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Chapter 1

Overview and definitions of polycystic ovary syndrome and the polycystic ovary

Adam Balen

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous collection of signs and symptoms that, gathered together, form a spectrum of a disorder with a mild presentation in some but a severe disturbance of reproductive, endocrine and metabolic function in others. The pathophysiology of PCOS appears to be multifactorial and polygenic. The definition of the syndrome has been much debated, with key features including menstrual cycle disturbance, hyperandrogenism and obesity (see Box 1.1). There are many extra-ovarian aspects to the pathophysiology of PCOS but ovarian dysfunction is central.

The joint European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) consensus meeting in 2003 agreed a refined definition of PCOS, namely the presence of two of the following three criteria:[1] (1) oligo-ovulation and/or anovulation, (2) hyperandrogenism (clinical and/or biochemical), (3) polycystic ovaries; with the exclusion of other causes of menstrual cycle disturbance or androgen excess (see Table 1.1).

The morphology of the polycystic ovary has been defined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or an increased ovarian volume (more than 10 cm^3).[2]

There is considerable heterogeneity of symptoms and signs among women with PCOS and, for an individual, these may change over time.[3] PCOS appears to be familial and various aspects of the syndrome may be differentially inherited.[4] Polycystic ovaries can even exist without clinical signs of the syndrome, which may then become expressed over time. There are a number of interlinking factors that may affect expression of PCOS. For example, a gain in weight is associated with a worsening of symptoms, while weight loss may ameliorate the endocrine and metabolic profile and symptomatology.[5]

Various factors influence ovarian function, and fertility is adversely affected by an individual being overweight or having elevated serum concentrations of luteinising hormone (LH). Strategies to induce ovulation include weight loss, oral anti-estrogens (principally clomifene citrate), parenteral gonadotrophin therapy and laparoscopic ovarian surgery.

The features of obesity, hyperinsulinaemia and hyperandrogenaemia that are commonly seen in PCOS are also known to be factors that confer an increased risk

Box 1.1 Signs and symptoms of polycystic ovary syndrome

Symptoms:
- hyperandrogenism (acne, hirsutism, alopecia – *not* virilisation)
- menstrual disturbance
- infertility
- obesity
- sometimes: asymptomatic, with polycystic ovaries on ultrasound scan

Serum endocrinology:
- increasing fasting insulin (not routinely measured; insulin resistance or impaired glucose tolerance assessed by oral glucose tolerance test)
- increasing androgens (testosterone and androstenedione)
- increasing luteinising hormone, usually normal follicle-stimulating hormone
- decreasing sex hormone-binding globulin, results in elevated 'free androgen index'
- increasing estradiol and estrone (neither measured routinely as there is a very wide range of values)
- increasing prolactin

Possible late sequelae:
- diabetes
- dyslipidaemia
- hypertension
- cardiovascular disease
- endometrial carcinoma
- breast cancer (although data are conflicting)

of cardiovascular disease and type 2 diabetes (see Table 1.2).[6] There are studies which indicate that women with PCOS have an increased risk for these diseases that pose long-term risks for health, and this evidence has prompted debate as to the need for screening women for polycystic ovaries.

Elevated serum concentrations of insulin are more common in both lean and obese women with PCOS than in weight-matched women without the syndrome. Indeed, it is hyperinsulinaemia that seems to be key to the pathogenesis for many women with PCOS as insulin stimulates androgen secretion by the ovarian stroma and appears to affect the normal development of ovarian follicles, both by the adverse effects of androgens on follicular growth and possibly also by suppressing apoptosis and permitting the survival of follicles otherwise destined to disappear. The realisation of an association between hyperinsulinaemia and PCOS has resulted in the use of insulin-sensitising agents such as metformin, although they have not provided the benefit that was originally hoped.[7]

What is polycystic ovary syndrome?

Polycystic ovaries are commonly detected by ultrasound or other forms of pelvic imaging, with estimates of the prevalence in the general population being of the order of 20–33%.[8,9] However, not all women with polycystic ovaries demonstrate the clinical and biochemical features that define the syndrome. 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.

