Commentary

A comment on the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine consensus of the polycystic ovarian syndrome

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Abstract

This commentary on the European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) consensus on diagnosis, nomenclature and long-term health risks of the polycystic ovarian syndrome (PCOS) (conference in Rotterdam, Netherlands, March 2003) questions whether the preservation of the term PCOS sufficiently considers the modern aspects of the aetiology and pathogenesis of this complex syndrome. The misleading and simplified term PCOS, which comprises a variety of different entities, carries with it the risk of misinterpretation and under- and overestimation of symptoms, as well as of overlooking contraindications. Additionally, bias in future studies is pre-programmed. In this commentary, it is proposed that the term polycystic should be substituted with polyfollicular, and the term PCOS with functional hyperandrogenism, which is further subdivided into five additional groups. By using this new classification, most of the patients’ dysfunctions belonging to the unspecifically termed PCOS are clearly defined, which leads on to the assumption that the diagnostic and therapeutic approaches required will improve, and the amount of bias in both basic and clinical studies will be reduced, respectively.

Keywords: hirsutism, hyperandrogenism, hyperinsulinaemia, infertility, obesity, PCOS

The European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) Rotterdam ‘Consensus on diagnosis, nomenclature and long-term health risks of the polycystic ovarian syndrome (PCOS)’ (conference in Rotterdam, Netherlands, March 2003) (Fauser, 2003) defines polycystic ovarian syndrome (PCOS) by oligo-anovulation, hyperandrogenism (clinical and/or biochemical) and polycystic ovary (PCO) (with ultrasound), thereby excluding other criteria, and states that at least two out of these three parameters should be fulfilled.

In my opinion, this ‘new’ definition is not sufficiently able to contribute to the clarification of this complex issue. My concern is related both to the terms oligo-anovulation, hyperandrogenism, PCO and PCOS, and the overall definition, respectively. It is possible that the definition came about under the pressure of getting a consensus. Nevertheless, the definition appears highly simplified and carries the risk of misinterpretation and under- and overestimation of symptoms, as well as of overlooking contraindications. There also appears to be no clear improvement for avoiding bias in further studies.

In general, the term PCOS covers an extensive spectrum of variability, ranging from a mono- to a multi-symptomatic phenotype, involving one or many organs, occurring intermittently or being evident throughout an entire life, and might be a mono- or interdisciplinary dysfunction/disease. The problem is not so much the number of symptoms but rather the fact that completely different entities are defined by one term without clearly defined subgroups.

For further discussion it is necessary to look at the definition in detail. Oligo-anovulation is a weak criterion. It occurs in a large scale of completely different forms of ovarian insufficiency (Breckwoldt, 1989). Anovulation is sufficiently defined (= no ovulation); however, there is – to my knowledge – no clear definition concerning oligo-ovulation. Both states are not easy to prove. The cheapest, sometimes for the patient inconvenient, method to indicate an ovulation is the body temperature curve; if the body temperature curve is not suitable for the patient (e.g. because of irregular sleeping phases), an extensive and expensive endocrine-sonographical process would be required. Anyway, the clear proof of oligo-ovulation, a symptom projected mainly to infertility, is, particularly in cases of patients who do not want children, of limited relevance.

Gynaecologists usually associate a cyst in the ovary with a pathological structure, which could be a hazard due to the risk of malignancy. Cysts are not endocrinologically active in most cases. Therefore, the term PCO is misleading. Using the term PCO, the ‘cysts’ are defined sonographically (= hole), and not morphological-functionally (as expressed, for example, by the diagnostic tool folliculometry). Everybody agrees that the
‘holes’ (<12 mm) visualized by ultrasound are equivalent to antral follicles carrying a fertilizable egg. When this fact is accepted, it appears more than logical to substitute cystic with follicular (Geisthövel et al., 1983), and therefore to use the term polyfolicula ovary (PFO) (Geisthövel and Schulze, 2000; Geisthövel, 2003a,b), instead of PCO. In any case, the Rotterdam criteria oligo-anovulation and PCO contain an inherent inconsistency, which is found similarly in a recently presented paper by Dewailly and co-workers (Dewailly et al., 2003). Changing the term PCO to PFO is more than a semantic measure.

The criterion clinical hyperandrogenism is also problematic. Pubertal acne (clinical hyperandrogenism), for instance, is a simple and harmless, as well as short-term, dysfunction of the skin, but together with a transient oligo-anovulation, which is very common in puberty and adolescence, would lead to the diagnosis PCOS, even if no other symptom was present. I assume that there is agreement that this is not a case of PCOS. Clinical hyperandrogenism is predominantly related to cutaneous symptoms (acne, hirsutism or alopecia), but this criterion is too weak to serve as one of the three full criteria for the diagnosis PCOS. Thus, it has to be feared that the Rotterdam criteria are not able to limit the worldwide misuse of the diagnosis PCOS. However, if oligo-anovulation is associated with true virilization (clitoris hypertrophy, muscle hypertrophy, deepening of the voice, breast atrophy, severe cutaneous androgenizing symptoms etc.), a severe C19-sex steroid excess through an androgen-producing tumour, an insufficiently treated congenital adrenal hyperplasia or anabolic steroid abuse have to be assumed rather than PCOS.

