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

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Abstract

Since the 1990 NIH-sponsored conference on polycystic ovary syndrome (PCOS),it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology. PCOS remains a syndrome and,as such,no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. Its clinical manifestations may include: menstrual irregularities,signs of androgen excess,and obesity. Insulin resistance and elevated serum LH levels are also common features in PCOS. PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events.

Key words: diagnostic criteria/long-term health risks/polycystic ovary syndrome/revised 2003 consensus

Introduction

Nearly 15 years have passed since the first international conference on polycystic ovary syndrome (PCOS) was held. During that initial meeting at the National Institutes of Health (NIH) in Bethesda, MD,there was considerable discussion with little consensus, though a questionnaire led to the current diagnostic criteria that stand today (see Table I). Based on the majority opinion rather than clinical trial evidence,the following diagnostic criteria were recommended: clinical or biochemical evidence of hyperandrogenism,chronic anovulation and exclusion of other known disorders (Zawadski and Dunaif,1992). These criteria were an important first step towards standardizing diagnosis and led to a number of landmark randomized multi-centre clinical trials in PCOS (Nestler *et al.*,1998; Azziz *et al.*,2001). Since that time and as outlined during a number of subsequent international conferences (Chang and Katz,1999),there has been a gradually increasing awareness that the clinical expression of PCOS may be broader than that defined by the 1990 NIH criteria.

Table I. 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 and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries
and exclusion of other aetiologies (congenital adrenal hyperplasias,androgen-secreting tumours,Cushing's syndrome)

Thorough documentation of applied diagnostic criteria should be done (and described in research papers) for future evaluation.

Rotterdam consensus on diagnostic criteria for PCOS

PCOS is a syndrome of ovarian dysfunction. Its cardinal features are hyperandrogenism and polycystic ovary (PCO) morphology (Laven *et al*.,2002). Its clinical manifestations may include: menstrual irregularities,signs of androgen excess,and obesity. PCOS is associated with an increased risk of type 2 diabetes (Ehrmann *et al*.,1999; Legro *et al*.,1999). Since the 1990 NIH-sponsored conference on PCOS,it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria (Table I). It is now recognized that women with regular cycles and hyperandrogenism,and/or PCO may be part of the syndrome (Adams *et al*.,1986; Franks,1989; Carmina and Lobo,2001). It has also been recognized that some women with the syndrome will have PCO without clinical evidence of androgen excess, but will display evidence of ovarian dysfunction.

PCOS remains a syndrome and,as such,no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. PCOS also remains a diagnosis of exclusion. Known disorders which mimic the PCOS phenotype should be excluded.

Diagnostic criteria for clinical trials and familial studies

The above-mentioned diagnostic criteria may not be suitable for trials focusing on clinical outcomes in women with PCOS. For instance,trials focusing on pregnancy as an outcome may place greater emphasis on anovulation as the identifying symptom, rather than the presence of PCO or clinical hyperandrogenism. Similarly,trials seeking an improvement in hirsutism may de-emphasize baseline ovulatory function and require some pathological terminal hair growth for entry. Moreover,women with chronic anovulation and hyperandrogenism and/or PCO appear to be at substantially greater risk for insulin resistance than those with hyperandrogenism and regular cycles (Dunaif *et al*.,1987; Robinson *et al*.,1993). Accordingly,it is essential that studies of the metabolic features of PCOS stratify affected women according to ovulatory function (i.e. chronic oligo-/amenorrhea versus regular cycles).

Family studies are critical to understanding the spectrum of phenotypes,and for identifying susceptibility genes for PCOS. More narrow diagnostic criteria may be used in familial studies to identify affected individuals,such as the presence of PCO alone (Carey *et al*.,1993),or hyperandrogenemia *per se* (Legro *et al*.,1998). A rigid definition of PCOS based on the present or past proposed diagnostic criteria may hamper our understanding of this heterogeneous disorder.

