What is polycystic ovarian syndrome?

A proposal for a consensus on the definition and diagnosis of polycystic ovarian syndrome

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The criteria for diagnosis and definition of polycystic ovarian syndrome used by clinicians and investigators are almost as heterogeneous as the syndrome itself. This has confused and seriously hindered the clarification of the genetics, aetiology, clinical associations and assessment of treatment and later sequelae of the syndrome. This article proposes a consensus for a unifying balanced and practical working definition for use as a standard. The proposal incorporates confirmation of the diagnosis suggested by clinical symptoms by ultrasound, and the use of hormonal estimations if typical ultrasound features are not seen and for the purpose of defining subsets of the syndrome. This consensus proposal attempts to bridge the gap between predominately American biochemical marker-based diagnosis and predominately European reliance on ultrasound as a *sine qua non* for diagnosis. It has been deliberately designed to be simple, practical and cheap, and if universally adopted as a standard could contribute much to all future work involving this most prevalent of syndromes.

Key words: consensus/definition/diagnosis/polycystic ovarian syndrome/ultrasound

Introduction

It has become painfully apparent that it is not only the Atlantic Ocean that divides North America from Europe, but also the definition and diagnosis of polycystic ovarian syndrome (PCOS). The use of many and varied definitions of the syndrome by investigators has seriously confused the literature and has hampered the scientific clarification of the genetics, aetiology, clinical associations and assessment of the treatment and later sequelae of this prevalent syndrome. Unfortunately, the arguments have usually generated more heat than light, so here I will attempt to present a balanced, unifying, practical, working definition to be used as a standard for all future work.

The present position

As in any negotiations, let us first examine the opening statements of each side.

The predominantly European definition of PCOS requires an ultrasonically diagnosed typical morphological appearance of the ovary [usually according to the criteria of Adams *et al.* (Adams *et al.*, 1985)] associated with menstrual disturbance (usually oligo- or amenorrhoea) and/or signs of hyperandrogenism (hirsutism, acne or alopoecia). No hormonal parameters are required to make the diagnosis. The diagnosis of polycystic ovaries may be made on ultrasound, but if this finding exists without any of the above clinical symptoms, this situation is not regarded as a syndrome.

As for the predominantly North American view, the 1990 National Institute of Health (NIH) conference on PCOS (Dunaif, 1997) recommended that diagnostic criteria should include biochemical evidence of hyperandrogenism and ovarian dysfunction (in the absence of non-classical adrenal hyperplasia) without regarding the morphological diagnosis of polycystic ovaries by ultrasound as an essential part of the diagnosis.

Prevalence

Whatever the definition applied, it is obvious that PCOS is an extremely prevalent syndrome. Using the American criteria, reports of prevalence vary from 4% (Knockhauer *et al.*, 1998), 6.5% (Asuncion *et al.*, 2000), 8% (Michelmore *et al.*, 1999) to 9% (Diamanti-Kandarakis *et al.*, 1999) in the female population of fertile age.

Several studies have been performed to assess the prevalence of polycystic ovaries on ultrasound examination in the general female population of fertile age. The findings have been remarkably constant at 21–22% (Polson *et al.*, 1988; Tayob *et al.*, 1990; Clayton *et al.*, 1992; Farquhar *et al.*, 1994; Cresswell *et al.*, 1997). A very large study (*n* = 1078) (Botis *et al.*, 1995) found a prevalence of 17% (95% confidence interval 14–19%) and a further survey (Michelmore *et al.*, 1999) found a prevalence of 33%. Even taking into account the problems of volunteer populations, it is probable that one woman in five has polycystic ovaries that can be demonstrated on ultrasound examination. On further examination and questioning of the women in these population studies who had...
1. Symptoms

Menstrual disturbance
Hirsutism
Acne
Anovulatory infertility

2. Ultrasound examination

Positive: diagnosis confirmed

3. Biochemical examinations

Elevated serum testosterone
Elevated LH concentrations
Fasting glucose: insulin <4.5
(Elevated free androgen index)

If one or more positive: diagnosis confirmed

Proposal (Figure 1)

In the search for a unifying concept for the diagnosis of PCOS, I have attempted to apply several simple principles in order neither to ‘miss’ women who need attention nor include those who do not. The criteria employed should be practical and should not exclude women who have confirmed symptoms of hyperandrogenism and/or menstrual disturbances associated with biochemical signs of hyperandrogenism, elevated LH concentration or hyperinsulinism, but do not have the typical ultrasonically demonstrated morphology. Neither should it include women who have the typical morphological features of polycystic ovaries but are asymptomatic and have none of the biochemical changes noted above.

