Polycystic ovary syndrome and type 2 diabetes

David Haslam

Polycystic ovary syndrome (PCOS) is the most common endocrine disturbance in women (Balen et al, 2006). PCOS and type 2 diabetes have a lot in common: they are both extremely widespread in the population, frequently encountered in primary care and is almost certain to increase in prevalence as a result of the current obesity epidemic. They are both directly linked with obesity as a consequence of the complex metabolic cascade stemming from the endocrine properties of visceral fat, which cause the clustering together of pathological conditions sometimes known as the metabolic syndrome. This article discusses the aetiology and diagnosis of PCOS, highlighting its links with type 2 diabetes, and clinical management of the condition.

Polycystic ovary syndrome (PCOS) and type 2 diabetes share an aetiological pathway so the two conditions often coexist: the presence of type 2 diabetes in obese women with PCOS is at least 11% (Dunaif, 1997). Both conditions may develop over a number of years before being diagnosed, both progress insidiously, usually as a consequence of weight gain. People with one or both conditions are at greater risk of cardiovascular disease (CVD) and other related comorbidities, including non-alcoholic steatohepatitis, sleep apnoea and certain cancers (Haslam and James, 2005).

Aetiology

The exact nature of the metabolic pathways involved is complex and not yet fully understood, but the fundamental link between the two conditions is insulin resistance. In the case of type 2 diabetes, insulin resistance drives up blood glucose levels by reducing glucose uptake by skeletal muscle, and increasing glucose production by the liver. Raised blood glucose concentration stimulates the pancreatic β-cells to produce more insulin, leading to compensatory hyperinsulinaemia. Eventually the β-cells fail to maintain insulin production, and impaired glycaemic control and frank diabetes develop.

Insulin resistance occurs only in muscle, liver and adipose tissue; other organs of the body are described as 'innocent bystanders' of the hyperinsulinaemic state, and react in different ways (Morrin, 2000). The ovaries respond to excess insulin by secreting androgens that are pathognomonic of PCOS, which in turn disrupt the entire hormonal axis. Androgens are absorbed by adipose stores, and converted under the influence of aromatase to oestrogens, which promote endometrial dysfunction, and are influential in the aetiology of postmenopausal breast cancer.

Insulin also appears to affect the normal development of ovarian follicles through its deleterious androgenic effects, and by

Article points

1. Diabetes and PCOS share aetiological pathways and a link with obesity, and thus often coexist.
2. The fundamental link between the two conditions is insulin resistance.
3. Both conditions have distressing sequelae and are costly and time consuming to manage in primary care.
4. There is considerable overlap in treatment (diet, lifestyle and pharmacotherapy).
5. Unlike diabetes, PCOS is poorly understood, under-recognised and under-diagnosed, and merits greater awareness in primary care.

Key words

- Insulin resistance
- Obesity
- Polycystic ovary syndrome
- Type 2 diabetes

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Page points

1. There is a great deal of evidence demonstrating insulin resistance and hyperinsulinaemia in both obese and non-obese women with PCO.
2. Obesity and PCOS appear to have a synergistic effect on the degree and severity of insulin resistance.
3. PCOS may be an incidental finding in an asymptomatic patient or an additional finding in a known patient with diabetes or CVD.
4. Investigations specific to PCOS include serum testosterone, sex hormone binding globulin (SHBG), luteinising hormone (LH) and follicle-stimulating hormone (FSH) (preferably on days 1–3 of a menstrual bleed), prolactin and pelvic ultrasound.

promoting the survival of follicles that would otherwise disappear. There is a great deal of evidence demonstrating insulin resistance and hyperinsulinaemia in both obese and non-obese women with PCOS, and obese women with PCOS have been shown to be more insulin resistant than weight-matched controls (Duanif, 1997). Obesity and PCOS appear to have a synergistic effect on the degree and severity of insulin resistance and consequent hyperinsulinaemia in women who are obese and have PCOS.

