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PCOS: Backgrounds, evidence and problems in diagnosing the syndrome

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Abstract. PCOS constitutes a heterogeneous clinical picture harbouring different subsets of patients. Recently an attempt was made to define the diagnosis of PCOS based on existing clinical evidence. Oligo- or anovulation, clinical or biochemical hyperandrogenism and polycystic ovaries constitute the key clinical features on which the diagnosis should be based. No single diagnostic criterion is sufficient for clinical diagnosis. Based on this new consensus the spectrum of women with PCOS has been considerably broadened. The purpose of this paper is to review the evidence for this new classification and to address problems in diagnosing PCOS using these new criteria.

Keywords: PCOS; PCO; Anovulation; Oligomenorrhea; Amenorrhea; Hyperandrogenism; LH; Insulin resistance and obesity

1. Introduction

Up till the year 2003 the consensus in diagnosis of PCOS was mainly based on a majority opinion rather than on clinical trial evidence. The following diagnostic criteria were recommended during several consensus sessions in the last decades of the previous century: Clinical or biochemical evidence of hyperandrogenism, chronic anovulation and exclusion of other known disorders. However, during the last 10 years there has been an

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Table 1
Revised diagnostic criteria of PCOS

1999 criteria (both 1 and 2)
1. Chronic anovulation
2. Clinical and/or biochemical signs of hyperandrogenism, and exclusion of other aetiologies
Revised 2003 criteria (2 out of 3)
1. Oligo- and/or anovulation
2. Clinical or biochemical signs of hyperandrogenism
3. Polycystic ovaries
Exclusion of other aetiologies (congenital adrenal hyperplasias, androgen-secreting tumors, Cushing's syndrome)

increasing awareness that the clinical expression of PCOS may be broader than defined by previous consensus workshops [1].

The cardinal features of PCOS constitute hyperandrogenism and polycystic ovaries (PCO). Its clinical manifestations may include menstrual irregularities, signs of androgen excess and obesity. The syndrome seems to be associated with an increased risk for DM type II. Since it has recognized that women with regular cycles and hyperandrogenism in combination with PCO as well as women suffering from PCO and ovarian dysfunction only might be part of the PCOS spectrum as well diagnostic criteria needed revision [1].

Based on the latest so called Rotterdam ESHRE/ASRM-sponsored PCOS consensus meeting in 2003 PCOS is defined as a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and PCO provided that other causes of hyperandrogenism (NCAH, Cushing's disease, Adrenal tumors, HAIRAN syndrome, exogenous androgen excess) are excluded (Table 1). The purpose of this paper is to review the evidence for this new classification and to address problems in diagnosing PCOS using these new criteria [1].

2. Classification criteria and their evidence

Initial analysis and work-up of patients suspected to suffer from PCOS should include serum determinations of 17-Hydroxy Progesterone, Estradiol and Follicle-stimulating hormone (FSH) as well as Luteinizing hormone (LH), TSH and Prolactin levels [1].

2.1. Oligo- or anovulation

Oligo-and anovulation are almost always associated with menstrual irregularities. The intercycle interval is therefore a sensitive marker for these clinical entities. Oligo ovulation is defined as less than 8 ovulations in a year. Therefore the intercycle interval should exceed 35 days. In case anovulation is present no menstrual bleeding occurs and hence the intercycle interval always exceeds 6 months or 183 days.

Well-designed longitudinal follow-up studies concerning ovulatory cycles are lacking. It seems that amenorrheic women constitute a different subset of women since their response on ovulation induction as well as pregnancy rates are different compared to oligomenorrheic women [2]. Last but not the least it seems that ovarian ageing has an impact on the length of intercycle interval since in some women a normal cycle length is established with increasing age [3].

2.2. Hyperandrogenism

The clinical indicator for hyperandrogenism is hirsutism. Acne seems a sensitive marker for hyperandrogenism but study results are conflicting. Similarly, the presence of alopecia androgenica appears to be a poor marker for hyperandrogenism [1].

Biochemical hyperandrogenism is defined as hyperandrogenaemia. It has to be noted that a considerable number of patients may not demonstrate elevated androgen levels [2]. Notwithstanding these limitations the assessment of the free Testosterone (T) or free T (free Androgen index (FAI)) are the more sensitive methods of determining hyperandrogenaemia. Measurement of other androgens like dehydroepiandrosterone (DHEA) and its sulphated form DHEAS as well as Androstenedione (AD) seem to be of limited value. Sex-hormone binding globulin (SHBG) determinations however are mandatory in order to calculate the FAI [4–6].

