DEBATE

What is polycystic ovary syndrome?

Are national views important?*

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Polycystic ovary syndrome (PCOS) is a true syndrome, being a heterogeneous collection of signs and symptoms that gathered together form a spectrum of a disorder with a mild presentation in some, whilst in others there is a severe disturbance of reproductive, endocrine and metabolic function. There has been much debate about phenotype and, more recently, genotype. There has also been scepticism in some quarters, with a feeling that we may be looking at one end of a spectrum that is in reality ‘normal’, or perhaps a consequence of the modern disease of obesity. Whilst the polycystic ovary is at the centre of the syndrome, it is external effects such as hyperinsulinaemia, that influence its expression. There is no consensus on the definition of PCOS and so studies that compare epidemiology and treatments often have very different starting points, and so cannot be compared. In this debate we wish to re-explore our current thinking on PCOS, with a particular emphasis on the British and European perspective and invite others to contribute to the discussion which could form the basis for an international consensus.

Key words: hyperandrogenism/hyperinsulinaemia/ovarian ultrasound/polycystic ovaries/polycystic ovary syndrome

Introduction

In this debate we wish to open up discussion on the diagnosis and classification of the polycystic ovarian syndrome (PCOS). Perhaps through the pages of this journal we might be able to reach an international consensus by the time of the next consensus meeting on PCOS to be held by the European Society of Human Reproduction (ESHRE) in 2003. PCOS is the commonest endocrine disturbance affecting women. There is not, however, an international consensus on the definition of the syndrome or, indeed, as to what constitutes a polycystic ovary. Terminology is important and it is gratifying to see a shift away from the term ‘polycystic ovarian disease’ to the more commonly accepted polycystic ovary syndrome. This confirms the notion of PCOS as a collection of signs, symptoms and endocrine disturbances and reinforces the heterogeneous nature of the condition (Balen et al., 1995).

There are those, including the authors, who take a pragmatic approach to the management of an individual’s symptoms and needs, which may change over time. Hence an argument could be made that a precise definition of the condition does not help when providing therapy. Yet we feel that, whilst having practical relevance, this argument is flawed because it is necessary to evaluate scientifically the outcomes of treatment. It is then only possible to compare outcomes if the same starting points are employed. Furthermore, whilst PCOS is a familial condition, it is proving impossible to establish the genetic basis for the syndrome without a clear view of the phenotype—another reason to aim for a consensus in defining PCOS. The issue to tax us in this debate is whether the syndrome and its presentation differ around the globe, or whether researchers in different countries are simply using different criteria to define the same condition. The other recurring theme in this debate is the requirement of polycystic ovaries to define the syndrome, a notion that has certainly been adopted in the UK and much of Europe.

What is PCOS?

Polycystic ovaries are commonly detected by ultrasound or other forms of pelvic imaging, with estimates of the prevalence in the general population being in the order of 20–33% (Polson et al., 1988; Clayton et al., 1992; Farquhar et al., 1994a,b; Michelmore et al., 1999). However, not all women with polycystic ovaries demonstrate the clinical and biochemical features which define the syndrome of PCO. These features include menstrual cycle disturbances, obesity, hirsutism, acne, and abnormalities of biochemical profiles including elevated serum concentrations of LH, testosterone, androstenedione, and insulin. Presentation of the syndrome is so varied that

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one, all, or any combination of the above features may be present in association with an ultrasound picture of polycystic ovaries—the defining feature of PCOS in the UK and much of Europe (Balen, 1999). There is considerable heterogeneity of symptoms and signs amongst women with PCOS and for an individual these may change over time (Balen et al., 1995). PCOS is familial (Franks et al., 1997) and various aspects of the syndrome may be differentially inherited. Polycystic ovaries can exist without clinical signs of the syndrome, which may then become expressed over time. There are a number of interlinking factors that affect expression of PCOS. A gain in weight is associated with a worsening of symptoms whilst weight loss will ameliorate the endocrine and metabolic profile and symptomatology (Clarke et al., 1995).

