Reproductive history: A tool for determining metabolic risk in overweight and obese women

Julie Tomlinson, Jonathan Pinkney, Elizabeth Stenhouse

Obesity is a major public health concern; 24.9% of the female population in the UK are classified as obese and a further 32.2% are classified as overweight (National Obesity Observatory, 2012). Polycystic ovary syndrome (PCOS) and gestational diabetes mellitus (GDM) appear to be two overlapping conditions that are both strongly associated with excess weight (Chu et al, 2007; Tomlinson et al, 2010) and have common cardiometabolic comorbidities. Both conditions are associated with insulin resistance, hypertension and dyslipidaemia, thereby increasing the likelihood of developing type 2 diabetes and increasing cardiovascular risk. A reproductive history in women who are overweight or obese provides an opportunity to identify women with PCOS or previous GDM; preventive measures can be then taken to reduce their cardiometabolic risk.

Obesity is considered a major public health concern (Haslam and James, 2005); 24.9% of the female population in the UK are classified as obese, and a further 32.2% are classified as overweight (National Obesity Observatory, 2012). As obesity is strongly associated with polycystic ovary syndrome (PCOS; Tomlinson et al, 2010) and gestational diabetes mellitus (GDM; Chu et al, 2007), it is probable that both PCOS and GDM, with their associated comorbidities (including type 2 diabetes and cardiovascular disease [CVD]), will become increasingly prevalent.

Traditionally, the clinical management of PCOS and GDM has not focused on weight management; for GDM, management is primarily about having a safe, low-risk pregnancy resulting in a healthy baby; for PCOS, management is more often about preventing infertility or minimising the cosmetic effects of hyperandrogenism, including hirsutism or acne (Tomlinson and Pinkney, 2007).

It has been demonstrated that a high proportion of women with type 2 diabetes and cardiovascular risk factors, including hypertension, a family history of diabetes and obesity, or so-called "cardiometabolic disease" (CMD), have had previous GDM (Kim et al, 2002). Furthermore, of 47 women attending a diabetes clinic in the USA, 26.7% reported having previous PCOS (Peppard et al, 2001). This poses an interesting question for the clinician; could the reproductive history be used as a tool for predicting CMD in overweight and obese women? This article explores this concept further, and highlights recommendations for clinical practice.

PCOS

PCOS is a common endocrine disorder affecting as much as 15% of the female population (Fauser et al, 2012) and characterised by androgen

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Article points

1. Polycystic ovary syndrome (PCOS) and gestational diabetes mellitus (GDM) are associated with cardiometabolic disease (CMD), such as type 2 diabetes and cardiovascular disease.
2. PCOS and GDM are strongly linked with obesity, and are becoming increasingly prevalent.
3. Reproductive histories are essential in women who are overweight or obese to identify those with PCOS or previous GDM, who are at increased risk of CMD, so that preventive measures can be implemented.
4. Management of obesity will reduce the CMD risks associated with PCOS and GDM.

Key words

- Cardiometabolic disease
- Gestational diabetes mellitus
- Obesity
- Polycystic ovary syndrome
- Reproductive history

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Page points

1. Although there is no definitive conclusion as to the aetiology of polycystic ovary syndrome (PCOS), gaining excess weight seems to be a powerful modifying factor in the subsequent development of the condition.
2. PCOS is a known risk factor for type 2 diabetes, and increased cardiovascular disease (CVD) risk factors include waist circumference >88 cm, dyslipidaemia and hypertension; obesity is strongly associated with these increased risks.
3. Thus PCOS is an important indicator of long-term cardiometabolic disease, and presents potential opportunities for long-term health improvements through its management.
4. The aetiology of gestational diabetes mellitus (GDM) is complex and is associated with abnormal glucose metabolism. GDM has been strongly associated with obesity, and women who embark on pregnancy who are already obese or severely obese have an especially high risk of developing GDM.

excess (resulting in clinical or biochemical hyperandrogenism, or both), chronic anovulation and polycystic ovaries. PCOS is associated with insulin resistance (Dunaif et al, 1989), and is a known risk factor for type 2 diabetes and CVD (Tomlinson et al, 2010).