Establishing clinical hyperandrogenism might be hampered by fact that normative population data are still lacking. Moreover, the assessment of hirsutism is rather subjective, since most clinicians do not use standardized scoring methods. Finally, hirsutism has been treated often before it is evaluated clinically and there are notable ethnic differences that might complicate the diagnosis. Biochemical assessment of hyperandrogenaemia might be hampered by the fact that normative data, especially in adolescent women, are lacking. Since there is a wide variability within and between different populations normative data should be established using proper control populations. Moreover, there are multiple androgens that are not considered but might be important in some subsets of patients. The phenotype of hyperandrogenaemia is considerably influenced by age and weight (Body Mass Index) and therefore these parameters should be considered too. Finally, androgens are suppressed very rapidly due to exogenous hormone administration and may remain suppressed even after therapy has been discontinued [1].

2.3. Polycystic ovaries (PCO)

PCO is nowadays defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or an increased ovarian volume (>10 mL). Follicle distribution seems not of any value as is stromal echogenicity and the subjective appearance of PCO. The measurement of ovarian volume constitutes a good substitute for stromal echogenicity. Only one ovary fitting this definition is sufficient to define PCO. Ultrasound should be performed preferably through the transvaginal approach using state of the art equipment. Regularly menstruating women and those having had a progestagen withdrawal bleeding should be scanned on days 3–5 in the early follicular phase. All other women should be scanned at random. Ovarian volume should be determined using the simplified formula for a prolate ellipsoid ($0.5 \times \text{length} \times \text{width} \times \text{thickness}$). Follicle number should be estimated in both longitudinal and antero-posterior cross sections. The size of follicles less than 10 mm should be expressed as the mean of diameters measured on the two sections [7].

Women having only PCO without hyperandrogenism or menstrual cycle irregularities are not considered to have PCOS. Similarly, women taking oral contraceptive pills might modify the phenotype of PCO. Finally, women with only PCO might behave similar as

PCOS women during ovulation induction or ovarian hyperstimulation however, they are not considered as having PCOS [1].

2.4. Luteinizing hormone (LH)

Elevated LH levels are frequently encountered in PCOS despite normal serum FSH concentrations. Serum levels of LH above the 95th percentile of a normal population can be found in up to 60% of women with PCOS whereas the FSH/LH ratio might be elevated in up to 95% of subjects. It should be emphasized that the interpretation of a single LH estimate is not without difficulties because of the pulsatile nature of LH-release, differences in specificity between assays, as well as timing of blood sampling. It has been suggested that LH levels may be lower following spontaneous or progestin induced bleeding due to negative feedback action of steroids at the pituitary level. However, our own large cross-sectional set of data in WHO-II infertile patients suggest that LH serum concentrations are independent from timing in relation to bleeding in oligomenorrheic patients [1,2].

It has been suggested that hyperinsulinaemia, through direct stimulation of the gonadotroph cell, might be causally related to hypersecretion of LH. However, since it has been demonstrated that obese hyperinsulinaemic women are more hyperandrogenemic and exhibit lower LH levels, it seems that androgen secretion is not primarily driven by LH. Recent studies provide further evidence that abnormalities in the production of intra-ovarian regulators of LH secretion rather than a primary hypothalamic defect are the cause of LH hypersecretion. Although it has been previously reported that elevated serum LH concentrations were associated with increased miscarriage rates, oocyte and embryo quality or in vitro fertilization implantation and pregnancy rates data are still conflicting. It has been shown that initial LH concentrations neither predicted ovarian response to clomiphene citrate induction of ovulation nor chances to conceive. Consistent with this is the observation that treatment of PCOS subjects with a combination of a GnRH antagonist and pulsatile GnRH re-establishes a normal LH secretion pattern but does not induce ovulation. The failure to induce ovulation suggests the existence of an inherent ovarian defect in PCOS women. Finally, recent observations from large repeated miscarriage clinics show convincingly that initial LH levels are normal in these women [2].

In summary, it seems reasonable to propose that elevated LH levels should be regarded as an epiphenomenon associated with, rather than causally related to, PCOS. Hence, PCOS patients with elevated LH levels do not constitute a different subset of patients and therefore an elevated LH serum level is no longer a necessity for the diagnosis of PCOS [1,2,5].