Table 1.1 Investigations for polycystic ovary syndrome

Test	Normal range (may vary with local laboratory assays)	Additional points
Pelvic ultrasound		To assess ovarian morphology and endometrial thickness; a transabdominal scan is usually adequate in women who are not sexually active (depends on body habitus)
Testosterone (T)	0.5–3.5 nmol/litre	A total T measurement is adequate for general screening; it is unnecessary to measure other androgens unless the total testosterone is more than 5 nmol/litre, in which case referral is indicated
Sex hormone-binding globulin (SHBG)	16–119 nmol/litre	Insulin suppresses SHBG, resulting in a high FAI in the presence of a normal total T; the measurement of SHBG is not required in routine practice and will not affect management
Free androgen index (FAI): T × 100 / SHBG	< 5	
Estradiol		Measurement is generally unhelpful to make diagnosis; estrogenisation may be confirmed by endometrial assessment
Luteinising hormone (LH)	2–10 IU/litre	FSH and LH are best measured during days 1–3 of a menstrual bleed; if oligomenorrhoeic or amenorrhoeic, then random samples are taken
Follicle-stimulating hormone (FSH)	2–8 IU/litre	
Antimüllerian hormone (AMH)	Assays differ and still being evaluated	AMH is a good representative of the number of antral follicles[47]
Prolactin	< 500 mU/litre	Measures if the woman is oligomenorrhoeic or amenorrhoeic
Thyroid-stimulating hormone (TSH) for thyroid function	0.5–5 IU/litre	
Fasting insulin	< 30 mU/litre	Not routinely measured; insulin resistance can be assessed by an oral glucose tolerance test

Table 1.2 Definitions of glucose tolerance

	Test	
	Fasting glucose (mmol/litre)	2-hour glucose (mmol/litre)
Diabetes	≥ 7.0	≥ 11.1
Impaired glucose tolerance (IGT)	< 7.0	≥ 7.8 and < 11.1
Impaired fasting glycaemia	≥ 6.1 and < 7.0	< 7.8

A 75 g oral glucose tolerance test should be performed in women with PCOS and body mass index (BMI) > 30 kg/m²; it has been suggested that South Asian women should have an assessment of glucose tolerance if their BMI is greater than 25 kg/m² because of the greater risk of insulin resistance at a lower BMI than seen in the white population

Despite the ESHRE/ASRM consensus meeting and definitions, controversy still exists in some quarters over a precise definition of the syndrome and whether or not the diagnosis should require confirmation of polycystic ovarian morphology. The original case series of Stein and Leventhal[10] in 1935 described seven women who had enlarged polycystic ovaries and amenorrhoea. Over the years, it was appreciated that

the cardinal symptoms are chronic anovulation (oligomenorrhoea or amenorrhoea) and hyperandrogenism (usually hirsutism and acne, and sometimes alopecia). The 1990 National Institutes of Health (NIH) conference on PCOS recommended that the 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 was not essential (in a paper that is in book form only and no longer readily available).[11] In Europe and Australasia, ovarian imaging by ultrasound became an important component in the diagnosis, largely because ovarian morphology was part of the original disease description. Despite a degree of concordance between the NIH definition and the addition of ovarian imaging, it became necessary to try to gain transatlantic harmony with a new consensus held under the auspices of the ESHRE and the ASRM, which resulted in the 'Rotterdam criteria'.[1]

The generally accepted view in Europe and much of the world is that a spectrum exists that ranges 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.

A new group, the Androgen Excess and PCOS Society (AEPS), has more recently proposed that PCOS should be further redefined.[12] The latest suggestion is that two criteria are required: hyperandrogenism (clinical hirsutism and/or biochemical hyperandrogenaemia) and ovarian dysfunction (oligo-ovulation or anovulation and/or polycystic ovaries) after exclusion of other causes of androgen excess or related disorders.