The pathogenesis of polycystic ovaries and the associated syndrome is unknown, but the heterogeneity of presentation of PCOS suggests that a single cause is unlikely. Recent genetic studies have identified a link between PCOS and disordered insulin metabolism, and indicate that the syndrome may be the presentation of a complex genetic trait disorder (Franks et al., 2001). The features of obesity, hyperinsulinaemia and hyperandrogenaemia which are commonly seen in PCOS are also known to be factors which confer an increased risk of cardiovascular disease and non-insulin dependent diabetes mellitus (NIDDM) (Rajkowha et al., 2000; comprehensive review). There are studies which indicate that women with PCOS have an increased risk for these diseases which pose long-term risks for health, and this evidence has prompted debate as to the need for screening women for polycystic ovaries. There are also associations between the presence of PCOS and some cancers (Balen, 2001). For studies of the long-term risks it also absolutely essential to have a clear definition.

Definitions

Historically the detection of the polycystic ovary required visualization of the ovaries at laparotomy and histological confirmation following biopsy (Stein and Leventhal, 1935). Laparotomy was later superseded by improvements in laparoscopic techniques. As further studies identified the association of certain endocrine abnormalities in women with histological evidence of polycystic ovaries, biochemical criteria became the mainstay for diagnosis. Raised serum levels of LH, testosterone and androstenedione, in association with low or normal levels of FSH and abnormalities of estrogen secretion, described an endocrine profile which many believed to be diagnostic of PCOS (Franks, 1995). Well recognized clinical presentations included menstrual cycle disturbances (oligo/amenorrhoea), obesity, and hyperandrogenism manifesting as hirsutism, acne or androgen-dependent alopecia. These definitions proved inconsistent, however, as clinical features were noted to vary considerably between women, and indeed some women with histological evidence of polycystic ovaries consistently failed to display any of the common symptoms. Likewise, the biochemical features associated with PCOS were not consistent in all women. Thus consensus on a single biochemical or clinical definition for PCOS has been thwarted by the heterogeneity of presentation of the disorder.

The advent of high resolution ultrasound scanning provided a non-invasive technique for the assessment of ovarian size and morphology. Good correlation has since been shown between ultrasound diagnoses of polycystic morphology and the histopathological criteria for polycystic ovaries in studies examining ovarian tissue obtained at hysterectomy or after wedge resection (Saxton et al., 1990; Takahashi et al., 1994). The histopathological criteria have been defined as the observation of increased numbers of follicles, hypertrophy and luteinization of the inner theca cell layer, and thickened ovarian tunica. Transabdominal and/or transvaginal ultrasound have since become the most commonly used diagnostic methods for the identification of polycystic ovaries. Although the ultrasound criteria for the diagnosis of polycystic ovaries have never been universally agreed, the characteristic features are accepted as being an increase in the number of follicles and the amount of stroma when compared with normal ovaries. Established transabdominal ultrasound criteria (Adams et al., 1986) define a polycystic ovary as one which contains, in one plane, at least 10 follicles (usually between 2–8 mm in diameter) arranged peripherally around a dense core of ovarian stroma or scattered throughout an increased amount of stroma. These criteria have been adopted by many studies which have used ultrasound scanning to detect polycystic ovaries (Kiddy et al., 1990; Clayton et al., 1992; Farquhar et al., 1994; Balen et al., 1995).

It has been argued that transvaginal ultrasound is a more sensitive method for the detection of polycystic ovaries and that the transvaginal definition of a polycystic ovary should require the presence of at least 15 and usually >20 follicles (2–10 mm in diameter) in a single plane (Fox et al., 1991). However, other authors examining transabdominal versus transvaginal ultrasound have not found significant differences in the detection rate of polycystic ovaries (Farquhar et al., 1994). The recent innovation of three-dimensional ultrasound, and the use of colour and pulsed Doppler ultrasound, are techniques which may further enhance the detection of polycystic ovaries, and which may be more commonly employed over time (Zaidi et al., 1995; Kyei-Mensah et al., 1996). The use of magnetic resonance imaging (MRI) for the visualization of the structure of pelvic organs has been claimed to have even greater sensitivity than ultrasound for the detection of polycystic ovaries (Faure et al., 1989). However, the substantial cost and practical problems involved with this imaging technique may limit its use as an easily accessible diagnostic tool for use in general clinical practice.

