Polycystic ovary syndrome: Why are women at increased risk of type 2 diabetes?

Julie Tomlinson

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Article points

1. Polycystic ovary syndrome (PCOS) is a common condition and is found in approximately 15% of pre-menopausal women. It carries a substantial long-term risk of developing type 2 diabetes.
2. A diagnosis of PCOS provides an opportunity to screen for impaired glucose tolerance and type 2 diabetes (T2D), and offer proactive clinical management similar to other high-risk groups.
3. Although the UK and US guidance recommends that overweight and obese women with PCOS should be screened for T2D, there is a lack of clear guidance around which screening test to use. An Australian guideline suggests that these women should be screened every 2 years using an oral glucose tolerance test.

Key words

- Polycystic ovary syndrome
- Type 2 diabetes

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Polycystic ovary syndrome (PCOS) is a common condition found in 15% of pre-menopausal women. It is recognised as a significant risk factor for developing type 2 diabetes (T2D) and, as such, poses a major public health concern in terms of cardiometabolic health and the future resources that will be required to treat women. Although the American Diabetes Association and Diabetes UK recommend that women with PCOS should be screened for T2D regularly, there is a lack of clear guidance around which screening test to use and on which women. This article explores why PCOS is a risk factor for T2D by examining prevalence of T2D in PCOS and the associations between PCOS with insulin resistance, beta-cell function, incretin hormones and obesity. It also makes recommendations that we adopt the evidence-based guidelines produced in Australia for screening all women with PCOS every 2 years (annually if at increased risk) using an oral glucose tolerance test.

Polycystic ovary syndrome (PCOS) is an under-diagnosed but common endocrine condition with a prevalence of approximately 15% of the pre-menopausal female population (Fauser et al, 2012). While PCOS has typically been associated with reproductive and cosmetic features, it has been poorly recognised as a significant risk factor for type 2 diabetes (T2D; Tomlinson and Pinkney, 2007). The risk of T2D in PCOS was confirmed in a systematic review and meta-analysis that demonstrated PCOS was associated with higher rates of impaired glucose tolerance (IGT), T2D and metabolic syndrome (MS; Moran et al, 2010).

Although Diabetes UK (DUK) and the American Diabetes Association (ADA) have recommended that women with PCOS are screened for T2D, the optimal screening test has not been specified. Furthermore, their guidance disagrees on whether only to screen obese women with PCOS or include those who are overweight too (Diabetes UK, 2015; American Diabetes Association, 2015).

This article reviews the evidence implicating PCOS as a risk factor for T2D and IGT, and makes recommendations for clinical management of PCOS.

What is polycystic ovary syndrome?

The pathophysiology of PCOS is complex, involving various glands, organs and insulin sensitive tissues that make it a condition of both the reproductive and endocrine systems. Worldwide, the diagnostic criteria varies. However, in the UK, PCOS is diagnosed using the Rotterdam classification (Rotterdam PCOS Consensus Working Group, 2004). This classification is shown in *Box 1*.

Box 1. The Rotterdam criteria for the diagnosis of polycystic ovary syndrome (Rotterdam, 2004).

A diagnosis of PCOS may be made if any two of the following features are present:

1. The presence of menstrual irregularities (oligomenorrhoea and/or anovulation).
2. The presence of clinical and/or biochemical signs of hyperandrogenism.
3. The presence of polycystic ovaries.

after:

4. Excluding other potential causes of menstrual irregularity or hyperandrogenism.

The prevalence of IGT and T2D in PCOS

When examining the literature for evidence that PCOS is associated with T2D, a high degree of caution is required because of the different criteria that have been used to diagnose PCOS in Europe and the more restrictive criteria used in the US. Figures from US studies indicate that women with PCOS have between 6.6–10% prevalence of T2D and up to 30–40% prevalence of IGT (Ehrmann et al, 1999; Legro et al, 1999; Apridonidze et al, 2005; Ehrmann et al, 2005). Women with a family history of T2D were found to be most insulin resistant and therefore at highest risk of T2D (Ehrmann et al, 2005). In contrast, European studies have found lower prevalence rates of T2D and it is believed that this was likely to be because the women in the US studies were more obese (Ciampelli et al, 1999).

A Scandinavian study measured metabolic characteristics through the climacteric in women with PCOS (n=33) and women without PCOS (control group, n=132), using a risk model. The authors found that women with PCOS were more centrally obese than controls and by the menopause, 16% had developed T2D. Furthermore, women with PCOS had a seven-fold higher incidence of T2D and myocardial infarction than matched controls (Dahlgren et al, 1992). Although this study was small, it highlighted that women with PCOS are at increased cardiometabolic (cardiovascular and diabetes) risk and demonstrated the need for further research into long-term health risks in women with PCOS.