This is a practical, pragmatic approach which differentiates those who probably require treatment depending on individual needs from those who do not need medical attention at the time of the examination. It also simplifies the diagnostic process in that the ultrasound examination, if positive in the presence of any of the typical symptoms, will confirm the diagnosis without the strict necessity to perform blood examinations. The latter should be done if the ultrasound examination demonstrates normal ovaries in the presence of symptoms. In this case, an elevated LH, testosterone or free androgen index (in the absence of non-classical adrenal hyperplasia) or a fasting glucose:insulin ratio <4.5 will confirm the diagnosis.

Discussion

One of the complicating issues encountered in the precise definition of PCOS is that some women with ultrasonically diagnosed polycystic ovaries have neither symptoms nor biochemical markers of the syndrome. Conversely, some symptomatic patients with positive biochemical markers do not have demonstrable polycystic ovaries on ultrasound examination. Both these eventualities are catered for in the present proposal by utilizing a positive ultrasound examination or positive biochemical marker(s) as confirmation of diagnosis of the syndrome in the presence of symptoms.

To completely ignore the typical morphological appearance of a polycystic ovary on ultrasound examination as a diagnostic parameter would be a strange decision indeed for several reasons. It is a non-invasive technique which has a high concordance rate with laparoscopic examination (Eden, 1988) and with histological examination (Saxton et al., 1990). With ultrasound we are looking directly at the hub of the problem, i.e. the ovary. The typical ultrasound features of the polycystic ovary are easily the commonest detectable sign associated with any of the typical symptoms, whether these be oligomenorrhoea (65–87% had demonstrable polycystic ovaries on ultrasound) (Adams et al., 1986; Gadir et al., 1992), hirsutism (60–92%) (Adams et al., 1986; O’Driscoll et al., 1994) or acne (83%) (Bunker et al., 1989) (and 45% in women with acne as a
sole symptom) (Peserico et al., 1989). The notorious variability, heterogeneity and inconsistency of clinical and endocrinological features of the syndrome (Franks, 1989; Balen et al., 1995) strengthen the case for the inclusion of an ultrasound examination, characteristically constant in the fertile age group, as a cornerstone in the diagnostic process.

Two arguments have been put forward to neutralize the use of the ultrasound examination in the diagnosis of PCOS. Firstly, the criteria for the typical appearance of polycystic ovaries on ultrasound first suggested by Adams et al. and widely used since (i.e. more than eight discrete follicles of <10 mm diameter in one plane of the ovary, usually peripherally arrayed around, but sometimes scattered throughout, an enlarged, hyperechogenic, central stroma (Adams et al., 1985)) have been criticized for not quantifying the stromal volume. The increased stromal volume of the polycystic ovary is important as insulin resistance, serum testosterone production, hirsutism and body mass index all correlate positively with ovarian volume and echogenicity (Franks, 1989; Pache et al., 1993; Dewailly et al., 1994; Kyei-Mensah et al., 1996). The polycystic ovary can be easily distinguished from a multicystic ovary, which has many small follicles but a reduced volume of stroma and is often seen at the time of puberty and in low weight-related or exercise amenorrhoea. While the criterion of a stromal volume occupying >25% of the ovarian volume was originally suggested (Adams et al., 1986), the quantification of the stromal volume has proved difficult in distinguishing the polycystic from the normal ovary. Various attempts include a computerized ultrasonic technique (Dewailly et al., 1994), three-dimensional as well as colour and pulsed Doppler ultrasound (Zaidi et al., 1995; Kyei-Mensah et al., 1996), magnetic resonance imaging (Faure et al., 1989) and ultrasound assessment of the ratio of ovarian stromal area to total ovarian area (Fulghesu et al., 2001). However, they have not yet been widely adopted for reasons of complexity or cost. If the diagnosis of polycystic ovaries is not immediately obvious on ultrasound and some quantification of the stromal volume is required, it is suggested that either the original criterion of Adams et al. of a stroma occupying >25% of the ovarian volume (Adams et al., 1986) or that of Fulghesu et al. necessitating a stroma/total area ratio of >0.34 be employed (Fulghesu et al., 2001).