The term polycystic ovary might in some respects add to the confusion that surrounds its diagnosis. Indeed the prerequisite of a certain number of cysts may be of less relevance than the volume of ovarian stroma, which has been shown to closely correlate with serum testosterone concentrations (Kyei-Mensah et al., 1996). Furthermore, it has been suggested recently that an ultrasound assessment of the ratio of ovarian stromal area to total ovarian area gives the greatest sensitivity and specificity (both 100%) for the diagnosis of PCOS (Fulghesu et al., 2001). Whilst this would appear to be an attractive proposition, there are other studies that have examined various ultrasound
parameters and found limited predictive value for abnormal hormone levels (van Santbrink et al., 1997).

While it is now clear that ultrasound provides an excellent technique for the detection of polycystic ovarian morphology, identification of polycystic ovaries by ultrasound does not automatically confer a diagnosis of PCOS. Controversy still exists over a precise definition of the syndrome and whether or not the diagnosis should require confirmation of polycystic ovarian morphology. Some authors suggest that the definition of PCOS should be based on biochemical evidence of ovarian hyperandrogenism rather than an ultrasound appearance, as hyperandrogenism may exist in women who have normal ovarian morphology as detected by ultrasound (Ehrmann et al., 1992). This viewpoint has been adopted in the United States, and the 1990 National Institute of Health Conference on PCOS recommended that diagnostic criteria should include evidence of hyperandrogenism and ovulatory dysfunction, in the absence of non-classic adrenal hyperplasia, and that evidence of polycystic ovarian morphology is not essential (Dunaif, 1997). However, the more generally accepted theory in the UK and Europe is that a spectrum exists, ranging from women with polycystic ovarian morphology and no overt abnormality at one end, to those with polycystic ovaries associated with severe clinical and biochemical disorders at the other end. It is important also to appreciate that in-vitro studies have demonstrated that theca cells from ovulatory women with polycystic ovaries produce increased androgens compared with normal ovaries, strengthening the argument for a fundamental dysfunction of ovarian steroidogenic activity (Gilling Smith et al., 1994, 1997). Using a combination of clinical, ultrasonographic, and biochemical criteria, the diagnosis of PCOS is usually reserved for those women who exhibit an ultrasound picture of polycystic ovaries, and who display one or more of the clinical symptoms (menstrual cycle disturbances, hirsutism, obesity, hyperandrogenism), and/or one or more of the recognized biochemical disturbances (elevated LH, testosterone, androstenedione or insulin) (Conway et al., 1989; Balen et al., 1995; van Santbrink et al., 1997). This definition of PCOS requires the exclusion of specific underlying diseases of the adrenal or pituitary glands (e.g. hyperprolactinaemia, acromegaly and congenital adrenal hyperplasia) which could predispose to similar ultrasound and biochemical features.

We favour the following definitions (Balen, 1999). First, the term polycystic ovaries should be used in cases where an ultrasound appearance of polycystic morphology has been described in the absence of overt symptoms of the syndrome. Second, the UK definition of polycystic ovary syndrome (PCOS1) should be given in cases where polycystic ovaries have been identified ultrasonographically and where one or more of the clinical symptoms or biochemical features are present (i.e. oligo-/amenorrhoea, hyperandrogenism, obesity, elevated serum testosterone or LH concentrations). Thus, using this definition it is possible to have PCOS when polycystic ovaries are present together with obesity as the only other sign. However, it is usually the case that more than one symptom, sign or biochemical disturbance co-exists with polycystic ovaries. Furthermore, the condition is dynamic and features in an individual may change over time. Third, the North American definition (PCOS2) requires evidence of hyperandrogenism and ovulatory dysfunction, in the absence of non-classic adrenal hyperplasia, without specific evidence of polycystic ovarian morphology. Nevertheless, it is widely recognized in the USA that positive ovarian findings predominate and there is considerable overlap between the European and USA definitions. Hence a truly international consensus meeting has been long-awaited.

