EC GYNAECOLOGY
Editorial

Polycystic Ovary Syndrome (PCOS): The Pros and Cons of Various Diagnostic Criteria

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Classical polycystic ovarian syndrome (PCOS) is characterized by hyperandrogenism (clinical and/or biochemical), chronic ovulatory dysfunction (oligo-ovulation and/or anovulation) and polycystic ovarian morphology (polycystic and/or enlarged ovary). PCOS is the most common reproductive endocrine disorder in women of reproductive age with a prevalence between 5-15% depending on diagnostic criteria used [1,2].

The first scientific description of PCOS was published in 1935 [3] with publication title as "amenorrhea associated with bilateral polycystic ovaries". Authors presented 7 cases of infertile women with bilateral enlarged polycystic ovary (all cases) and amenorrhoea (5 cases) or oligomenorrhoea (2 cases) with normal level of urinary 17-KS (to exclude congenital adrenal hyperplasia, androgen producing tumor or severe hyperandrogenemia of any etiology) and FSH (to exclude premature ovarian failure/menopause). Some of the women also had hirsutism (about 50%) and smaller than normal breast size (about 50%) and/or uterine size (about 75%) meaning clinical hyperandrogenism in about 75% case (at maximum) and without hyperandrogenism in about 25% cases (at minimum). However, authors did not give much importance of clinical hyperandrogenism in their paper including title or even in discussion leading to criticisms subsequently [4]. Author also described restoration of menstruation in all cases and fertility in 2 cases after wedge resection of ovaries [3] and on follow up fertility was restored in 5 cases [5]. However, the first description as case report of the disorder was probably given by Vallisneri in 1721 [6]. Vallisneri described an obese woman with infertility and large white shiny ovary as like pigeon egg. Another report on the disorder can be traced to Chereau in 1844 [7]. Chereau described fibrous and sclerotic ovary with hydropic follicle (sclerocystic ovary). Thereafter, hyper-thecosis of ovary was reported with the disorder [8]. All these older descriptions are indicating ovarian pathology (either enlarged and/or polycystic) associated with the condition. Later, the disease was linked with high LH and testosterone as key parameters for diagnosis [9,10] for short period of time and later abandoned.

Since PCOS scientific description by Stein and Leventhal in 1935 i.e., more than 85 years ago, there is no consensus on almost all the aspects of PCOS like name, etiology, clinical features or even treatment. Hence the disease named differently by different authors like Stein-Leventhal syndrome, Stein syndrome, sclerocystic/fibrocystic or microcystic/polycystic ovaries, cystic degeneration of ovary, polycystic ovarian disease (PCOD) [11,12], polycystic ovarian syndrome [13,14] and finally polycystic ovary syndrome (PCOS).

Similarly, the diagnostic criteria are still subject of debate. Diagnostic criteria as consensus declaration on PCOS was first proposed at a National Institutes of Health (NIH) sponsored conference in 1990. At present various specialized groups have recommended diagnostic criteria for PCOS somehow differently. These are National Institute of Health (NIH) criteria 1990 (modified in 2012), Rotterdam criteria 2003 (modified in 2012) and AE PCOS (androgen excess polycystic ovary syndrome) society criteria 2006 (modified in 2016). The NIH 1990 criteria [2] are chronic anovulation and hyperandrogenism (clinical/biochemical). Both criteria are required for diagnosis but need to exclude congenital adrenal hyperplasia/ androgen producing tumor. This proposed criteria for PCOS diagnosis however completely ignored ovarian pathology (polycystic/enlarged ovary) which was one of the major criteria of original description as well as disease/

syndrome name. The NIH 1990 criteria seems misnomer as disease name (PCOS) and criteria do not match. The NIH 1990 criteria also excludes PCOS cases without hyperandrogenism which are very common in southeast Asian countries [15,16]. In our experience NIH 1990 criteria picks up most secondary causes of PCOS and required extensive testing including genomic screening (in particular for atypical congenital adrenal hyperplasia) for exclusion. The Rotterdam 2003 criteria are oligo/anovulation, hyperandrogenism (clinical and/or biochemical) and polycystic ovary [17]. Any two out of three criteria are required for diagnosis. Although this consensus group included polycystic ovary as one of the criteria but diluted its importance as not being essential criteria. The AE PCOS 2006 criteria are hyperandrogenism (clinical/biochemical) and ovarian dysfunction (oligo/ amenorrhoea) and/or polycystic ovarian morphology (PCOM). Both the criteria are required for PCOS diagnosis [18]. The AE PCOS 2006 criteria was revised in 2015 by adding Anti Mullerian Hormone in place of ultrasound findings [19]. The AE PCOS criteria is also problematic as this will exclude all cases with normal androgen which are commonest phenotype in India (excluding north India) and Indonesia [15,16]. At present commonly followed PCOS diagnostic criteria is the NIH criteria 2012 i.e., Rotterdam criteria (2003) with modifications in the form of phenotypic classifications [20,21]. This approach classifies PCOS cases into four phenotypes. These are phenotype A (hyperandrogenism, ovulatory dysfunction and polycystic and/or enlarged ovary), phenotype B (hyperandrogenism and ovulatory dysfunction), phenotype C (hyperandrogenism and polycystic and/or enlarged ovary) and phenotype D (ovulatory dysfunction and polycystic and/or enlarged ovary).

Many efforts were made in past and still evolving for the precise diagnosis however unfortunately even today there is no consensus in diagnostic criteria. But question remains why we have ignored the original definition of Stein and Leventhal. Was that necessary? Stein and Leventhal described infertile women with bilateral enlarged ovary and amenorrhoea/oligomenorrhoea with hirsutism (50%) and/or other features of hyperandrogenism (small breast or uterus; 50 - 75%) i.e. phenotype A (with hyperandrogenism in majority of their cases) and phenotype D (without hyperandrogenism in minority of cases) of NIH 2012 phenotypic criteria. Phenotype B and C were not included in Stein and Leventhal's description. Our experience also indicates phenotype B should not be included in the definition of PCOS unless supported by AMH value or until excluded all possible secondary causes, which is very difficult without molecular analysis for example atypical CAH. We are working on PCOS since long and found secondary causes (CAH, DSD, POF, etc.) most often with phenotype B. We have also observed high anti Mullerian hormone best correlated with phenotype A and phenotype D. However, we have also observed statistically significant contrasting differences between phenotype A (high value) and phenotype B (low/normal value) with androgens, DHEAS, LH, bisphenol A, DNA methylation, higher age group and higher body mass index indicating epigenetic influence but opposite differences with fasting insulin (higher in phenotype D). We think ovarian pathology (polycystic and/or enlarged ovary) should be the essential criteria for PCOS diagnosis. We also think etiologically two distinct phenotypes are phenotype A (probably epigenetic in nature due to association with high BMI, high BPA, high androgen, hypermethylation, higher age group, etc.) and phenotype D (probably genetic nature due to younger age group with high fasting insulin).

In conclusion despite multiple efforts from the NIH, the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine to find acceptable diagnostic criteria of PCOS, we are still away from consensus. We like to emphasize importance of polycystic ovarian morphology (polycystic ovary and/or enlarged ovary) in the clinical diagnosis of PCOS and should be the essential criteria with ovarian dysfunction (amenorrhoea/oligomenorrhoea) and/or hyperandrogenism. Phenotype B (hyperandrogenism and oligo/amenorrhoea) should be investigated extensively for secondary causes of PCOS and excluded from assigning as PCOS.

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