Exclusion of related disorders

In order to establish the diagnosis of PCOS,it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia,Cushing's syndrome and androgen-secreting tumours. Exclusion of 21-hydroxylase-deficient non-classic adrenal hyperplasia (NCAH) can be performed using a basal morning 17-hydroxyprogesterone level,with cut-off values ranging between 2 and 3 ng/ml (Azziz *et al*.,1999). Some participants felt that the routine screening of hyperandrogenic patients for NCAH should take into account the prevalence of this autosomal recessive disorder in the population under study.

The routine exclusion of thyroid dysfunction in patients deemed to be hyperandrogenic was felt to have limited value,as the incidence of this disorder among these patients is no higher than that in normal women of reproductive age. However,because screening for thyroid disorders may be advisable in all women of reproductive age,the routine measurement of thyroid-stimulating hormone in the hyperandrogenic patient need not be discouraged.

The initial work-up in women presenting with oligo-/anovulation may also include the assessment of serum FSH and estradiol (E_2) levels in order to exclude hypogonadotropic hypogonadism (i.e. central origin of ovarian dysfunction) or premature ovarian failure characterized by low E_2 and high FSH concentrations, according to World Health Organization (WHO) classification (ESHRE Capri Workshop,1995; Rowe *et al*.,2000). PCOS is part of the spectrum of normogonadotropic normo-estrogenic anovulation (WHO 2) (van Santbrink *et al*.,1997; Laven *et al*.,2002). It should be emphasized,however,that serum LH concentrations are frequently elevated in these patients,as will be discussed later.

Most participants felt that the routine measurement of prolactin in the evaluation of hyperandrogenic patients should be performed to exclude hyperprolactinaemia with a caveat that many hyperandrogenic patients may have prolactin levels in the upper normal limit or slightly above normal.

Finally,syndromes of severe insulin resistance (e.g. for the diagnosis of the hyperandrogenic insulin-resistant acanthosis nigricans or HAIRAN syndrome) (Moller *et al.*,1994),Cushings syndrome (Kreisberg,1994),androgen-secreting neoplasms (Kreisberg, 1994; Waggoner *et al.*,1999) or high dose exogenous androgens (Pache *et al.*,1991) should be excluded if clinically suspected.

Hyperandrogenism

Clinical phenotyping of PCOS involves determining the presence of clinical and/or biochemical androgen excess (hyperandrogenism), while excluding related disorders.

Clinical hyperandrogenism.

Most participants felt that the primary clinical indicator of androgen excess is the presence of hirsutism (Diamanti-Kandarakis *et al.*,1999). However,the following issues should be emphasized:

• Normative data in large populations are still lacking.

• The assessment of hirsutism is relatively subjective.

• Few physicians in clinical practice actually use standardized scoring methods.

• Hirsutism is often treated well before the patient is ever evaluated endocrinologically.

• Hirsutism may be significantly less prevalent in hyperandrogenic women of East Asian origin (Carmina *et al.*,1992),or in adolescence (Ruutiainen *et al.*,1988).

The sole presence of acne was also felt to be a potential marker for hyperandrogenism,although studies are somewhat conflicting regarding the exact prevalence of androgen excess in these patients (Slayden *et al.*,2001). The sole presence of androgenic alopecia as an indicator of hyperandrogenism has been less well studied. However,it appears to be a relatively poor marker of androgen excess,unless present in the oligo-ovulatory patient (Futterweit *et al.*,1988). Overall,the clinical evidence of hyperandrogenism is an important feature of patients with PCOS,notwithstanding the above-mentioned limitations.

Biochemical hyperandrogenism.

Most patients with PCOS have evidence of hyperandrogenaemia, and recent observations suggest that circulating androgen levels may also represent an inherited marker for androgen excess (Legro *et al.*,1998). However,it was clearly denoted that a proportion of PCOS patients may not demonstrate an overt abnormality in circulating androgens (Knochenhauer *et al.*,1988; Pugeat *et al.*,1993; Balen *et al.*,1995; Asuncion *et al.*,2000; Laven *et al.*,2002).

