Polycystic ovary syndrome

Stephen Franks

Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. It typically presents with symptoms of anovulation associated with clinical and/or biochemical evidence of androgen excess, although its spectrum of presentation includes women with hyperandrogenism who have regular periods. It is the most common cause of anovulatory infertility, and is now recognized as a major risk factor for the development of type 2 diabetes mellitus. Its aetiology remains unclear, but both genetic and environmental factors are involved. Typical biochemical features are raised serum concentrations of testosterone and luteinizing hormone, particularly in anovulatory women. The diagnosis is made primarily on clinical criteria. A finding of raised serum testosterone and/or luteinizing hormone complements the clinical diagnosis. In obese women, an oral glucose tolerance test should be undertaken to detect impaired glucose tolerance. Management of PCOS includes treatment of infertility, menstrual regulation in women who do not desire pregnancy and treatment of associated symptoms of hyperandrogenism. Another important aspect of management is the introduction of diet and lifestyle changes for overweight and obese women with PCOS; this improves fertility and also helps prevent the possible long-term consequences of the metabolic disturbance characteristic of anovulatory women with PCOS.

Keywords Anovulation; impaired glucose tolerance; insulin resistance; MRCP; ovary; type 2 diabetes mellitus

Key points

- Polycystic ovary syndrome is the most common endocrine disorder in women of reproductive age
- It is a major cause of menstrual disturbances, infertility and hirsutism
- Overweight and obesity worsen the clinical and biochemical abnormalities
- It is also a metabolic disorder and carries an increased risk of development of type 2 diabetes mellitus
- Its aetiology is uncertain, but genetic factors play an important part

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder in women. It typically presents with symptoms of anovulation (amenorrhoea, oligomenorrhoea, irregular cycles) associated with clinical and/or biochemical evidence of androgen excess (hirsutism, acne, alopecia). It is the most common cause of anovulatory infertility and is now recognized to be a major risk factor for the development of type 2 diabetes mellitus.[1–3]

Until recently, the most widely accepted clinical definition of PCOS was an association between hyperandrogenism and chronic anovulation in women without specific underlying disease of the adrenal or pituitary gland. Early descriptions were based on ovarian morphology, but this was not considered an essential requirement for diagnosis. However, the recent application of modern, high-resolution diagnostic ultrasonography has again tipped the balance towards a more morphologically based diagnosis. It is now recognized that the spectrum of presentation of PCOS includes both women with hirsutism and regular cycles, and non-hirsute women with anovulation.

In view of these findings, the diagnostic criteria for PCOS were revised at a consensus conference jointly sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in Rotterdam, the Netherlands, in 2003 (Table 1). The final report of the recent National Institutes of Health (NIH) Office of Disease Prevention Evidence Workshop on PCOS recommended the use of the broader (ESHRE/ASRM) diagnostic criteria (https://prevention.nih.gov/docs/programs/pcos/FinalReport.pdf). The diagnosis now requires the presence of at least two of the following features:

- polycystic ovaries
- oligo-ovulation or anovulation
- clinical and/or biochemical evidence of androgen excess.

In all recently published series characterized by the Rotterdam definition of PCOS, the largest subgroup is that defined by the NIH criteria (i.e. women with oligo- or anovulation together with clinical or biochemical evidence of androgen excess). The subclassification also has implications for predicting a risk of metabolic abnormalities (outlined below).

Aetiology

The aetiology of PCOS remains unclear, but both genetic and environmental (particularly nutritional) factors are involved. It is clear that the ovary is the principal source of the excess androgens, suggesting that this represents a primary ovarian disorder. This is supported by recent data indicating an abnormality of the earliest (gonadotrophin-independent) stages of ovarian follicle development, which may contribute to the mechanism of anovulation. PCOS is a familial disorder with evidence of heritability of endocrine and metabolic indices, but its genetic basis remains

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Diagnostic criteria for PCOS

US NIH, 1990	ESHRE/ASRM, Rotterdam, 2003
• Chronic anovulation	• Oligo-ovulation and/or anovulation
• Clinical and/or biochemical signs of hyperandrogenism	• Clinical and/or biochemical signs of hyperandrogenism
	• Polycystic ovaries

The NIH definition requires both criteria to make the diagnosis; the ESHRE/ASRM diagnostic criteria[4] require at least two of the three. In both definitions, the diagnosis assumes exclusion of other diagnoses that can replicate the symptoms of PCOS (e.g. non-classical congenital adrenal hyperplasia caused by 21-hydroxylase deficiency).