The arguments for a 'tighter definition' include the potential for better prospects for providing genetic and proteomic causes of PCOS and concerns about avoiding overdiagnosis because of 'potential lifelong and insurability implications', yet the latest consensus 'recognises that there may be a number of women who have features suggestive of PCOS but who do not fulfil the criteria'.[12] Furthermore, there appears not to have been complete consensus, as some members of the AEPS group 'disagreed with the strong emphasis placed on hyperandrogenism', particularly as there is a high degree of inaccuracy in both the clinical and biochemical assessment of androgen excess.[12,13]

The latest proposed definition also raises concerns about allowing the presence of polycystic ovaries as a separate defining feature. We recognise that polycystic ovaries are detected in 19–33% of women in the general population, of whom approximately 80% have symptoms of PCOS, albeit often mild.[9] The biochemical features of the syndrome, namely elevated serum concentrations of testosterone, androstenedione, LH and insulin, may vary between individuals and change with time. The ovary is the source of excess androgens, which result from dysregulation of steroidogenesis combined with an excess of external promoters, principally LH and insulin.

Many consider that insulin resistance and hyperinsulinaemia are at the heart of the pathophysiology of PCOS but these features are clearly not essential in the development of the syndrome, particularly in lean women. Nevertheless, even if insulin resistance/hyperinsulinaemia is not the initiating cause, it is certainly an amplifier of hyperandrogenism in those who gain weight. The common association of PCOS and obesity has a synergistic deleterious impact on glucose homeostasis and can worsen both hyperandrogenism and anovulation. Hyperinsulinaemia also decreases the synthesis of sex hormone-binding globulin (SHBG) by the liver, leading to an increase in circulating free testosterone.

There are likely to be many routes to the development of PCOS, including genetic predisposition, environmental factors and disturbances of a number of endocrine pathways. There also appear to be significant racial differences in the expression of

PCOS, for example women from South Asia have worse symptoms, hormonal and metabolic disturbance and a greater likelihood of developing type 2 diabetes.[14]

PCOS is a well-recognised and common condition that causes considerable morbidity. A pragmatic approach is required in making the diagnosis and excluding other causes of menstrual cycle disturbance and hyperandrogenism.[15] Too exclusive a definition would leave many women at the milder end of the PCOS spectrum without a diagnosis even though they have an equal right to medical care and management of their symptoms. Indeed, there is significant psychological morbidity and negative impact on quality of life related to PCOS, even in adolescence,[16] whether related to the dermatological manifestations, disturbed menstrual cycle and subsequent infertility or associated obesity and metabolic problems. The diagnosis of mild PCOS or even the presence of polycystic ovaries alone may alert the individual and allow the physician to offer advice, for example about lifestyle, that may potentially help prevent a worsening of the syndrome and increased long-term morbidity.[17] In conclusion, the Rotterdam consensus definition of PCOS satisfies these criteria and allows a pragmatic approach for both diagnosis and management.

Defining the polycystic ovary: historical and histopathological considerations

Historically, the detection of a polycystic ovary required visualisation of the ovaries at laparotomy and histological confirmation following biopsy.[10] 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 follicle-stimulating hormone (FSH) and abnormalities of estrogen secretion, described an endocrine profile that many believed to be diagnostic of PCOS. Well-recognised clinical presentations included menstrual cycle disturbances (oligomenorrhoea/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 was thwarted by the heterogeneity of presentation of the disorder.