The limitations of defining androgen excess by the measurement of circulating androgen levels were felt to be due in part to the inaccuracy and variable laboratory methods of measurements often used (Rosner,1997; Boots *et al*.,1998; Vermeulen *et al*., 1999):

• There are multiple androgens that may not be considered (Rittmaster,1993).

• There is wide variability in the normal population.

• Normative ranges have not been well established using well-characterized control populations.

• Age and body mass index (BMI) have not been considered when establishing normative values for androgen levels (Moran *et al*.,1999; Bili *et al*.,2001).

• Few normative data are present in adolescent and older women;

• Androgens are suppressed more rapidly by hormonal suppression than other clinical features and may remain suppressed even after discontinuation of hormonal treatment.

Notwithstanding these limitations,it was felt that the measurements of free testosterone (T) or the free T (free androgen) index (FAI) (Vermeulen *et al*.,1999) were the more sensitive methods of assessing hyperandrogenaemia (Cibula *et al*.,2000; Imani *et al*.,2000). Recommended methods for the assessment of free T included equilibrium dialysis (Rosner,1997; Vermeulen *et al*.,1999),calculation of free T from the measurement of sex hormone-binding globulin and total T,or ammonium sulphate precipitation (Tremblay and Dube,1974). It was the uniform impression that currently available direct assays for free T have limited value, particularly in the evaluation of hyperandrogenic woman.

It was noted that the sole measurement of total T may not be a very sensitive marker of androgen excess. A small fraction of patients with PCOS may have isolated elevations in dehydroepiandrosteronesulphate (DHEA-S). Some felt that the measurement of total T and DHEA-S had some value in the detection of the patient with an androgen-secreting tumour (Meldrum and Abraham,1979),although more recent data suggest that the best predictor of these neoplasms is the clinical presentation (Derksen *et al*.,1994).

Finally,few data are available on the value of routinely measuring androstenedione in hyperandrogenic patients (Laven *et al*.,2002), although it was noted that it might be somewhat more elevated in patients with 21-hydroxylase-deficient NCAH than PCOS. Nonetheless, the paucity of normative and clinical data with androstenedione precluded its recommendation for the routine assessment of hyperandrogenaemia.

Polycystic ovaries (PCO)

Workshop participants felt that PCO should now be considered as one of the possible criteria for PCOS (see Table I). According to the available literature (Pache *et al*.,1992; van Santbrink *et al*.,1997; Jonard *et al*.,2003),the criteria fulfilling sufficient specificity and sensitivity to define PCO are the following: ‘presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter,and/or increased

ovarian volume (>10 ml)' (for a review see Balen *et al*., 2003). The subjective appearance of PCO should not be substituted for this definition. The follicle distribution should be omitted as well as the increase in stromal echogenicity and volume. Although increased stromal volume is a feature of PCO (Bucket *et al*.,2003),it has been shown that the measurement of the ovarian volume is a good surrogate for the quantification of stromal volume in clinical practice (Dewailly *et al*.,1994). This definition does not apply to women taking the oral contraceptive pill,since its use modifies ovarian morphology in normal women and putatively in women with PCO (Christensen *et al*.,1997). Only one ovary fitting this definition is sufficient to define PCO. If there is evidence of a dominant follicle (>10 mm) or a corpus luteum,the scan should be repeated the next cycle. The presence of an abnormal cyst or ovarian asymmetry (which may suggest a homogeneous cyst) necessitates further investigation.

A woman having PCO in the absence of an ovulatory disorder or hyperandrogenism ('asymptomatic' PCO) should not be considered as having PCOS,until more is known regarding the clinical presentation (Dewailly,1997). In addition to its role in the definition of PCOS,ultrasound is helpful to predict fertility outcome of clomiphene citrate (Imani *et al*.,2002), risk of ovarian hyperstimulation syndrome (OHSS) (Balen *et al*., 2003) and assist in deciding whether the *in vitro* maturation of oocytes is desirable (Tan *et al*.,2002).