Heterogeneity of PCOS

A few years ago we reported what we believe to be the largest published series of women having polycystic ovaries detected by ultrasound scan (Balen et al., 1995). All of the patients had at least one symptom of polycystic ovary syndrome, and the definition ‘PCOS1’ was employed. In total, 38% of the women were overweight, body mass index (BMI) (>25kg/m²). Obesity was significantly associated with an increased risk of hirsutism, menstrual cycle disturbance and an elevated serum testosterone concentration. Obesity was also associated with an increased rate of infertility and menstrual cycle disturbance. In total, 26% of patients with primary infertility and 14% of patients with secondary infertility had a BMI >30kg/m². Approximately 30% of the patients had a regular menstrual cycle, 50% had oligomenorrhoea and 20% amenorrhea. In this study the classical endocrine features of raised serum LH and testosterone were found in only 39.8 and 28.9% of patients respectively (Balen et al., 1995).

Many other groups have similarly reported heterogeneity in their populations with PCOS, for example, Franks’ series, from England, related to 300 women recruited from a specialist endocrine clinic (Franks, 1989). Some years earlier Goldzieher compiled a comprehensive review of 1079 cases of surgically proven polycystic ovaries (Goldzieher, 1981). The features of these series are represented in Tables I and II.

Although the frequency of clinical symptoms and signs in these women are similar, it is difficult to know if the criteria for hirsutism, acne and alopecia are comparable between the studies. The differences noted in the prevalence of menstrual cycle disturbance and infertility probably reflect selection bias created by the specialist nature of the clinics from which the women for these studies were recruited. Of particular note is that the women included in the Goldzieher review demonstrated symptomatology which at that time was considered significant enough to warrant surgical intervention, and thus the recorded frequencies of amenorrhoea and infertility would be expected to be higher. The prevalence of obesity is consistently high in all of these studies and obese women with polycystic ovaries were found to be more likely to be hirsute and to have menstrual cycle irregularities than lean women with polycystic ovaries (Franks, 1989; Balen et al., 1995). The frequencies noted in these studies are compared with studies where recruitment was based on more ‘normal’ populations of women (see below).

The biochemical features of these women with PCOS are not easily compared as the criteria for elevated serum concentrations of LH, testosterone and prolactin and their methods of measurement were not consistent between the
studies. However, raised levels of LH and testosterone are clearly shown to be common, though not universal features of PCOS, whilst elevated prolactin concentrations are less commonly noted.

In the Franks study (1989), and in an earlier study (Conway et al., 1989) which concerned an early subset from the same database used in Balen’s study, (Balen et al., 1995) the results of the women with PCOS were compared with those obtained from ‘reference’ groups of ‘normal’ women who were described as having normal menstrual cycles and normal ovaries on ultrasound. Conway (1989) demonstrated a higher mean ovarian volume in the women with ultrasound diagnosed polycystic ovaries compared with the control group. In addition, Franks (1989), with a larger number of controls, demonstrated a significantly larger uterine area, and a nearly double mean ovarian volume in the PCOS group.

Each study attempted to identify direct associations between biochemical and clinical features within the women with PCOS. Franks found BMI to be positively associated with hirsutism and menstrual cycle disturbances. Balen et al. (1995) described highly significant correlations between BMI and hirsutism, menstrual cycle disturbances and infertility, and elevated levels of serum testosterone (Balen et al., 1995). BMI was also found to correlate with ovarian volume and uterine cross-sectional area. It is probable that the much larger population observed by Balen et al. allowed for the detection of some associations which may not have been noted in the smaller sample size in Franks’ earlier study. Alternatively, the discrepancies between the studies may reflect the population biases of each study.