Numerous descriptions have been made of the morphology of the polycystic ovary and these have been refined over time, alongside advances in imaging technology. The histology of the polycystic ovary was an ovary with prominent theca, fibrotic thickening of the tunica albuginea and multiple cystic follicles.[10] The number of antral follicles (2–6 mm in diameter) was described as 'excessive' by Goldzieher and Green in 1962 but not quantified.[18] Good correlation has been shown between ultrasound diagnoses of polycystic morphology and the histopathological criteria for polycystic ovaries by studies examining ovarian tissue obtained at hysterectomy or after wedge resection.[19] The histological data of Hughesdon[20] indicated a two- to three-fold increase in the follicle number in polycystic ovaries, from the stage of primary follicles up to tertiary follicles, and identified the cystic structures as follicles as opposed to pathological cysts. A more recent study of ovarian cortical biopsies described a lower proportion of healthy primordial follicles in polycystic ovaries compared with

normal ovaries and a greater proportion of primary follicles that had started growing, indicating abnormalities in folliculogenesis.[21]

Ultrasound descriptions of the polycystic ovary

The advent of high-resolution ultrasound scanning has provided a non-invasive technique for the assessment of ovarian size and morphology. Although the ultrasound criteria for the diagnosis of polycystic ovaries have not been universally agreed, the characteristic features are accepted as being an increase in the number of follicles and the amount of stroma as compared with normal ovaries. Ultrasound was initially used to describe the ovarian appearance in women classified as having PCOS (by symptoms and serum endocrinology) rather than to make the diagnosis. There was often no record of timing of the scan in relation to the menstrual cycle in either women with suspected PCOS or those in a control group.

The transabdominal ultrasound criteria of Adams *et al.*[22] defined a polycystic ovary as one that contains, in one plane, at least ten follicles (usually between 2 and 8 mm in diameter) arranged peripherally around a dense core of ovarian stroma or scattered throughout an increased amount of stroma. Polycystic ovaries were found to have a higher volume ($14.6 \pm 1.1\,cm^3$) than either multicystic ($8.0 \pm 0.8\,cm^3$) or normal ovaries ($6.4 \pm 0.4\,cm^3$).[23] Uterine cross-sectional area was also greater in women with PCOS than those with multicystic or normal ovaries ($26.0 \pm 1.4\,cm^2$ versus $13.1 \pm 0.9\,cm^2$ versus $22.4 \pm 1.0\,cm^2$), which is a reflection of the degree of estrogenisation.

Multicystic and polycystic ovaries

The multicystic ovary is one in which there are multiple (at least six) cysts, usually 4–10 mm in diameter, with normal stromal echogenicity.[23] This is the characteristic appearance during puberty and in women recovering from hypothalamic amenorrhoea – both situations being associated with follicular growth without consistent recruitment of a dominant follicle. There may be confusion among inexperienced ultrasonographers, radiologists and gynaecologists, hence the need for careful consideration of the clinical picture and endocrinology. Polycystic ovaries may be evident in adolescent girls as a distinct entity from multicystic ovaries.[24] Indeed, it appears that PCOS manifests for the first time during the adolescent years, which are critical for future ovarian and metabolic function.

Transvaginal ultrasound

Transabdominal ultrasound has been largely superseded by transvaginal scanning because of greater resolution and, in many cases, patient preference, as the need for a full bladder is avoided, which saves time and may be more comfortable.

A study that set out to assess variability in the detection of polycystic and normal ovaries demonstrated intra-observer agreement of 69.4% and inter-observer agreement of 51%.[25] This suggests either that the diagnostic criteria are too subjective or that their measurement is too insensitive. Amer *et al.*[25] concluded that the use of three-dimensional ultrasound might provide a more reliable and reproducible diagnostic tool, although they did not perform a similar evaluation of observer variability.

The Rotterdam consensus definition[2] was based largely on the paper by Jonard *et al*,[26] who studied 214 women with PCOS and 112 with normal ovaries to determine the importance of follicle number per ovary (FNPO). Three different categories of follicle size were analysed separately (2–5, 6–9 and 2–9 mm). The mean FNPO was

similar between normal and polycystic ovaries in the 6–9 mm range but significantly higher in the polycystic ovaries in both the 2–5 and 2–9 mm ranges.[26] Within the 2–5 mm range, there were significant positive correlations with serum testosterone, androstenedione and LH concentrations. There was an inverse correlation within the 6–9 mm range between FNPO and testosterone, body mass index and fasting insulin concentrations, and a positive correlation with inhibin B concentrations. The mean FNPO in the 2–5 mm range was significantly greater in the polycystic ovaries than in those of women in the control group, while it was similar in the 6–9 mm range. The authors suggest that intra-ovarian hyperandrogenism promotes excessive early follicular growth up to 2–5 mm, with more follicles able to enter the growing cohort which then become arrested at the 6–9 mm size. An FNPO of 12 or more follicles of 2–9 mm gave the best threshold for the diagnosis of PCOS (sensitivity 75%; specificity 99%).[26]