Recent Health Survey for England figures show an increasing trend in women to expanding waist size (The Information Centre, 2006), which is likely to translate into a surge in levels of comorbidities, including CVD, type 2 diabetes and cancers, as well as obstetric and gynaecological conditions such as pre-eclampsia, infertility and PCOS.

Diagnosis

Definition

PCOS is defined by the presence of two of the following three criteria.

- Oligo- and/or anovulation.
- Clinical or biochemical evidence of hyperandrogenism.
- Polycystic ovaries (an ovary with 12 or more follicles measuring 2–9 mm in diameter, and/or increased ovarian volume [> 10 cm^3]).

Presentation

PCOS may be an incidental finding in an asymptomatic patient or an additional finding in a known patient with diabetes or CVD, or may present with symptoms such as menstrual irregularity or complete absence of periods. Abdominal pain and bloating may result from the stimulation of an excess of follicles (ovarian hyperstimulation syndrome). Androgenic effects may include acne, alopecia and hirsutism, typically of male pattern distribution, including chin, upper lip, chest, back, abdomen, upper arm, thigh and buttocks. Alternatively, concern about weight gain may be the reason for the initial consultation.

The consultation

History should cover the presenting complaint, nature, duration and severity, which may be acne or hirsutism, infertility, dysmenorrhoea, or oligo- and/or anovulation. Gynaecological and obstetric history are of particular interest, as is a history of weight gain. Questioning should explore when and why excess weight was gained, successful or otherwise attempts to lose weight and a nutritional and activity history, possibly with the aid of a food and activity diary.

Family history is important, as weight, PCOS and diabetes all have hereditary components. Social history should include ethnicity, deprivation, smoking and alcohol consumption.

Drug history should include drugs that may cause weight gain, such as the combined oral contraceptive, antipsychotics, steroids, β-blockers, and many hypoglycaemic agents including sulphonylureas and insulin. Thiazolidinediones (TZDs), while improving insulin sensitivity, can cause peripheral weight gain and fluid retention. Direct questioning should attempt to elicit symptoms of other elements of the metabolic syndrome such as polyuria, polydipsia, unnatural fatigue, angina or breathlessness on exertion.

Examination should include height, weight, and therefore BMI, waist circumference and blood pressure. Investigations of the obese patient should include fasting blood glucose, glucose tolerance test if available (although this is often impossible to use as a regular screening tool in primary care), and fasting lipid profile. Urea and electrolytes, liver function tests and thyroid profile are important, and other tests such as chest X-ray and ECG will be indicated in certain clinical circumstances.

Investigations specific to PCOS include serum testosterone, sex hormone binding globulin (SHBG), luteinising hormone (LH) and follicle-stimulating hormone (FSH) (preferably on days 1–3 of a menstrual bleed), prolactin and pelvic ultrasound (*Table 1*).

Treatment

As insulin resistance is the main precursor to PCOS, insulin sensitisers, particularly metformin (Moghetti et al, 2000), have an important role in treatment. Metformin enhances the sensitivity of peripheral tissue to insulin, and reduces the production of glucose by the liver. Metformin in

this context was the subject of a Cochrane review (Lord et al, 2003), which concluded that the drug is effective in achieving ovulation in women with PCOS, and has a significant effect in reducing fasting insulin levels, blood pressure and LDL-cholesterol:

'Metformin is an effective treatment for anovulation in women with PCOS. Its choice as a first-line agent seems justified, and there is some evidence of benefit on parameters of the metabolic syndrome.'

In PCOS, metformin can have the effect of improving hyperandrogenism, and restore fertility. As metformin is unlicensed in PCOS it should only be prescribed in conjunction with secondary care.

A combined oral contraceptive will regulate periods and protect the endometrium by inducing a regular withdrawal bleed; alternatively, periodic induction of withdrawal bleeds by oral progesterone on a 3-monthly basis may be appropriate. Presentation of PCOS may be delayed until the eventual realisation of infertility caused by anovulation. Ovulation, and hence fertility, can be induced in secondary care by the introduction of anti-oestrogens such as clomiphene, although ultrasound monitoring is essential because of the risk of multiple pregnancy.