Along a similar line, the symptoms in the case of a normogonadotrophic, normoandrogenemic oligo-amenorrhoea may also be overestimated by the Rotterdam criteria (oligo-anovulation). One will find sonographically in most of these cases a distinct PFO-status (‘PCO’). According to my clinical experience, these symptoms lead frequently to the over-diagnosis of PCOS. Although this ovary is hypersensitive to gonadotrophin stimulation (Keck and Geisthövel, 1999) (see below) and shares therefore a certain dysfunctional feature with the PCOS, the endocrine pathogenesis underlying this ovarian high response has nothing to do with the so-called ‘PCOS’; these patients do not have an increased LH/FSH ratio, absolute hyperandrogenemia, hyperinsulinemia, hypo-SHBG-aemia (sex hormone-binding globulin) or dyslipidaemia; often this dysfunctional status occurs in the post-menarche, during adolescence or in phases of somatic or mental stress with weight loss. A reduced gonadotrophin pulsatility is associated with this dysfunction (Santoro and Crowley, 1986) instead of an often exaggerated pulse pattern in patients with hyperandrogenism (PCOS) (Rebar et al., 1976); in both cases, several follicles are recruited but a selection and maturation of the dominant follicle do not, or rarely, occur. By contrast to the manifested PCOS, which is a chronic disease, this dysfunction follows a transient course in many cases.

However, the Rotterdam criteria underestimate the significance of the adrenal source of C19-sex steroids; elevated dehydroepiandrosterone sulphate concentrations (biochemical hyperandrogenism) are often associated with oligo-anovulation and with a slight polyfolicular state of the ovaries; by using the Rotterdam criteria, the ovary, but not the adrenal gland, becomes the centre of interest. When administering glucocorticoids to these patients they become pregnant very easily; or those patients with hirsutism benefit from suppression of adrenal, rather than of ovarian, function. Furthermore, it might be easily overlooked that adrenal hyperandrogenism may be associated with heterozygous CYP21B mutation; in cases of infertility, a male CYP21B screening is then required for prediction and therapeutic prevention against androgenization in a female embryo/fetus with homozygous congenital adrenal hyperplasia. These examples again show that the term PCOS may be misleading in making the right choice of therapeutic approach.

As already mentioned above, the term PCOS places at the centre of the consideration the ovarian dysmorphology. In a considerable number of patients, ovarian dysmorphology is of minor, if any, relevance; however, the over-accentuation of this symptom in the term PCOS might lead to wrong conclusions for diagnostic and therapeutic approaches. Here are two examples: in an 18-year-old woman with cutaneous androgenizing symptomatology, early-onset-obesity, PFO, hypertestosteronemia, hyperinsulinemia with impaired glucose tolerance and dyslipidaemia without presently desiring a child, PCOS underestimates the high risk of developing the type-2 diabetes/metabolic syndrome. What happens to such young women in practice daily? With the false perception that oral contraceptive pills (ethinyl oestradiol/antiandrogenic progestagen) can cure the ‘ovarian disease, PCOS’ by reducing pituitary gonadotrophin release, such drugs are prescribed to these women. However, this might be contraindicative, and it would be much more beneficial to treat the metabolic dysfunction first. This imbalanced meaning of the phenotype is even more evident in the second example, in which similar findings are present in a 35-year-old mother who does not want any more children; in these cases, the diagnosis PCOS brings to the foreground a symptom (PCO) that is completely irrelevant for this patient and might underestimate the need for other diagnostic and therapeutic approaches, such as weight reduction, diet, antilipids, antidiabetics, antithrombotics etc. (see below). Using an irrelevant term does not make the diagnosis right.

The term PCOS underestimates the risk of hypersensitivity to gonadotrophin stimulation (Keck and Geisthövel, 1999). If one is aware of the polyfolicular state in functional ovarian hyperandrogenism, then the prediction of ovarian high response is a more logical consequence; and by being aware of that prediction, the therapeutic regimen is more likely to be set in a safer way to prevent an ovarian hyperstimulation syndrome (OHSS). In studies presented at the EHSRE meeting in 2003 (Elter et al., 2003; Klinkert et al., 2003), the number of follicles, rather than cysts, has been used as a parameter for the prediction of ‘poor’ or ‘high’ responders, and these studies also suggest that the term follicle is being applied by an increasing number of researchers as the appropriate term under the clinical view in reproductive medicine.