A wide variation in both the phenotype of women with PCOS and the prevalence rates of the syndrome are partly a result of the lack of consensus over the diagnostic criteria. Most studies from the US report the prevalence to be around 6% (Azziz et al, 2004), and this is largely because of the use of the National Institutes of Health 1990 diagnostic criteria, where PCOS is diagnosed if women have chronic anovulation as well as clinical or biochemical hyperandrogenism, or both (Zawadski and Dunaif, 1992). This compares with Europe, where the Rotterdam consensus of 2003 (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) set the diagnostic criteria for PCOS as having two out of three of the following:

- Oligomenorrhoea or amenorrhoea.
- Clinical or biochemical hyperandrogenism, or both.
- Polycystic ovaries.

Using the Rotterdam criteria broadens the phenotype of women diagnosed; an Australian community study demonstrated that prevalence rates of PCOS using the Rotterdam criteria increased to 17.8±2.8% (March et al, 2010). However, the increasing prevalence of obesity in many populations may also be responsible for the apparent increasing prevalence of PCOS in later studies.

The aetiology of PCOS is not fully understood. A strong familial aggregation of PCOS suggests there is a genetic predisposition that is enhanced by environmental factors, such as nutrition (Franks et al, 1997). Although there is no definitive conclusion as to the aetiology of PCOS, gaining excess weight seems to be a powerful modifying factor in the subsequent development of the condition.

PCOS is a known risk factor for type 2 diabetes, and increased CVD risk factors include waist circumference >88 cm, dyslipidaemia and hypertension (Ehrmann et al, 2006); obesity is strongly associated with these increased risks. Various studies demonstrate that although all women with PCOS have higher CMD risk, those who are obese or overweight have much higher CMD risks than lean women with PCOS (Tomlinson et al, 2010). Furthermore, in studies where women with PCOS have lost weight through diet and exercise, medication including metformin, glucagon-like peptide-1 analogues and orlistat, or bariatric surgery, their CMD risk has decreased accordingly (Tomlinson et al, 2010). Therefore, PCOS is an important indicator of long-term CMD risk, and presents potential opportunities for long-term health improvements through its management.

GDM

GDM is defined as: "carbohydrate intolerance of variable severity with onset during pregnancy with return to normal after delivery" (Scott et al, 2002). The prevalence of GDM ranges between 2 and 6% depending on diagnostic test and criteria, as well as the population studied (King, 1998). The aetiology of GDM is complex and is associated with abnormal glucose metabolism; the pathophysiology of abnormal glucose metabolism in pregnancy is well established. In normal pregnancy, insulin resistance is accompanied by compensatory increases in insulin secretion by the pancreatic beta-cells (Richardson and Carpenter, 2007); in GDM, beta-cell dysfunction leads to relative insulin deficiency. A variety of underlying mechanisms may contribute to GDM, including genetic predisposition, impaired glucose transport, adipokines and other inflammatory mediators (Battista et al, 2011). Furthermore, GDM has been strongly associated with obesity, and women who embark on pregnancy who are already obese or severely obese have an especially high risk of developing GDM (Chu et al, 2007).

There is well-documented evidence that women with previous GDM have high rates of progression to type 2 diabetes, ranging from 17 to 63% within 5–16 years following the index pregnancy (Kim et al, 2002). For women with pregnancies complicated by GDM there is also evidence of an increased risk of hypertensive disorders in pregnancy, such as pregnancy-induced hypertension and pre-eclampsia. One study following up women with GDM 4 years

after delivery found they had elevated systolic blood pressure compared with controls without GDM (Madarasz et al, 2009). Another study has shown that women who have had GDM have a greater risk of developing dyslipidaemia (Akinci et al, 2010) and the metabolic syndrome (Bo et al, 2004).

Thus a history of GDM is strongly associated with the emergence of a range of metabolic risk factors and vascular function abnormalities that are thought to represent early indicators of CVD (Bentley-Lewis, 2009); these risk factors include type 2 diabetes, hypertension, dyslipidaemia, the metabolic syndrome and being overweight or obese. As a result of these findings, women with a pregnancy complicated by GDM should be screened for CMD and potentially considered for interventions that may reduce their risk of developing type 2 diabetes and CVD.

The associations between PCOS and GDM and their link with obesity

Despite PCOS and GDM being two distinct clinical conditions, there is a clear association between the two. A large community-based study found that women with PCOS have a 2.4-fold increase in the chances of developing GDM (Lo et al, 2006). A subsequent meta-analysis supported this, suggesting that women with PCOS had a statistically higher risk of developing GDM (Toulis et al, 2009). Thus GDM and PCOS appear to be two overlapping conditions, both strongly influenced by obesity and with common cardiometabolic comorbidities.