It is recognized that the appearance of PCO may be seen in women before undergoing ovarian stimulation for IVF in the absence of overt signs of PCOS. These ovaries,when stimulated,behave like the ovaries of PCOS women and are at increased risk for hyperstimulation and OHSS (McDougall *et al*.,1992).

In addition,ultrasound provides the opportunity to screen for endometrial hyperplasia in these patients.

The following technical recommendations should be highlighted:

• State-of-the-art equipment is required and should be operated by appropriately trained personnel.

• Whenever possible,the transvaginal approach should be utilized,particularly in obese patients.

• Regularly menstruating women should be scanned in the early follicular phase (cycle days 3–5). Oligo-/amenorrhoeic women should be scanned either at random or between days 3 and 5 after a progestin-induced withdrawal bleeding.

• Calculation of ovarian volume is performed using the simplified formula for a prolate ellipsoid (0.5 x length x width x thickness) (Swanson *et al*.,1981).

• Follicle number should be estimated in both longitudinal and antero-posterior cross-sections of the ovaries. The size of follicles <10 mm should be expressed as the mean of the diameters measured on the two sections.

Insulin resistance

Insulin resistance is associated with reproductive abnormalities in women with PCOS (see also Table II). Improving insulin sensitivity through both lifestyle and pharmacological intervention can ameliorate these abnormalities. Insulin resistance,defined as decreased insulin-mediated glucose utilization,is commonly found in the larger population (10–25%) when sophisticated dynamic studies of insulin action are performed (Ferrannini *et al*.,1997). However,the criteria for selecting an abnormal cut-off point vary. Insulin resistance in women with PCOS appears even more common (up to 50%),in both obese and non-obese women (Dunaif *et al*.,1989). Reports of the prevalence of insulin resistance in women with PCOS vary dependent on the sensitivity and specificity of the tests employed and the heterogeneity of PCOS.

Table II. Summary of 2003 PCOS consensus regarding screening for metabolic disorders

Summary of consensus
1. No test of insulin resistance is necessary to make the diagnosis of PCOS,nor are they necessary to select treatments.
2. Obese women with PCOS should be screened for the metabolic syndrome,including glucose intolerance with an oral glucose tolerance test.
3. Further studies are necessary in non-obese women with PCOS to determine the utility of these tests,although they may be considered if additional risk factors for insulin resistance,such as a family history of diabetes,are present.

There is currently no validated clinical test for detecting insulin resistance in the general population. Dynamic invasive tests such as the euglycaemic clamp and frequently sampled glucose tolerance test are research procedures,due to their intensive utilization of time and resources. Calculated indices based on fasting levels of insulin and glucose correlate well with dynamic tests of insulin action. However,there are multiple flaws which limit their widespread clinical use,including changes in β-cell function with the development of diabetes (which alters the sensitivity of the tests),normal physiological fluctuation in insulin levels and the lack of a standardized universal insulin assay.

Other consensus conferences also recommended against screening for insulin resistance in both the general population and in high-risk populations,because of these concerns along with concerns regarding the value of these tests to predict clinical events (American Diabetes Association,1997). Instead,criteria have been developed for defining a metabolic syndrome,that includes components associated with the insulin resistance syndrome, including centripetal obesity,hypertension,fasting hyperglycaemia and dyslipidaemia (Table III) (Expert Panel on Detection, Evaluation,and Treatment of High Blood Cholesterol in Adults, 2001).

Table III. Criteria for the metabolic syndrome in women with PCOS

Risk factor	Cut-off
1. Abdominal obesity(waist circumference)	>88 cm (>35 in)
2. Triglycerides	≥150 mg/dl
3. HDL-C	<50 mg/dl
4. Blood pressure	≥130/≥85 mmHg
5. Fasting and 2 h glucose from OGTT	110–126 mg/dl and/or 2 h glucose 140–199 mg/dl

Three out of five qualify for the syndrome.

