volume > 10 mL (13). However, PCO is observed in 20 - 30% of the general population, and also, 23% of eumenorrheic and non-hirsute women have PCO, therefore including PCO, as a criterion for developing the PCOS definition, is questionable (14).

Excluding other androgen excess related disorders is also problematic. It is not clear why all PCOS suspicious women should be screened for thyroid disturbances, while the prevalence of thyroid dysfunction among androgen excess women is similar to that of the general population (15). The paradox is also observed for hyperprolactinemia as well; PCOS is associated with an increase of prolactin, and hyperprolactinemia is associated with excess production of adrenal androgens.

Besides several dilemmas in the precise measurement of prolactin, due to several issues (e.g. assay problems, several confounders, macroprolactinemia), it is not clearly defined whether its prevalence among PCOS women is significantly higher than in normal women; if not, then the necessity for universal screening of hyperprolactinemia of all suspicious PCOS women is questionable. Excluding other androgen excess disorders is also challenging. The majority of data are not in agreement with routine screening, when there are not enough clinical indications, this approach may not guarantee the detection all androgen secreting tumors, because precise thresholds of androgen, that identify those suspicious women for further assessments, have not been introduced, and more than half of women with androgen secreting tumors did not have high androgen levels at the time of diagnosis (9).

In conclusion, while the term PCOS has been introduced over two decades before, there are many uncertainties regarding its diagnosis criteria and objective measurement, which need to be addressed by further expert committees.

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