The Rotterdam consensus definition of the polycystic ovary proposed the presence of 12 or more follicles of 2–9 mm diameter (as a mean of both ovaries) and/or increased ovarian volume (more than 10 cm^3).[2] Further work by Jonard *et al.*[27] has suggested reducing the threshold volume to 7 cm^3. The same group reported a series of 457 women with polycystic ovaries and found that the number of 2–5 mm follicles gave the strongest correlation with the severity of follicular arrest, followed by age and then fasting insulin concentration.[28]

Stromal echogenicity

The increased echodensity of the polycystic ovary is a key histological feature[20] but is a subjective assessment that may vary depending on the settings of the ultrasound machine and the patient's body habitus. Stromal echogenicity has been described in a semi-quantative manner with a score of 1 for normal, 2 for moderately increased and 3 for frankly increased.[29] In this study, the total follicle number of both ovaries combined correlated significantly with stromal echogenicity. Follicle number also correlated significantly with free androgen index. A further study comparing women with PCOS with women in a control group found that the sensitivity and specificity of ovarian stromal echogenicity in the diagnosis of polycystic ovaries were 94% and 90%, respectively.[30]

Echogenicity has been quantified as the sum of the product of each intensity level (ranging from 0 to 63 on the scanner) and the number of pixels for that intensity level divided by the total number of pixels in the measured area:

$$\text{mean} = \left(\sum x_i f_i\right) \Big/ n$$

where n = total number of pixels in the measured area, x = intensity level (from 0 to 63) and f = number of pixels corresponding with the level.[31] The stromal index was calculated by dividing the mean stromal echogenicity by the mean echogenicity of the entire ovary to correct for cases in which the gain was adjusted to optimise image definition.[31]

Another approach used a 7.5 MHz transvaginal probe with histogram measurement of echogenicity.[32] The mean echogenicity was defined as the sum of the product of each intensity level (from 0 to 63) using the same formula as Al-Took *et al.*[31] Women with PCOS had greater total ovarian volume, stromal volume and peak stromal blood flow compared with normal ovaries, yet mean stromal echogenicity was similar. The stromal index was higher in PCOS owing to the finding of a reduced mean echogenicity of the entire ovary.[32] The inference was that the subjective impression of increased stromal echogenicity was due both to increased stromal volume and reduced

echogenicity of the multiple cysts. Morever, the increased stromal blood flow was suggested as a more relevant predictor of ovarian function.[32]

A large study compared 80 women with oligomenorrhoea/amenorrhoea and PCOS with a control group of 30 women using a 6.5 MHz transvaginal probe.[33] Based on mean ± 2 SD data from the control group, the cut-off values were calculated for ovarian volume (13.21 cm^3), ovarian total area (7.00 cm^2), ovarian stromal area (1.95 cm^2) and stromal : ovarian area ratio (0.34). The sensitivities of these parameters for the diagnosis of PCOS were 21%, 4%, 62% and 100%, respectively, suggesting that a stromal : ovarian area ratio above 0.34 is diagnostic of PCOS.[33] Further studies of a series of 418 women described stromal : ovarian area ratio as the most significant predictor of biochemical androgen excess, with above 0.32 as the best cut-off.[34,35]