HDL-C,high density lipoprotein-cholesterol; OGTT,oral glucose tolerance test.

Other groups have recommended adding an oral glucose tolerance test (OGTT) to these fasting blood tests and to evaluate the 2 h glucose level after a 75 g oral glucose challenge for glucose intolerance [WHO criteria,impaired glucose tolerance (IGT) >140–199 mg/dl] (Bloomgarden,2003a,b). IGT has long been recognized as a major risk factor for diabetes (Norman *et al*.,2001),and recent studies have shown that progression to diabetes in individuals with IGT can be delayed by lifestyle changes and pharmacological intervention (Buchanan *et al*.,2002; Knowler *et al*.,2002). Additionally,IGT identifies individuals at risk for excess mortality,especially women (Anonymous,1999; Tominaga *et al*.,1999). Given the high prevalence of IGT and type 2 diabetes as diagnosed by the OGTT among obese women with PCOS,it is prudent to screen obese women (BMI >27 kg/m^2) with PCOS with an OGTT (Ehrmann *et al*.,1999; Legro *et al*., 1999). Further studies of the prevalence of features of the metabolic syndrome are necessary in both lean and obese women with PCOS.

Currently there are scant data to indicate that markers of insulin resistance predict responses to treatment (Moghetti *et al*., 2000; Imani *et al*.,2000; Azziz *et al*.,2001). Therefore,the role of these markers in the diagnosis of PCOS,as well as in selecting specific treatments is uncertain. Tests of insulin sensitivity are of greatest interest in research studies of: (i) the pathophysiology of PCOS; (ii) young adolescents with a combined history of low birth weight and excessive postnatal catch-up; (iii) mechanisms of response to therapy; and (iv) family phenotypes.

Further studies to identify predictive factors or early response factors to treatments of PCOS are needed.

LH

Both the absolute level of circulating LH and its relationship to FSH levels are significantly elevated in PCOS women as compared with controls (Fauser *et al.*,1991; Taylor *et al.*,1997). This is due to an increased amplitude and frequency of LH pulses (Waldstreicher *et al.*,1988). Elevated LH concentrations (above the 95th percentile of normal) can be observed in ~60% of PCOS women (van Santbrink *et al.*,1997; Laven *et al.*,2002),whereas the LH/FSH ratio may be elevated in up to 95% of subjects (Taylor *et al.*,1997) if women who have ovulated recently are excluded. LH levels may be influenced by the temporal relationship to ovulation,which transiently normalizes LH,by the BMI (being higher in lean PCOS women) and by the assay system used.

The potential negative actions of LH on human reproduction are highly controversial. Some authors have suggested that high LH levels could have detrimental effects on oocyte maturity and fertilization (Tarlatzis *et al.*,1995),as well as lower pregnancy and higher miscarriage rates (Balen *et al.*,1993). However,other studies have shown no untoward actions of LH on oocyte and embryo quality,or on fertilization,implantation and pregnancy rates (Gordon *et al.*,2001; Mendoza *et al.*,2002). Reduction of endogenous LH levels with GnRH agonists also provided conflicting results,as some studies have suggested that this maneouvre could reduce miscarriage rates (Homburg *et al.*,1993), while others have questioned this therapeutic effect (Clifford *et al.*,1996; Hughes *et al.*,2000). LH levels or the administration of exogenous LH were not found to affect the chances of ovulation or achievement of pregnancy using clomiphene citrate (Imani *et al.*,2000, 2002) or exogenous gonadotropins (Al-Inani *et al.*,2003; Mulders *et al.*,2003).