Table 1

uncertain. It is a complex trait in which more than one, and perhaps several, genes are involved. Progress in understanding the genetic basis of PCOS has come from recent genome-wide association studies that have shed new light on the aetiology of the syndrome.

Metabolic disorder in polycystic ovary syndrome

PCOS is now known to be associated with a characteristic metabolic disorder comprising hyperinsulinaemia, insulin resistance (Figure 1) and dyslipidaemia. There is an interaction between the effects of PCOS and obesity, such that the metabolic abnormalities in women with PCOS are amplified to a greater degree by obesity than in weight-matched controls. The metabolic abnormalities appear to be a particular feature of women with the classical syndrome (hyperandrogenism, anovulation), whereas equally hyperandrogenaemic women with polycystic ovaries but regular menses (or with anovulation without androgen excess) tend to exhibit normal secretion and action of insulin.

These findings have significant implications for long-term health. It is estimated that 15–40% of obese young women with PCOS have impaired glucose tolerance (IGT) or frank type 2 diabetes mellitus. In older women with a history of PCOS, the risk of developing type 2 diabetes is estimated to be 2–6-fold greater than in a matched reference population. Epidemiological studies are in broad agreement with these figures, suggesting a doubling of risk independent of obesity, and a 3–4-fold increase in risk in obese women with PCOS. A recently published population-based study emphasizes the role of obesity in increasing the risk of type 2 diabetes and suggests that the risk is not increased in lean women with PCOS.[3] As in individuals without PCOS, a family history of diabetes, previous gestational diabetes and, of course, IGT are additional factors that can amplify the risk. These women also appear to be at increased risk of cardiovascular disease, but there is little direct information regarding cardiovascular morbidity in these patients.

Investigations

Serum concentrations of testosterone and other androgens are raised in PCOS. Hypersecretion of luteinizing hormone (LH) – in the presence of a normal concentration of follicle-stimulating hormone (FSH) – is common, particularly in anovulatory women. It is a specific but not very sensitive index of the syndrome as many patients with all the other clinical and biochemical features of PCOS have normal LH concentrations. The diagnosis is made primarily on clinical and ultrasonographic criteria (Figure 2). The finding of raised serum testosterone and/or LH merely complements the clinical diagnosis.

Nevertheless, it is important to measure serum testosterone (or androstenedione) in hirsute women because greatly increased concentrations (i.e. more than twice the upper limit of the normal range) are an indication for further investigation. More serious causes of hirsutism (e.g. Cushing's syndrome, adrenal or ovarian tumours) are rare but can masquerade as PCOS (polycystic ovaries are commonly found on ultrasonography in these conditions), and measurement of serum testosterone is a useful screening procedure. A short history of hirsutism or rapid worsening of hyperandrogenic symptoms should alert the physician to the likelihood of one of these less common, but more serious, causes.

In contrast to patients with other causes of amenorrhoea, amenorrhoeic women with PCOS are not oestrogen-deficient: their serum oestradiol concentrations tend to be in the normal, early to mid-follicular phase range.

Investigation of metabolic abnormalities

Fasting plasma glucose estimation in overweight and obese women with PCOS (body mass index (BMI) >25 kg/m^2) identifies those with previously undiagnosed type 2 diabetes mellitus, but is not useful for uncovering IGT. The proceedings of the Rotterdam consensus meeting suggest that, in obese women (BMI >30 kg/m^2), an oral glucose tolerance test should be undertaken to detect IGT, and a fasting lipid profile determined. Obese patients with PCOS must be considered to be at risk of type 2 diabetes and should be offered dietary advice (see below). The BMI threshold for metabolic testing in women with PCOS may need to be adjusted (downwards) for populations at increased risk of insulin resistance (e.g. South-Asian women), and it has been suggested that waist circumference is a better index of risk than BMI.

Management

Management of PCOS includes:

- treatment of infertility
- menstrual regulation in women who do not desire pregnancy
- treatment of associated symptoms of hyperandrogenism
- prevention of the possible long-term consequences of the metabolic disturbance characteristic of anovulatory women with PCOS.

Induction of ovulation

Induction of ovulation can be accomplished in 75–80% of women with PCOS by using anti-oestrogens, typically clomifene citrate. This is given as a 5-day course at a starting dose of 50 mg/day at the onset of menses or a progestagen-induced withdrawal bleed. It is wise to monitor the first cycle of treatment

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