Treatment of hirsutism includes cosmetic therapies, such as electrolysis, waxing, bleaching and lasers, as well as eflornithine, which inhibits the enzyme ornithine decarboxylase in hair follicles and has recently been developed as a topical treatment.

The preferred way to improve insulin sensitivity in type 2 diabetes or PCOS is by weight loss. The three main strategies for weight loss are diet, activity and behavioural change. Diet should be well balanced: high in fruits and vegetables, low in saturated fats, and mildly hypocaloric for weight loss. Many experts recommend a reduction in refined carbohydrates in favour of those with lower glycaemic index/load, bearing in mind the insulin-resistant state. Physical activity should be built into routine daily life: 10 000 steps per day are recommended, 30 minutes of brisk activity a day are advised to maintain health, and 60 or

Continued on page 121

Table 1. Tests that may aid diagnosis of polycystic ovary syndrome.

Test	Normal range (may vary with local laboratory assays)	Additional points
Pelvic ultrasound	To assess ovarian morphology and endometrial thickness	Transabdominal scan satisfactory in women who are not sexually active.
Testosterone (T)	0.5–3.5 nmol/l	It is unnecessary to measure other androgens unless total T is >5 mmol/l, in which case referral is indicated.
Sex hormone binding (SHBG) Free androgen index (FAI): T X 100/SHBG	16–119 nmol/l <5	Insulin suppresses SHBG resulting in a high FAI in the presence of a normal total T.
Estradiol	Measurement is unhelpful in diagnosis	Oestrogenisation may be confirmed by endometrial assessment.
Luteinising hormone (LH) Follicle stimulating hormone (FSH)	2–10 iu/l 2–8 iu/l	LH and FSH are best measured during days 1–3 of a menstrual bleed. If oligo- or amenorrhoeic, then random samples are taken.
Prolactin, thyroid function, thyroid-stimulating hormone (TSH)	<500 mu/l 0.5–5 iu/l	Measure if oligo- or amenorrhoeic.
Fasting insulin (not measured; insulin resistance assessed by glucose tolerance test)	<30 mu/l	

➥ *Continued from page 116*

90 minutes to aid weight reduction or maintain weight loss (DoH, 2004; Haslam and James, 2005).

Anti-obesity drugs have a major role to play in the prevention and treatment of type 2 diabetes and other obesity-related diseases, but their specific role in the management of PCOS is still being evaluated. Orlistat is a pancreatic lipase inhibitor which results in around 30% of dietary fat being passed unabsorbed through the bowels, and can be used in conjunction with diet and lifestyle advice. The XENDOS trial of orlistat looked at 3304 obese patients over 4 years and found that orlistat induced a 37% relative risk reduction in the development of diabetes compared with placebo (Torgerson et al, 2004).

Sibutramine is a centrally acting serotonin and noradrenaline reuptake inhibitor, which enhances satiety. Both actions induce weight loss and improve metabolic markers of disease. Gokcel et al (2002) compared the effects of metformin, orlistat and sibutramine after 6 months, and found that all three agents induced a reduction in BMI, waist circumference, fasting blood glucose, insulin resistance and other markers of CVD risk. Their role in PCOS is still being assessed (Sabuncu et al, 2003). In another study, orlistat produced a significant reduction in weight and total testosterone; the reduction in total testosterone was similar to that seen following treatment with metformin (Jayagopal et al, 2005).

Conclusion

Diabetes and PCOS have many things in common, including aetiological pathways and excess weight as a root cause, and therefore coexist in many patients. They both lead to sequelae that are distressing for the patient, as well as being costly and time consuming to manage in primary care. There is also a great degree of overlap in treatment, both diet and lifestyle, and pharmacotherapy. However, there are also profound differences between the two conditions.