Several studies have examined obesity in relation to PCOS and GDM, in particular identifying central fat distribution or visceral fat in association with PCOS (Douchi et al, 1995; Kirchengast and Huber, 2001) and as a predictor for GDM (Martin et al, 2009). Although the extent of the impact of weight gain and fat distribution on CMD risk in women with PCOS or previous GDM is not well defined, weight control is likely to reduce the long-term risk of CMD in both conditions.

Implications for practice

Could a woman's reproductive history be used as a tool for determining potential for CMD in overweight and obese women? Since PCOS or a history of GDM, or both, are strongly associated with the risk of developing CMD, especially in overweight and obese women, there are clear implications for clinical practice:

- The diagnoses of PCOS or GDM, or both, may be elicited or suspected by taking a reproductive history.
- Weight control may be an option to reduce long-term risks of CMD.

The UK prevalence of diagnosed GDM will significantly increase if new screening criteria published in the USA (American Diabetes Association, 2012) are accepted in the UK. Currently, the NICE (2008) guidance is being reviewed, and it is likely that the screening threshold will be lowered for GDM to include women who are classified as overweight and not only those who are obese. In addition to this, factors including rising maternal age and increasing obesity rates are likely to further increase the frequency of GDM.

However, it is important to remember that classification is dependent upon firstly correctly identifying the patients to screen and then ensuring that the glucose tolerance test (GTT) is performed accurately. Despite being thought of as the "gold standard" test, the GTT has been shown to produce variability in test results, and this is often because of the wide inconsistency in screening practices in the UK (Scott et al, 2002). Nevertheless, it is currently the test of choice to screen for glucose intolerance and diabetes in PCOS (Tomlinson et al, 2010) and in screening for GDM (NICE, 2008).

Making a diagnosis of PCOS is much more complicated than GDM because the diagnosis depends on arbitrary clinical and non-standardised biochemical criteria, whereas GDM is diagnosed on widely accepted biochemical ranges. Furthermore, ovarian scans are not always convenient or available for the diagnosis of PCOS and require careful interpretation before a classification of "polycystic" may be given. Nevertheless, a simple question about menstrual frequency and regularity is a useful pre-screening question to ask, as PCOS is likely to be the most common single cause of oligomenorrhoea or secondary amenorrhoea.

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Box 1 highlights important features of a reproductive history that may indicate increased CMD risk in women. As there is often no standardised definition for each clinical feature, this should be used as a guideline in conjunction with local clinical policies.

The identification of central obesity in these women is an important marker for CMD risk. Clinical guidelines recommend measuring this by taking waist circumference rather than BMI as it is an indirect measure of visceral fat mass (Bosy-Westphal et al, 2010). Management of excess weight is recommended to reduce risks of CMD (NICE, 2006) and is therefore a primary objective. Women with a history of GDM or who are planning a pregnancy should be offered lifestyle advice including weight control, diet and exercise (NICE, 2008). Women with PCOS also benefit from weight loss, with improvements in their hyperandrogenism, fertility, glucose tolerance and hyperinsulinaemia (Tomlinson et al, 2010).

Conclusion

Taking a reproductive history to elicit whether a woman has ever had PCOS or GDM, or both, is of paramount importance because of the associations between these conditions and CMD. However, it is important to remember that, especially in the case of PCOS, a diagnosis may not have been previously made and so clinicians must be alert to suggestive histories including oligomenorrhoea, amenorrhoea, hirsutism and infertility.

As the global epidemic of obesity continues to rise, PCOS and GDM pose a substantial public health threat that is likely to result in substantial increases in their prevalence rates. Clinicians in all settings (not only in primary care) should be mindful of the importance of taking a reproductive history in women to identify those who are at high risk of CMD, which would therefore enable targeted screening and prevention strategies. However, screening of all the identified high-risk women would inevitably fall upon general practice, and in the current economic climate the resourcing of this would have to be considered. Furthermore, resourcing obesity management in these women is of paramount importance to reduce their risk of CMD and the resulting burden on individuals and health services. ■

Box 1. Reproductive history that may suggest increased cardiometabolic risk.