In summary, the prevalence of T2D in women with PCOS may be as high as 10%, depending upon the population studied and research methodology. The association between PCOS and T2D is supported by the high prevalence of IGT found in PCOS. Obesity, insulin resistance (IR), IGT and a family history of T2D all appear to predispose women with PCOS to T2D.

Evidence for IR in PCOS

IR is a term describing the resistance of insulin sensitive tissues to the normal action of insulin to stimulate glucose uptake. The principal insulin sensitive tissues are the liver, skeletal muscle and adipose tissue. Insulin sensitivity is the same phenomenon from the opposing viewpoint and the terms are often used interchangeably. Under conditions of reduced insulin sensitivity, insulin levels are elevated, in compensation for the increased resistance to insulin-stimulated glucose uptake. Hyperglycaemia occurs when the pancreas can no longer compensate for IR with increased insulin production, and this results in the states of IGT and T2D.

Previous research has demonstrated that PCOS is associated with IR and defects in insulin action (Balen et al, 1993). Furthermore, IR has been found to be present in both lean and overweight women with PCOS (Dunaif et al, 1989). These findings were later substantiated by another study in which 53% of women with PCOS were found to have IR (Legro et al, 1998). Subsequent research found that IR in PCOS is mainly, but not entirely, obesity-related (Ciampelli et al, 1997). More recent research also found that IR is significantly higher in women with PCOS compared with matched controls, although obesity significantly exacerbates the underlying IR (Stepto et al, 2013).

The proportion of women with PCOS found to have IR is strongly influenced by the criteria used to diagnose PCOS and the population studied (i.e. differences in ethnicity, age and

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2. Figures from US studies indicate that women with PCOS have between 6.6–10% prevalence of T2D and up to 30–40% prevalence of impaired glucose tolerance. In contrast, European studies have found lower prevalence rates of T2D and it is believed that this was likely to be because the women in the US studies were more obese.
3. The prevalence of T2D in women with PCOS may be as high as 10%, depending upon the population studied and research methodology.

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1. Having polycystic ovary syndrome (PCOS), irrespective of age, weight and diagnostic criteria used, is associated with increased insulin resistance (IR), compared with women without PCOS.
2. Type 2 diabetes (T2D) develops when pancreatic beta-cells are unable to compensate for increasing IR. Therefore, for anyone to develop T2D, both beta-cell dysfunction and IR are required.

weight). Studies from the US have generally employed different diagnostic criteria (the National Institutes of Health [NIH] 1990 criteria; Zawadski, 1992; see *Box 2*). Use of the NIH criteria tends to detect higher rates of IR in PCOS than studies from Europe and Australia, where the Rotterdam criteria are used. Both the diagnostic criteria used and the populations studied are likely to influence the level of IR. For example, there is some evidence that oligo/amenorrhoeic women are more prone to IR than women with normal length menstrual cycles (Robinson et al, 1993).

Nevertheless, the evidence is clear: having PCOS, irrespective of age, weight and diagnostic criteria used, is associated with increased IR, compared with women without PCOS. However, since IR is often associated with obesity, it is not clear why lean women with PCOS have increased IR compared to matched controls. It is believed that there are genetic influences present in women with PCOS (Abbott et al, 2002) and so the increased IR observed in PCOS is likely to have a hereditary component that is exacerbated further if a woman gains excessive weight.

Evidence for beta-cell dysfunction in PCOS

T2D develops when pancreatic beta-cells are unable to compensate for increasing IR. Therefore, for anyone to develop T2D, both beta-cell dysfunction and IR are required. Over time, beta-cell function deteriorates, insulin production falls and blood glucose rises. The question whether PCOS is intrinsically associated with beta-cell dysfunction and if this defect is independent of obesity has attracted much interest. However, the data are difficult to interpret and have significant limitations. As a result, this association has not been fully clarified.

An early study found that women with PCOS and a family history of T2D might have abnormal beta-cell function (Ehrmann et al, 1995). Subsequently, it was reported that all women with PCOS showed evidence of beta-cell dysfunction and IR (Dunaif and Finegood, 1996). However, the methodology used in this study was the frequently sampled intravenous glucose tolerance test with injections of glucose and tolbutamide. This method does not mimic natural human insulin secretion in response to consumption of oral glucose and therefore has limitations.

Box 2. The National Institutes of Health 1990 criteria for the diagnosis of PCOS (Zawadski, 1992).

A diagnosis of PCOS may be made if there is both:

1. Presence of hyperandrogenism with either clinical signs (hirsutism, acne, or male pattern balding) or biochemical signs of hyperandrogenaemia (high serum androgen concentrations).

and

2. Presence of chronic menstrual irregularity due to oligomenorrhoea/amenorrhoea.

after

3. Excluding other known disorders such as Cushing's syndrome, congenital adrenal hyperplasia, androgen-secreting tumours and hyperprolactinaemia.