Diabetes, although part of the same dysmetabolic cluster, is correctly perceived to be linked more closely with cardiovascular morbidity and mortality, leading to blindness, neuropathy, renal damage and amputations along the way. For this reason, the recognition, diagnosis and management of diabetes in primary care is excellent, and will improve as the nGMS contract tightens up on management of risk markers. PCOS, on the other hand, is poorly understood, under-recognised and under-diagnosed, and often inadequately managed outside secondary care. As a precursor for infertility and other major gynaecological and obstetric conditions, and because of the tendency to coexist with type 2 diabetes and CVD, it merits greater awareness in primary care, especially as the mainstay of treatment – weight loss – is feasible and effective in the primary care setting. ■

Balen A et al (2006) *The Polycystic Ovary Syndrome: Guidance for Diagnosis and Management*. PCOS UK, London

DoH (2004) *At least five a week: Evidence on the impact of physical activity and its relationship to health: A report from the Chief Medical Officer*. DoH, London

Dunaif A (1997) Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocrine Review* **18**: 774–800

Gokcel A H et al (2002) Evaluation of the safety and efficacy of sibutramine, orlistat and metformin in the treatment of obesity. *Diabetes, Obesity and Metabolism* **4**: 49–55

Haslam D, James W (2005) Obesity. *Lancet* **366**: 1197–209

Information Centre, The (2006) *Health Survey for England – updating of trend tables to include 2005 data*. Available at: http://live.theic.precedenthost.co.uk/statistics-and-data-collections/health-and-lifestyles/health-survey-for-england/health-survey-for-england--updating-of-trend-tables-to-include-2005-data (accessed 24.04.07)

Jayagopal V et al (2005) Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. *Journal of Clinical Endocrinology and Metabolism* **90**: 729–33

Lord JM et al (2003) Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. http://cochrane.org/reviews/en/ab003053.html (last accessed 5 April 2007)

Moghetti P et al (2000) Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *Journal of Clinical Endocrinology and Metabolism* **85**: 139–46

Morrin, L (2000) *An Interview with Gerald Reaven: Syndrome X: The Risks of Insulin Resistance*. Winnipeg, Canada. Available at: http://www.cacr.ca/news/2000/0009reaven.htm (accessed 24.04.07)

Sabuncu T et al (2003) Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. *Fertility and Sterility* **80**: 1199–204

Torgerson JS et al (2004) XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* **27**: 155–61

An historical look at obesity in women

Female obesity has occurred for at least 30,000 years, as demonstrated by the prehistoric statuette of 'Venus of Willendorf', an accurate depiction of a large-breasted abdominally obese woman, which ironically probably represented a fertility symbol and was designed to be carried in the palm of the hand. The ramifications of the obese state were known to Hippocrates, who recognised that corpulent women were likely to be infertile; with the advancement of science, the connection was more accurately defined. Over 250 years ago, Morgagni used anatomical dissection to demonstrate visceral fat deposits, nowadays shown clearly on CT, and identified intra-abdominal and mediastinal fat accumulation as the cause of diseases such as hypertension, hyperuricaemia, atherosclerosis and obstructive sleep apnoea syndrome (Enzi et al, 2003).

In 1795, Dr William Buchan wrote:

'we find that such girls as lead an indolent life, and eat great quantities of trash, are not only subject to obstructions of the menses, but likewise glandular obstructions.'

In 1893 Russell wrote that:

'…derangements of the 'menses' have much to do with the increase of embonpoint.'

In the 1950s the French physician Jean Vague described android and gynoid obesity – the classical gynoid or 'pear' shape assumed by women, whereby metabolically inactive fat accumulated around the hips and thighs, compared to the traditional android 'apple' of metabolically active intra-abdominal or visceral adipose deposits.

Buchan W (1795) Domestic Medicine. American edition. Philadelphia

Enzi G, Busetto L, Inelmen EM et al (2003) Historical perspective: visceral obesity and related comorbidity. In: Joannes Baptista Morgagni's 'De sedibus et causis morborum per anatomen indagata'. International Journal of Obesity and Related Metabolic Disorders 27: 534–5