High serum LH concentrations were found to be associated with infertility or menstrual cycle disturbances in both of the studies. In the study by Balen et al. (1995), high serum testosterone levels were associated with an increased risk of hirsutism, infertility, and cycle disturbances. Ovarian volume was significantly correlated with serum LH and with testosterone concentrations. Other authors have attempted to correlate predictors for the diagnostic criteria of women with PCOS. For example, one study (Fox et al., 1991) found that a combination of the free androgen index (FAI) with serum LH concentration was the most accurate combination for making the diagnosis of PCOS in women with oligomenorrhea. This group found that the progesterone challenge test, as an assay of estrogenisation, was also a good predictor and did not require the measurement of sex hormone binding globulin (SHBG)—an expensive and less commonly used test. In another series of women with oligomenorrhea, independent correlations with ovarian morphology were identified with LH concentrations and androgen levels (Pache et al., 1993). Furthermore, markers of insulin resistance correlated with ovarian volume and stromal echogenicity, which in turn have been correlated with androgen production (Pache et al., 1993; Dewailly et al., 1994; Kyei-Mensah et al., 1996).

### Population-based studies

Estimates of the prevalence of PCOS are greatly affected by the nature of the population which is being assessed. Populations of women who are selected on the basis of the presence of a symptom associated with the syndrome (e.g. hirsutism, acne and menstrual cycle disturbances) would be expected to demonstrate a prevalence greater than that which exists in the general population.

In a study of 173 women presenting with anovulation or hirsutism, a study (Adams et al., 1986) found the prevalence of polycystic ovaries (using ultrasound criteria for diagnosis) to be 26% in women with amenorrhea, 87% in women with oligomenorrhea and 92% in women with hirsutism and regular
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In another study of 389 women presenting with menstrual cycle disturbances (Gadir et al., 1992), the prevalence of polycystic ovaries was found to be 65%. Whereas in a third study of 350 women presenting with hirsutism and/or androgenic alopecia (O’Driscoll et al., 1994), polycystic ovaries were identified in 60% of 282 women whose ovaries were successfully visualized by ultrasound. In a fourth study examining 119 women with acne (Peserico et al., 1989), but no menstrual disorders, obesity, or hirsutism, the prevalence was found to be 45%. Thus reflecting that polycystic ovaries, and by definition PCOS, are very common in these specifically defined groups of women. However, the prevalence of PCOS in the general population has not been definitively determined. A cross-sectional study (Knochenhauer et al., 1998) examined the prevalence of PCOS in a population of American women and determined a prevalence rate of 4%. However this study applied the USA definition of PCOS and did not include polycystic ovarian morphology on ultrasound as part of the defining criteria.

Several studies have been performed to attempt to determine the prevalence of polycystic ovaries, as detected by ultrasound alone, in the general population, and have found remarkably similar prevalence rates in the order of 17–22%. The study designs and results are summarized in Table III. All of the studies used transabdominal ultrasound for the diagnosis of polycystic ovaries except for one (Cresswell et al., 1997), who converted to a transvaginal scan if the transabdominal picture was unclear.

The study populations recruited by Polson et al. (1988), Tayob et al. (1990) and by Botis et al. (1995) were all subject to a degree of selection bias due to the fact that they recruited women from hospital-associated populations (although Polson’s study admittedly recruited hospital workers and not patients) and not from the general population (Polson et al., 1988; Tayob et al., 1990; Botis et al., 1995). The low response rates achieved in community based studies (Clayton et al., 1992; Farquhar et al., 1994) might reduce confidence in the validity of their estimates of prevalence, but reassuringly Cresswell et al. (1997) who achieved a much higher response rate in their sample, determined a very similar prevalence. In this study women were first interviewed at home by a trained fieldworker before being invited to attend for a scan (Cresswell et al., 1997). The establishment of this personal rapport may have contributed to the higher response rate achieved in this cross-sectional study than in other studies (Clayton et al., 1992; Farquhar et al., 1994) which required participants to attend for a scan outright. However, in the absence of a large, cross-sectional population-based study, the prevalence rates detected above provide the best estimates of the occurrence of polycystic ovaries in the ‘normal’ population. The pooled prevalence is 19%, indicating that polycystic ovaries (as defined by their ultrasound appearance) are extremely common.