In a small study of obese adolescent females, girls with PCOS and IGT or T2D were compared with controls (girls without PCOS and normal glucose tolerance). The authors used a euglycaemic clamp to measure hepatic glucose production and insulin-stimulated glucose disposal, and found that glucose intolerance was associated with three quantifiable factors: 40% decrease in first phase insulin secretion; 50% decrease in glucose disposition index (a measure of insulin sensitivity and first phase insulin secretion that may predict the rate of conversion to T2D); and an increased hepatic glucose response, compared with controls with similar levels of IR.

It was proposed that a defect in insulin secretion (i.e. the inability of beta-cells to compensate for IR) might be more important than IR in determining increased cardiometabolic risk in PCOS (Arslanian et al, 2001). In contrast, in a much larger study of women with PCOS and controls, in which IR and beta-cell function were measured using the Homeostasis Model Assessment (HOMA)

method (Matthews et al, 1985), IR was found to be present in 64.4% of women with PCOS, whereas only 2.6% of women with PCOS had beta-cell dysfunction (DeUgarte et al, 2005). This suggested that IR might be the main defect that predisposes women with PCOS to T2D, although the HOMA method may be an insensitive and therefore inappropriate method to detect subtle beta-cell dysfunction.

In summary, compared with the abundance of research regarding IR, there is more limited data about beta-cell function in PCOS. It remains unclear therefore whether PCOS is intrinsically associated with beta-cell dysfunction and, if so, whether this might be the main explanation for the increased risk of T2D in PCOS.

Evidence for impaired incretin hormones in PCOS

Following the ingestion of food, two hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released into the circulation by cells in the small intestine (Ranganath et al, 1996; Ceperuelo-Mallafre et al, 2014). A key function of these hormones is to amplify or increase insulin secretion by the pancreatic beta-cells (Cernea and Raz, 2011), an action that led to these hormones becoming known as "incretin" hormones. Incretins are believed to be responsible for approximately 70% of the total insulin response during a meal. However, in people with obesity, T2D and other insulin-resistant conditions, the production and action of incretins is significantly impaired (Svendsen et al, 2009). It is not clear, however, whether incretin production is also abnormal in women with PCOS and therefore could be another potential factor in the increased T2D risk.

Several studies have investigated incretin secretion in PCOS, but due to small sample sizes and inconsistent results, these are often difficult to interpret. One small study of lean women with PCOS and controls found no differences in GLP-1 or GIP secretion (Gama et al, 1996). However, another study observed increased GIP and lower late-phase GLP-1 levels in lean women with PCOS (Vrbikova et al, 2008). Svendsen and colleagues however, found lower GIP in obese women compared with lean women with PCOS, although there was no difference between PCOS and controls (Svendsen et al, 2009). Therefore, this suggested that obesity might influence the pattern of incretin hormone secretion in women with PCOS.

In summary, it remains uncertain whether PCOS, as well as obesity, is associated with defective incretin secretion. Defective incretin secretion, leading to impaired beta-cell function, might therefore predispose some women with PCOS to T2D.

The prevalence of obesity in PCOS

Obesity is defined as a body mass index (BMI) of >30 kg/m^2 and overweight as a BMI of 25–29.9 kg/m^2 (World Health Organization, 2006). In a study from the US, Yildiz and colleagues reported that 74% of women with PCOS were obese (Yildiz et al, 2008), which suggested a close association between obesity and PCOS. These findings appear to reflect the characteristics of the population being studied. When women from the US and Italy were compared, even using the same criteria to diagnose PCOS, only 38% of the Italian women were obese (Carmina et al, 2003). While the reasons for this difference are complex, these results suggest the prevalence of obesity in PCOS varies according to the population studied. It is not clear what the significance of this could be and how this might influence cardiometabolic risk. However, it could be speculated that PCOS may be associated with greater cardiometabolic risk when it occurs in obese women.

The influence of obesity in exacerbating T2D risk in PCOS

A recent systematic review and meta-analysis of the effects of obesity on PCOS demonstrated that excess body weight exacerbates many features of PCOS, including hyperandrogenism, menstrual disturbances and infertility, IR and hyperinsulinaemia, hyperglycaemia and dyslipidaemia. There is also an increased risk of IGT and T2D. The authors concluded

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1. It remains unclear whether polycystic ovary syndrome (PCOS) is intrinsically associated with beta-cell dysfunction and, if so, whether this might be the main explanation for the increased risk of type 2 diabetes (T2D) in PCOS.
2. In people with obesity, T2D and other insulin-resistant conditions, the production and action of incretin hormones is significantly impaired. It is not clear, however, whether incretin production is also abnormal in women with PCOS and therefore could be another potential factor in the increased T2D risk.
3. A recent systematic review and meta-analysis of the effects of obesity on PCOS demonstrated that excess body weight exacerbates many features of PCOS.