Three-dimensional ultrasound, Doppler and MRI

Three-dimensional ultrasound requires longer time for storage and data analysis, increased training and more expensive equipment, yet good correlations have been found between stromal volume and serum androstenedione concentrations.[36] Three-dimensional ultrasound has been shown to be a good tool for the accurate measurement of ovarian volume and more precise than two-dimensional ultrasound. Stromal volume also positively correlated with serum androstenedione concentrations in PCOS.[36] The higher sensitivity of three-dimensional ultrasound has also suggested that an FNPO of more than 20 is a more accurate cut-off for the diagnosis of polycystic ovaries.[37]

Stromal hypertrophy itself appears to be secondary to increased blood flow.[38] A number of studies of colour Doppler measurement of uterine and ovarian vessel blood flow have demonstrated a low resistance index in the stroma of polycystic ovaries (that is, increased flow) and correlations with endocrine changes. Battaglia *et al.*[39] reported a good correlation between both the serum androstenedione concentration and the LH : FSH ratio and the number of small follicles, and the LH : FSH ratio also correlated well with the stromal artery pulsatility index. Ovarian blood flow has also been shown to correlate not only with sex steroid concentrations but also with the degree of insulin resistance.[40] The combination of three-dimensional ultrasound and assessment of stromal vascularisation are therefore important tools in the assessment of functional and endocrine disturbances in PCOS.[41,42]

The use of magnetic resonance imaging (MRI) for the visualisation of the structure of pelvic organs has been claimed to have even greater sensitivity than ultrasound for the detection of polycystic ovaries.[43] MRI may also be useful in adolescent girls, particularly in those who are obese with ovaries that may be difficult to visualise by transabdominal ultrasound.[44] 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.

Exclusion of related disorders

To establish the diagnosis of PCOS it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, Cushing syndrome and androgen-secreting tumours.[1] The measurement of total testosterone is usually sufficient in most populations. In some populations, however, 21-hydroxylase-deficient non-classic adrenal hyperplasia is more prevalent than in others and this can be excluded by measuring a basal morning 17-hydroxyprogesterone level.[45]

The routine exclusion of thyroid dysfunction in women deemed to be hyperandrogenic is of limited value, as the incidence of this disorder among women with

hyperandrogenism is no higher than that in normal women of reproductive age (approximately 5% of the female population). The measurement of thyroid-stimulating hormone may, therefore, be a useful screening test but is certainly not obligatory in the diagnosis of PCOS.

If the woman presents with oligo-ovulation/anovulation, it is necessary to measure serum FSH, LH and estradiol (E_2) levels to exclude hypogonadotrophic hypogonadism (low FSH, LH and E_2) or premature ovarian failure (high FSH and LH and low E_2). PCOS is part of the spectrum of normogonadotrophic normo-estrogenic anovulation (WHO group II).[46] A measurement of prolactin should also be performed to exclude hyperprolactinaemia, although women with PCOS as a sole diagnosis may sometimes have moderately elevated serum prolactin concentrations.[3]

There may be clinical suspicions of syndromes of severe insulin resistance (for example, for the diagnosis of the hyperandrogenic insulin-resistant acanthosis nigricans [HAIR-AN] syndrome), Cushing syndrome, androgen-secreting neoplasms or the use of high-dose exogenous androgens and, if so, these should be excluded.

Conclusion

PCOS is a syndrome with varied manifestations both within different populations and between different populations. With recent increases in the understanding of the pathophysiology of PCOS and the recognition of the importance of ultrasound in defining the morphology of the polycystic ovary, the syndrome has now been defined as the presence of two of the following three criteria: (1) oligo-ovulation and/or anovulation, (2) hyperandrogenism (clinical and/or biochemical), (3) polycystic ovaries; with the exclusion of other aetiologies of menstrual disturbance and androgen excess.