The study by Tayob et al. was primarily designed to identify women who were at risk of breakthrough ovulation while taking the combined oral contraceptive pill (Tayob et al., 1990).

Although the ovaries were assessed by transabdominal ultrasound, blood samples were not collected and clinical symptoms of PCOS were not recorded. In the other studies,
clinical and biochemical features associated with PCOS were compared between women with and without polycystic ovaries. In all of the studies hirsutism was identified more commonly in women with polycystic ovaries. Menstrual cycle abnormalities were also found to be more common in the polycystic ovary groups, except in one study (Clayton et al., 1992) which detected no significant difference in menstrual patterns when comparing women with polycystic and normal ovaries. In the study by Polson et al. (1988) a surprisingly low frequency of irregular menstrual cycles were detected in those women with normal ovaries (Polson et al., 1988). The explanation for this is not clear as the definition of irregular cycles is similar to that used in other studies, but may be related to the way in which menstrual histories were recorded from the participants. Botis et al. (1995) noted a greater tendency towards obesity in their group of women with polycystic ovaries, but significant differences in obesity were not identified in the other reports (Botis et al., 1995). All of these studies determined higher mean ovarian volumes in women with polycystic ovaries when compared with women with normal ovaries. The frequency of symptoms and signs identified in women with and without polycystic ovaries is summarized in Table IV.

The inconsistencies between these studies may be due in part to differences in the definitions used for each symptom or sign which was recorded. However, the method of recruitment may also be relevant as the community based studies (Clayton et al., 1992) Farquhar et al. and Cresswell et al. show frequencies of menstrual cycle disturbances and of hirsutism which are much lower than those recorded in the larger studies of women with PCO recruited from reproductive/endocrine clinics (Farquhar et al., 1994b; Cresswell et al., 1997) (See Table I). One study (Botis et al., 1995) and another—which recorded clinical information about menstrual irregularities only (Polson et al., 1988)—recorded frequencies which resemble more closely those previously determined in the hospital-based studies, suggesting that their population was subject to greater selection bias.

Comparison of hormone levels between women with and without polycystic ovaries was further complicated by the high proportion of women using the OCP in these populations. This necessitated division of the ‘normal’ and ‘polycystic ovary’ groups of women into further subgroups dependent upon their oral contraceptive status. The differences in hormone levels which were detected were by no means consistent across the studies. For example, one study (Polson et al., 1988) did not detect any significant difference in the mean level of serum LH or testosterone concentrations between women with and without polycystic ovaries, but did identify a difference in the numbers of LH and testosterone observations which were above the normal range in women with polycystic ovaries. Clayton et al. detected significantly higher LH levels in women with polycystic ovaries compared with those with normal ovaries in their group of non-OCP users, but found no significant differences between the groups for any of the other hormones measured (Clayton et al., 1992). Farquhar et al. were only able to identify higher levels of free testosterone in their non-OCP group with polycystic ovaries (Farquhar et al., 1994b). Botis et al. who subdivided their group of women with polycystic ovaries into those with and without menstrual irregularities, determined significantly higher LH/FSH ratios and testosterone levels in those women with polycystic ovaries who had menstrual symptoms when compared with controls (Botis et al., 1995). Cresswell et al. reported significantly higher mean plasma concentrations of LH, and testosterone in their group of women with polycystic ovaries, and a higher ratio of LH to FSH (Cresswell et al., 1997).