2.5. Insulin resistance

Insulin resistance is associated with reproductive abnormalities in women with PCOS. Insulin resistance in women with PCOS is seen in up to 50% of patients in both obese and non-obese women. Reports addressing the prevalence vary depending on the sensitivity of tests used to establish insulin resistance. Improving insulin sensitivity through both lifestyle and pharmacological intervention can ameliorate these abnormalities [1,8].

Insulin resistance is generally measured by fasting glucose insulin ratio's, which correlate well with dynamic tests of insulin action. However, there are multiple flaws, which limit their widespread clinical use including differences in beta cell function, normal physiological fluctuations and a lack of standardized insulin assay. Oral glucose tolerance testing (OGTT) might constitute a better means for assessing glucose intolerance but these tests are time consuming and hence expensive [1,9].

Notwithstanding the above mentioned drawbacks it was recommended by the latest consensus workshop to screen obese PCOS women which are highly at risk for glucose intolerance and subsequent type 2 diabetes mellitus. Screening of the total population or subsets of women, which are at risk for insulin resistance, was not recommended because of the lack of uniformity in determining insulin serum levels and concerns regarding the predictive value of such test in predicting clinical events [1,9]. Instead criteria have been developed to define the metabolic syndrome, which includes insulin resistance, centripetal obesity, hypertension, fasting hyperglycemia and dislypidaemia [10]. Further studies are needed to elucidate the intricate relationship between insulin resistance, the metabolic syndrome and PCOS both as far as treatment outcome and health hazards are concerned [1].

3. Conclusions

Criteria used to diagnose PCOS obviously affect the remaining group of patients suffering from anovulatory infertility. When rigid criteria are used, the great majority of these patients will be classified as non-PCOS. From a clinical point of view, it does not seem to matter whether a patient is classified as PCOS or non-PCOS, since all normogonadotrophic anovulatory infertile patients start clomiphene citrate as the first line treatment option for ovulation induction. Literature regarding initial screening characteristics of patients in whom this treatment may be effective is scant. This becomes increasingly important given the trend to delaying childbearing, since precious time might be lost with ineffective treatment in these patients. This, in turn, decreases chances of subsequent therapeutic options. Obviously, the primary wish of an infertile couple is the birth of a healthy child. It would therefore appear logical to design the diagnostic approach of anovulatory infertile women with this endpoint in mind. The current consensus on PCOS is partially developed along these lines and has broadened the diagnosis considerably. Future studies should whenever possible adhere to the current PCOS criteria since this will provide comparable studies suitable for meta analysis instead of the currently available mostly underpowered and incomparable studies.

References

[1] Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, Hum. Reprod. 19 (1) (2004 Jan.) 41–47.

[2] J.S. Laven, et al., New approach to polycystic ovary syndrome and other forms of anovulatory infertility, Obstet. Gynecol. Surv. 57 (11) (2002 Nov.) 755–767.

[3] H. Bili, et al., Age-related differences in features associated with polycystic ovary syndrome in normogonadotrophic oligo-amenorrhoeic infertile women of reproductive years, Eur. J. Endocrinol. 145 (6) (2001 Dec.) 749–755.

[4] A. Vermeulen, L. Verdonck, J.M. Kaufman, A critical evaluation of simple methods for the estimation of free testosterone in serum, J. Clin. Endocrinol. Metab. 84 (10) (1999 Oct.) 3666–3672.
[5] B. Imani, et al., Free androgen index and leptin are the most prominent endocrine predictors of ovarian response during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility, J. Clin. Endocrinol. Metab. 85 (2) (2000 Feb.) 676–682.
[6] D. Cibula, M. Hill, L. Starka, The best correlation of the new index of hyperandrogenism with the grade of increased body hair, Eur. J. Endocrinol. 143 (3) (2000 Sep.) 405–408.
[7] A.H. Balen, et al., Ultrasound assessment of the polycystic ovary: international consensus definitions, Hum. Reprod. Updat. 9 (6) (2003 Nov.–Dec.) 505–514.
[8] A. Dunaif, et al., Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome, Diabetes 38 (9) (1989 Sep.) 1165–1174.
[9] Consensus Development Conference on Insulin Resistance, 5–6 November 1997, American Diabetes Association, Diabetes Care, vol. 21, 2, 1998 (Feb.), pp. 310–314.
[10] Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III), JAMA 285 (19) (2001 May 16) 2486–2497.