Key points

- There is considerable heterogeneity of symptoms and signs and these may change over time.
- The morphology of the polycystic ovary has been defined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (> 10 cm^3). A stromal : ovarian area ratio of more than 0.32 correlates with the degree of hyperandrogenism. The use of three-dimensional ultrasound technology may increase the cut-off to 20 follicles.
- Polycystic ovaries are commonly detected by ultrasound, with a prevalence in the general population of 20–33%, of whom approximately three-quarters will exhibit clinical features of the syndrome.
- Elevated serum concentrations of insulin are more common in both lean and obese women with PCOS than weight-matched women without PCOS and hyperinsulinaemia is a component of the pathogenesis of PCOS.
- Clinical hyperandrogenism is difficult to quantify and there are racial variations. Biochemical hyperandrogenism is assessed by a variety of assays, the methodology for which is fraught with problems.
- To establish the diagnosis of PCOS, it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, Cushing syndrome and androgen-secreting tumours.

References

1. Fauser B, Tarlatzis B, Chang J, Azziz R, Legro R, Dewailly D, *et al*; The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41–7.
2. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. *Hum Reprod Update* 2003;9:505–14.
3. Balen AH, Conway GS, Kaltsas G, Techatrasak K, Manning PJ, West C, *et al*. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. *Hum Reprod* 1995;10:2107–11.
4. Franks S, Gharani N, McCarthy M. Candidate genes in polycystic ovary syndrome. *Hum Reprod Update* 2001;7:405–10.
5. Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, *et al*. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* 1995;10:2705–12.
6. Rajkowha M, Glass MR, Rutherford AJ, Michelmore K, Balen AH. Polycystic ovary syndrome: a risk factor for cardiovascular disease? *Br J Obstet Gynaecol* 2000;107:11–18.
7. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database Syst Rev* 2010;(1):CD003053.
8. Polson DW, Adams J, Wadsworth J, Franks S. Polycystic ovaries – a common finding in normal women. *Lancet* 1988;1:870–2.
9. Michelmore KF, Balen AH, Dunger DB, Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. *Clin Endocrinol (Oxf)* 1999;51:779–86.
10. Stein I, Leventhal M. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 1935;29:181–5.
11. Zawadzki JK, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif A, Givens JR, Haseltine F, editors. *Polycystic Ovary Syndrome*. Boston: Blackwell Scientific; 1992. p. 377–84.
12. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, *et al*. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril* 2009;91:456–88.
13. Barth J, Yasmin E, Balen AH. The diagnosis of polycystic ovary syndrome: the criteria are insufficiently robust for clinical research. *Clin Endocrinol (Oxf)* 2007;67:811–15.
14. Wijeyaratne CN, Balen AH, Barth J, Belchetz PE. Clinical manifestations and insulin resistance (IR) in polycystic ovary syndrome (PCOS) among South Asians and Caucasians: is there a difference? *Clin Endocrinol (Oxf)* 2002;57:343–50.
15. Franks S. Diagnosis of polycystic ovarian syndrome: in defense of the Rotterdam Criteria. *J Clin Endocrinol Metab* 2006;91:786–9.
16. Jones GL, Hall JM, Balen AH, Ledger W. Health-related quality of life measurement in women with polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2008;14:15–25.
17. Balen AH, Homburg R, Franks S. Defining polycystic ovary syndrome. *BMJ* 2009;338:426.
18. Goldzieher MW, Green JA. The polycystic ovary. I. Clinical and histologic features. *J Clin Endocrinol Metab* 1962;22:325–38.
19. Takahashi K, Eda Y, Abu Musa A, Okada S, Yoshino K, Kitao M. Transvaginal ultrasound imaging, histopathology and endocrinopathy in patients with polycystic ovarian syndrome. *Hum Reprod* 1994;9:1231–6.
20. Hughesdon PE. Morphology and morphogenesis of the Stein-Leventhal Ovary and of so-called "hyperthecosis". *Obstet Gynecol Survey* 1982;37:59–77.
21. Webber LJ, Stubbs S, Stark J, Trew GH, Margara R, Hardy K, *et al*. Formation and early development of follicles in the polycystic ovary. *Lancet* 2003;362:1017–21.
22. Adams J, Polson DW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. *Br Med J* 1986;293:355–9.