Despite the problems of small sample populations and inconsistent methodology, these studies indicate a high prevalence (19%) of polycystic ovaries in the normal population. They have also shown that many of these women have symptoms and signs which may be attributable to PCOS, but reinforce the observation that in some women with polycystic ovaries no clinical or biochemical abnormalities are detected. The question of whether polycystic ovaries alone are pathological or a normal variant of ovarian morphology is still debated. Whilst the spectrum of normality might include the presence of polycystic ovaries in the absence of signs or symptoms of PCOS, there is evidence that women with polycystic morphology alone show typical responses to stresses such as gonadotrophin stimulation during IVF treatment or to weight gain as stimulated by sodium valproate therapy (Isojarvi et al., 1993; MacDougall et al., 1993). The difficulty in answering this question lies in the fact that to date there are no large scale, longitudinal prospective studies of women with

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**Table IV. Frequency of clinical symptoms and signs in women with and without polycystic ovaries**

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<td>n = 33**</td>
<td>n = 116**</td>
<td>n = 43</td>
<td>n = 144</td>
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<td>Menstrual cycle disturbance (%)</td>
<td>76</td>
<td>1</td>
<td>29**</td>
<td>46</td>
<td>41</td>
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<td>Hirsutism (%)</td>
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<td>14</td>
<td>23</td>
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<td>Obesity (%)</td>
<td>–</td>
<td>–</td>
<td>33</td>
<td>23</td>
<td>35</td>
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<td>Infertility primary/secondary (%)</td>
<td>–</td>
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<td>12</td>
<td>26</td>
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*Includes only women who have tested their fertility.

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**Notes:**
- **a**Value includes only non-OCP users with PCO.
- **b**Percentage calculated for non-OCP users with PCO where n = 34.

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polycystic ovaries, and also in that the pathophysiology of polycystic ovaries has not been defined.

We studied 224 normal female volunteers aged 18–25 years and identified polycystic ovaries using ultrasound in 33% of participants (Michelmore et al., 1999). A total of 50% of the participants were using some form of hormonal contraception, but the prevalence of polycystic ovaries in users and non-users of hormonal contraception was identical. Polycystic ovaries in the non-users of hormonal contraception were associated with irregular menstrual cycles and significantly higher serum testosterone concentrations when compared with women with normal ovaries, however only a small proportion of women with polycystic ovaries (15%) had elevated serum testosterone concentrations outside the normal range. Interestingly there were no significant differences in acne, hirsutism, BMI or body fat percentage between women with polycystic and normal ovaries and hyperinsulinism and reduced insulin sensitivity were not associated with polycystic ovaries in this group. Also, no significant differences were identified for β-cell function between the groups, unlike other studies which have shown pancreatic β-cell dysfunction in women with PCOS when compared with controls (Dunaif and Finegood, 1996).

In our study, the prevalence of PCOS was as low as 8% using the USA definition for PCOS, or as high as 26% if the broader European criteria were applied. However, features included in the European criteria: (menstrual irregularity, acne, hirsutism, BMI >25, raised serum testosterone, or raised LH) were found to occur frequently in women without polycystic ovaries, and 75% of women with normal ovaries had one or more of these attributes. Sub-group analyses of women according to the presence of normal ovaries, polycystic ovaries alone, or polycystic ovaries and features of PCOS, revealed a greater mean BMI in women with PCOS, but also indicated lower fasting insulin concentrations and greater insulin sensitivity in polycystic ovary and PCOS groups when compared with women with normal ovaries, which is in contrast to studies of older women (Conway et al., 1993; Dunaif, 1997). These interesting findings were difficult to interpret in the light of the current understanding of PCOS, but forced us to consider the possibility that this young, mainly non-overweight population, might reflect women early in the natural history of the development of PCOS, and that abnormalities of insulin metabolism might evolve following weight gain in later life.

In our study we were also able to determine genotype frequencies for the insulin gene minisatellite (INS VNTR) which has been linked to anovulatory PCOS (Waterworth et al., 1997). Genotype frequency distributions were found to be similar in women with polycystic and those with normal ovaries. However, subdivision of those women with polycystic ovaries according to the severity of PCOS (classified using polycystic ovaries alone, polycystic ovaries and PCOS by European criteria, and polycystic ovaries and PCOS by USA criteria), revealed increasing frequency of the III/III genotype with increasing severity of the PCOS phenotype (Michelmore et al., 2001). This could suggest that the INS VNTR locus may determine clinical severity of PCOS in women with polycystic ovaries, however larger studies would be necessary to determine this conclusively.