Based on the aforementioned data,the panel felt that measurement of serum LH levels should not be considered necessary for the clinical diagnosis of PCOS. LH levels could be useful as a secondary parameter (especially in lean women with amenorrhea,or in research). Additional research is needed to clarify further the clinical relevance of LH in PCOS and the potential effects of LH suppression with GnRH analogues or its enhancement through LH administration at different stages of follicular maturation.

Long-term health risks

PCOS women have multiple risk factors for diabetes including obesity,a family history of type 2 diabetes and abnormalities in insulin action (both insulin resistance and β-cell dysfunction). There is now clear evidence that women with PCOS are at increased (3–7 times) risk of developing type 2 diabetes (Dunaif *et al.*,1987; Dahlgren *et al.*,1992a; Ehrmann *et al.*,1999; Legro *et al.*,1999; Wild *et al.*,2000). There are several lines of evidence suggesting that women with PCOS are also at increased risk of cardiovascular disease (Dahlgren *et al.*,1992b). Insulin-resistant states are associated with greater than normal susceptibility to coronary heart disease. and women with PCOS have evidence of dyslipidaemia (Conway *et al.*,1992; Robinson *et al.*,1996; Talbott *et al.*,1998; Legro *et al.*,2001) and markers of abnormal vascular function (Talbott *et al.*,2000; Paradisi *et al.*,2001; Christian *et al.*,2003). However,limited epidemiological studies have shown no direct evidence of an increased incidence of coronary heart disease events in middle-aged women with a history of PCOS (although the incidence of stroke is slightly increased) (Wild *et al.*,2002).

Women with PCOS are also thought to be at increased risk for endometrial cancer through chronic anovulation with unopposed estrogen exposure of the endometrium. However,epidemiological evidence to support this hypothesis is limited (Hardiman *et al*.,2003).

Currently,no firm conclusions can be drawn,but the following statements represent the consensus view that PCOS is associated with an increased risk of type 2 diabetes.

(i)The risk is greater in anovulatory women with PCO,in obese subjects and those with a family history of type 2 diabetes.

(ii)The risk of cardiovascular disease is uncertain at present (Wild *et al*.,2002; Legro,2003). Limited epidemiological data have shown no increase in cardiovascular events,but two factors need to be borne in mind: The young age of the cohorts studied so far (~55 years) and the possibility that unknown factors(s) may be present in PCOS which protect the heart in the face of other risk factors.

More research is required to: (i) assess the level of risk; (ii) enable identification of patients at risk; (iii) provide longitudinal follow-up of PCOS cohorts into their 60s and beyond; and (iv) determine the place,timing and efficacy of interventional measures.

Although many questions remain to be answered,lifestyle changes (diet and exercise) should be strongly encouraged to reduce the risk of both type 2 diabetes and cardiovascular disease (Kiddy *et al*.,1992; Clark *et al*.,1995; Huber-Buchholtz *et al*.,1999; Moran *et al*.,1999,2003).

Acknowledgements

The symposium was held on May 1–3,2003,Rotterdam,The Netherlands. Congress chairmen: Tarlatzis (Greece),Fauser (The Netherlands). Scientific Committee: Chang (USA),Azziz (USA), Legro (USA),Dewailly (France),Franks (UK),Tarlatzis (Greece), Fauser (The Netherlands). Invited discussants; Balen (UK),Bouchard (France),Dahlgren (Sweden),Devoto (Chile),Diamanti (Greece), Dunaif (USA),Filicori (Italy),Homburg (Israel),Ibanez (Spain), Laven (The Netherlands),Magoffin (USA),Nestler (USA),Norman (Australia),Pasquali (Italy),Pugeat (France),Strauss (USA), Tan (Canada),Taylor (USA),Wild (USA),Wild (UK). Invited discussants not present during the meeting; Chang (USA),Guzick (USA),Ehrmann (USA),Lobo (USA). This symposium was financially sponsored by an unconditional grant from NV Organon and by ESHRE/ASRM.

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Submitted on October 16,2003; accepted on November 3,2003.