In addition, the Rotterdam PCOS consensus, although it puts in the title the ‘long-term health risks of PCOS’, still paradoxically underestimates the alarming worldwide adverse impact of obesity on a female reproductive and post-reproductive life, because obesity and the metabolic
dysfunctions are not expressed directly in the criteria. Subsuming obesity and metabolic dysfunctions into the term hyperandrogenism is at least confusing. Furthermore, in such patients, the Rotterdam PCOS criteria also underestimates the risk of gestational diabetes. Considering the pathogenesis in early-onset hyperandrogenaemic-hyperinsulinaemic-obese patients, the PFO/PCO status is quite likely to be the consequence and not the primary factor. Again, the term PCOS dominates per definitionem aetiological, pathogenetic and clinical features that are more important than the PCO characteristics.

Often the question arises ‘What about PCOS in menopausal transition/menopause?’ This question again discloses a profound misunderstanding. Using the Rotterdam criteria, PCOS in menopausal transition/menopause would be a possible diagnosis in, for example, hirsute perimenopausal women (clinical hyperandrogenism, oligo-anovulation). Clearly, hyperandrogenaemia in menopausal transition/menopause occurs; there might be a relative reduction of the C19-/C19-steroid ratio, or elevated C19-steroid concentrations may derive from stromal hyperactivity or from an androgen-secreting ovarian or adrenal tumour but no longer from follicular thecal cells. Per definitionem, menopausal transition is caused by a depletion of the entire follicular apparatus diagnosed by increasing FSH and decreasing oestradiol concentrations in the circulation, so that size of the follicular cohort decreases due to ovarian ageing (Elting et al., 2003), and the sonographical visualization of a PCO/PFO status after menopause is no longer possible. In these cases, by keeping the term PCOS, one would consequently end up with a diagnosis of a ‘non-PCO-PCOS’ – what an absolutely absurd idea! Talking about PCOS in menopausal transition/menopause underestimates the hazard of dangerous ovarian structures (polycystic–polyomorphic cystadenoma/malignoma) being not that rarely detected sonographically.

The Rotterdam criteria underestimates the wide range of the differential diagnosis: for instance, the Sjögren Syndrome being associated with severe acne-like alterations of the skin (clinical hyperandrogenism) (Witkowski et al., 1995) may lead to the wrong diagnosis of PCOS if the patient randomly shows an oligo-amenorrhoea (oligo-anovulation); this might also be the case with rare, severe obesity syndromes such as the Prader–Labhardt–Willy syndrome and others (Bray, 1998), which might be accompanied by a prolongation of the menstrual cycle (oligo-anovulation) and some of the PCOS phenotype features (clinical hyperandrogenism: android obesity).

Patients under anabolic steroid abuse (hyperandrogenism, oligo-anovulation) might be misdiagnosed by the Rotterdam criteria. When the criterion (‘exclusion of other criteria’) is applied here, then a list of exclusion criteria (compare also the described cases above) has to be presented. Anyway, that makes the daily use of the definition not much easier.

Including completely different entities under the term PCOS is the major reason why a large number of studies have been difficult to evaluate and compare in the past. Even meta-analysis has to be used with caution due to an extensive amount of bias. Therefore, studies should avoid the term PCOS as a definition and use instead the parameters that aim to be investigated (Geisthövel et al., 1994; Geisthövel et al., 1998; Geisthövel et al., 2001). Otherwise, severe bias will occur even in upcoming randomised controlled trial studies, because the Rotterdam criteria remain too unspecific.

In my opinion, hyperandrogenism is the term that best covers the variety of sub-phenotypes (Geisthövel and Schulze, 2000; Geisthövel, 2003a,b). By using the term hyperandrogenism, I propose a sub-grouping into three major groups: functional hyperandrogenism, tumorous hyperandrogenism and pharmaceutical hyperandrogenism (e.g. through anabolic steroids). Functional hyperandrogenism may be additionally sub-divided into five further groups: group I (skin), group II (ovary; = lean PCOS), group III (adrenal), group IV (obesity, hyperinsulinaemia; = obese PCOS), and group V (differential diagnosis). The grouping involves the personal history, and a somatic, sonographic, endocrine and metabolic check-up using an adequate algorithm. Applying this classification, it is relatively easy to sub-group the patient and choose the adequate therapeutic approach for both endocrine–metabolic dysfunctions and infertility. Also, miscellaneous cases frequently found can be sub-grouped with the related documentation into one of the groups I to IV, corresponding to the dominant symptom; when this is not possible, such a patient belongs to Group V. I have been applying this classification as a matter of routine in my daily clinical work for more than 2 years with great success and can highly recommend it for further studies.

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