**What is polycystic ovary syndrome?**

So is there evidence that the syndrome that we are discussing varies either in its prevalence or presentation around the world or in different racial groups within a country? Michelmore et al. (1999) demonstrated that 80% of those with PCO (which was 26% of those from the community) had features of PCOS based on the UK/European definition of PCOS, in their post-menarchal years (i.e. ages 18–24) (Michelmore et al., 1999). However, using the much more stringent USA criteria, which do not utilize ovarian morphology, the prevalence rate for PCOS ranged from 4.5–11.2% in an unselected group of white Europeans and blacks in a population-based study in Alabama (Knochenhauer et al., 1998), 9% in Greece (Diamanti-Kandarakis et al., 1999) and 6.5% in Spain (Asunciòn et al., 2000). The highest reported prevalence of PCO was 52%, amongst South Asian immigrants in Britain, of whom 49.1% had menstrual irregularity (Rodin et al., 1998). This study demonstrated that South Asian women with PCO had a comparable degree of insulin resistance to that of established type 2 diabetes mellitus. Nonetheless, there has been a paucity of data regarding the prevalence of PCOS among women of South Asian origin, among both migrant and native groups. Type 2 diabetes and insulin resistance have a high prevalence among indigenous populations in South Asia, with a rising prevalence among women. Insulin resistance and hyperinsulinaemia are common antecedents of type 2 diabetes, with a high prevalence in South Asians. Type 2 diabetes also has a familial basis, inherited as a complex genetic trait that interacts with environmental factors, chiefly nutrition, commencing from fetal life. We are currently exploring the hypothesis that ethnic variations in the overt features of PCOS (i.e. symptoms of hyperandrogenism, menstrual irregularity and obesity) in women of South Asian descent are linked to the higher prevalence and degree of insulin resistance in South Asians. We have already found that South Asians with anovular PCOS have greater insulin resistance and more severe symptoms of the syndrome than anovular Caucasians with PCOS (Wijeyaratne, Balen, Barth and Belchetz, unpublished observations). Furthermore, we have found that women from South Asia, living in the UK, appear to express symptoms at an earlier age than their Caucasian British counterparts.

Generally, ethnic differences in the prevalence of PCOS have not been well explored. An increased rate of PCOS among Caribbean Hispanic women has been reported (Dunaif et al., 1993). However, in a sample of 195 black women and 174 white women in the USA, the prevalence of PCOS among black women was found to be comparable with that of whites (3.4 versus 4.7%) (Knochenhauer et al., 1998). There may also be ethnic variation in overt features of PCOS when the prevalence of biochemical manifestations is similar across the races (Solomons, 1999). A study carried out comparing women with PCOS from the USA, Japan and Italy reported less obesity in Japanese women, yet comparable rates of androgen excess and insulin resistance (Carmina et al., 1992). The question remains as to whether differences in expression of the syndrome are due to dietary and lifestyle factors or genetic variations in hormone actions, such as polymorphisms.
in gonadotrophin subunits or receptor function (affecting the expression of androgens, gonadotrophins or insulin). The genetics of PCOS is beyond the scope of this paper and there are a number of candidate genes that have been proposed (Franks et al., 2001). It may be that some families or racial groups have genetic differences that effect the expression or presentation of PCOS—and we and others are working to try and identify such variations.

Conclusions
PCOS is one of the most common endocrine disorders and may present at one end of the spectrum with the single finding of polycystic ovarian morphology as detected by pelvic ultrasound. At the other end of the spectrum may present at one end of the spectrum with the single presentation of PCOS is probably the same the world over, although without an agreed definition one cannot say for sure that this is the case. There may be factors that effect expression and presentation—whether because of racial differences in the colour and distribution of hair (e.g. Japanese versus Mediterranean women) or variations in hormone production and receptor activity. Fundamentally the underlying condition is likely to be the same. Management should be directed towards an individual’s needs (whether cosmetic, reproductive or metabolic) and attention given to potential long term sequelae. In order to compare treatments and define the genotype we must be clear on the phenotype and so an international consensus is required.

References