The second reason for the rejection of the use of ultrasound as a diagnostic tool by some is the fact that some women with so-called functional ovarian hyperandrogenism do not have demonstrable polycystic ovaries on ultrasound examination (Ehrmann et al., 1992) and that an estimated 20% of women with ultrasonically demonstrable polycystic ovaries are asymptomatic. The present proposal incorporates these ‘loopholes’ by including one or more of the biochemical markers mentioned as diagnostic in symptomatic women even in the absence of polycystic ovaries on ultrasound, therefore eliminating the need to obtain the typical ultrasound appearance as a ‘sine qua non’ for diagnosis. Conversely, the finding of ultrasound features of polycystic ovaries in the absence of obvious clinical symptomatology should lead to a search for one or more of the biochemical markers mentioned. This attitude is justified by the fact that in a series of apparently normal, eumenorrhoeic women with ultrasonically demonstrated polycystic ovaries, >90% had a clinical or biochemical feature characteristic of PCOS (Polson et al., 1988). In similar groups of women, all ovulatory, those with polycystic ovaries were more likely to be troubled by subfertility (Eden et al., 1989; Kousta et al., 1999) and recurrent miscarriage (Sagle et al., 1988), both of which may be induced by elevated serum LH concentrations (Homburg et al., 1988). Furthermore, apparently normal eumenorrhoeic women with ultrasonically demonstrable polycystic ovaries respond to gonadotrophin stimulation in their typical fashion of multiple follicular development and rapidly rising serum estradiol concentrations (Homburg, 1996). Lastly, asymptomatic women in the normal body weight range but with polycystic ovaries frequently develop typical symptoms with a significant increase in weight, changes which can be reversed by reducing weight (Kiddy et al., 1990; Clarke et al., 1995). The ultrasonic appearance of polycystic ovaries should not therefore be regarded as merely a morphological variant of no clinical significance, and if associated with either typical clinical and/or biochemical features should be defined as PCOS. Those having the typical ultrasonic appearance but no associated clinical or biochemical manifestations are classified as having polycystic ovaries but not PCOS. This does not mean to say that they will not develop the syndrome at some later stage due to a triggering factor such as significant weight gain, but for purely practical purposes do not at present require any treatment.

The choice of hormone level examinations in the above proposal is aimed at being targeted, brief and cheap. Serum concentrations of LH and testosterone are easily and cheaply performed. Serum LH is raised in 40–50% and testosterone in 30–50% of women with ultrasonically diagnosed polycystic ovaries (Conway et al., 1989; Franks, 1989; Balen et al., 1995). Free androgen index is a better indicator than a simple total testosterone estimation, but is more expensive and less frequently performed. It is a useful addition if feasible and certainly valuable for research purposes. Non-classical adrenal hyperplasia should of course be excluded in the presence of high androgen concentrations, but this condition and PCOS frequently co-exist. As for a measurement of insulin metabolism, fasting insulin has not proved accurate enough and the use of insulin clamps or calculation of area under the curve during oral or i.v. glucose tolerance tests prove too cumbersome for the majority of units as a screening test. The test suggested in the proposed protocol is that put forward by Legro et al. which consists of an estimation of the insulin: glucose ratio in a single fasting sample of blood (Legro et al., 1998). If this ratio is <4.5 it is strongly suggestive of insulin resistance and correlates very well with the more cumbersome tests mentioned above. It is highly unlikely that insulin resistance will be the sole sign of PCOS, so even if it is not used in the plan for the basic diagnosis it is thought to be of value for accurate diagnosis, therapeutic decisions, possibility of follow-up of progress and for research purposes. An elevated serum LH, especially if consistent in two samples taken at the time of menstruation or randomly in oligo/a menorrhoeic patients, is highly suggestive of PCOS as no other condition
produces this disturbance in the presence of low normal or normal FSH serum concentrations. The LH:FSH ratio is of lesser importance in my opinion as an elevated LH level may be accompanied by FSH in the high range of normal and does not always achieve the ‘required’ ratio of \( \geq 2.5:1 \) to make the diagnosis. I have deliberately avoided defining ‘elevated’ LH or testosterone levels because these are very dependent on the local laboratory. In our laboratory, an LH \( >10 \) IU/l and testosterone \( >3.1 \) nmol/l are regarded as elevated.

Obesity has not been included as a symptom as this is thought to be too non-specific. For similar reasons, serum prolactin estimation is also not included although this may be slightly elevated in 20–40% of patients with PCOS.

Clearly for research purposes, many more sophisticated examinations can be performed, but the aim of this proposal is to present a unifying standard for the basic diagnosis of PCOS. In addition, any subdivisions of the syndrome following the establishment of the basic diagnosis can be easily made according to the predominant symptom or sign.

Conclusions

The need for a universally accepted standard for the diagnosis of PCOS is obvious for both clinical and research purposes. Changing the name of a syndrome which has been well known as PCOS for the last 67 years is going to confuse rather than help, especially as it is now widely accepted that the ovary is as PCOS for the last 67 years is going to confuse rather than help, especially as it is now widely accepted that the ovary is a cause of infertility in the ovulatory woman. Clin. Endocrinol. (Oxf.), 30, 77–82.


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