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1. There has been a long-standing interest in whether the effect of obesity in polycystic ovary syndrome (PCOS) is dependent on where the fat is distributed. In particular, intra-abdominal fat around the organs (visceral fat) has been associated with increased cardiometabolic risk.
2. The evidence presented clearly demonstrates that women with PCOS, particularly those who have excessive weight, are at substantially greater risk of developing T2D than women without PCOS.
3. Current UK and US guidelines suggest screening overweight and obese women with PCOS every 3 years. However, an expert consensus from Australia suggests screening every 2 years, with a oral glucose tolerance test.

that the evidence suggested obesity-related hyperinsulinaemia may stimulate the ovaries and adrenal glands to increase androgen production (Lim et al, 2013).

There has been a long-standing interest in whether the effect of obesity in PCOS is dependent on where the fat is distributed. In particular, intra-abdominal fat around the organs (visceral fat) has been associated with increased cardiometabolic risk (Despres et al, 2001) In a study that used computerised tomography to measure intra-abdominal fat in women with PCOS, visceral fat was strongly related to IR and it was concluded that visceral fat either causes, or is a very early consequence of IR (Lord et al, 2006).

Clinical practice recommendations for diabetes screening in PCOS

The evidence presented clearly demonstrates that women with PCOS, particularly those who have excessive weight, are at substantially greater risk of developing T2D than women without PCOS. The clinical implications are therefore that women with PCOS should be identified and targeted for regular diabetes screening.

There is a current lack of evidence about the optimal diabetes screening method for PCOS, or what the optimal screening interval should be. The American Diabetes Association (ADA) pragmatically suggests screening every 3 years with a fasting glucose, HbA_{1c} or oral glucose tolerance test (OGTT) in women aged 45 years or more, with a BMI >25 kg/m^2 (American Diabetes Association, 2015). In contrast, Diabetes UK have recommended that only women with PCOS and a BMI >30 kg/m^2 are screened. However, they also recommend screening every 3 years but do not recommend whether the test should be fasting glucose, HbA_{1c} or OGTT (Diabetes UK, 2015). Both the ADA and Diabetes UK suggest increasing the screening interval to annual screening in higher risk women. Clearly, there are discrepancies between the recommendations, but most notable is that neither acknowledges the evidence that the fasting plasma glucose test lacks sensitivity as an effective screening method for T2D in PCOS and fails to detect over half the cases of T2D. Furthermore, there is a current lack of data to support the use of an HbA_{1c} as a screening test for T2D in women with PCOS (Tomlinson et al, 2010).

Box 3. Australian clinical consensus guidelines: Recommendations for screening for T2D in PCOS (adapted from Teede et al, 2011).

1. To assess for risk of type 2 diabetes, in addition to polycystic ovary syndrome status, the following diabetes risk factors should be considered:
   - Age
   - Gender
   - Ethnicity
   - Parental history of diabetes
   - History of high blood glucose level
   - Use of antihypertensive medications
   - Smoking
   - Physical inactivity
   - Waist circumference
2. An oral glucose tolerance test should be performed every second year in all women with polycystic ovary syndrome and annually in those found to have additional risk factors for developing type 2 diabetes as outlined above.

An expert consensus was achieved in Australia, however, where recommendations were made specifically for T2D screening in PCOS. They advised the optimal test for screening all women with PCOS should be an OGTT every second year. As with the ADA and Diabetes UK, it is recommended that screening is increased to annual intervals in those women with further risk factors, as outlined in *Box 3*. Furthermore, measures such as weight reduction and increasing exercise should be encouraged to reduce risk. Teede et al (2011) said:

> *"The significantly increased risk of type 2 diabetes in PCOS represents a major health and economic burden. The recommendation to screen all women with PCOS and to use an OGTT will result in earlier detection of pre-diabetes and type 2 diabetes, and will present opportunities for prevention of type 2 diabetes and its complications through effective lifestyle intervention."*

Conclusion

PCOS is a very common female condition that carries a substantial long-term risk of developing T2D. A diagnosis of PCOS provides an opportunity to screen for IGT and T2D and offer proactive clinical management similar to other high-risk groups. While there is a lack of clinical guidance on diabetes screening and prevention in women with PCOS in the UK, clinicians should consider existing Australian guidelines to improve patient care (Teede et al, 2011). ■

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"While there is a lack of clinical guidance on diabetes screening and prevention in women with PCOS in the UK, clinicians should consider existing Australian guidelines to improve patient care."