Reproductive history	Recommended definition*
● Previous diagnosis of gestational diabetes mellitus or impaired glucose tolerance in pregnancy	Diagnosed with a 2-hour 75 g oral glucose tolerance challenge
● Previous diagnosis of polycystic ovary syndrome (PCOS)	Diagnosed using the Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004)
● Biochemical hyperandrogenism (possibly suggestive of undiagnosed PCOS)	Raised serum testosterone (see individual laboratory reference ranges)
● Clinical hyperandrogenism (possibly suggestive of undiagnosed PCOS)	Hirsutism or non-teenage acne
● Polycystic ovaries confirmed on ultrasound (possibly suggestive of undiagnosed PCOS)	>10 follicles of 2–8 mm in diameter
● History of oligomenorrhoea	Fewer than six menstrual cycles per year
● History of amenorrhoea	History of no menstrual cycles
● History of female infertility	Of unknown aetiology
● History of macrosomic baby	Birthweight >4.5 kg (>9 lb 15 oz)

*Where definitions are not universally agreed, the authors have provided a recommendation based upon commonly used criteria in the UK; these values may vary according to the population being assessed or local guidelines.

Akinci B, Celtik A, Genc S et al (2010) Evaluation of postpartum carbohydrate intolerance and cardiovascular risk factors in women with gestational diabetes. *Gynecol Endocrinol* **27**: 361–7

American Diabetes Association (2012) Standards of medical care in diabetes – 2012. *Diabetes Care* **35**(Suppl 1): S11–63

Azziz R, Woods KS, Reyna R et al (2004) The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* **89**: 2745–9

Battista MC, Hivert MF, Duval K, Baillargeon JP (2011) Intergenerational cycle of obesity and diabetes. *Exp Diabetes Res* 596060. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3205776 (accessed 07.09.12)

Bentley-Lewis R (2009) Late cardiovascular consequences of gestational diabetes mellitus. *Semin Reprod Med* **27**: 322–9

Bo S, Monge L, Macchetta C et al (2004) Prior gestational hyperglycaemia. *J Endocrinol Invest* **27**: 629–35

Bosy-Westphal A, Booke CA, Blocker T et al (2010) Measurement site for waist circumference affects its accuracy as an index of visceral and abdominal subcutaneous fat in a Caucasian population. *J Nutr* **140**: 954–61

Chu SY, Callaghan WM, Kim SY et al (2007) Maternal obesity and risk of gestational diabetes mellitus. *Diabetes Care* **30**: 2070–6

Douchi T, Ijuin H, Nakamura S et al (1995) Body fat distribution in women with polycystic ovary syndrome. *Obstet Gynecol* **86**: 516–9

Dunaif A, Segal KR, Futterweit W, Dobrjansky A (1989) Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. *Diabetes* **38**: 1165–74

Ehrmann DA, Liljenquist DR, Kasza K et al (2006) Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* **91**: 48–53

Fauser BC, Tarlatzis BC, Rebar RW et al (2012) Consensus on women's health aspects of polycystic ovary syndrome. *Fertil Steril* **97**: 28–38

Franks S, Gharani N, Waterworth D et al (1997) The genetic basis of polycystic ovary syndrome. *Hum Reprod* **12**: 2641–8

Haslam DW, James WP (2005) Obesity. *Lancet* **366**: 1197–209

Kim C, Newton KM, Knopp RH (2002) Gestational diabetes and the incidence of type 2 diabetes. *Diabetes Care* **25**: 1862–8

King H (1998) Epidemiology of glucose intolerance and gestational diabetes in women of childbearing age. *Diabetes Care* **21**: B9–13

Kirchengast S, Huber J (2001) Body composition characteristics and body fat distribution in lean women with polycystic ovary syndrome. *Hum Reprod* **16**: 1255–60

Lo JC, Feigenbaum SL, Yang J et al (2006) Epidemiology and adverse cardiovascular risk profile of diagnosed polycystic ovary syndrome. *J Clin Endocrinol Metab* **91**: 1357–63

Madarasz E, Tamas G, Tabak AG, Kerenyi Z (2009) Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. *Diabetes Res Clin Pract* **85**: 197–202

March WA, Moore VM, Willson KJ et al (2010) The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod* **25**: 544–51

Martin AM, Berger H, Nisenbaum R et al (2009) Abdominal visceral adiposity in the first trimester predicts glucose intolerance in later pregnancy. *Diabetes Care* **32**: 1308–10

National Obesity Observatory (2012) *Adult Obesity*. Available at: http://www.noo.org.uk/NOO_about_obesity/adult_obesity (accessed 07.09.12)

NICE (2006) *Obesity: Guidance on the Prevention, Identification, Assessment and Management of Overweight and Obesity in Adults and Children*. NICE Clinical Guideline 43. NICE, London

NICE (2008) *Diabetes in Pregnancy: Management of Diabetes and its Complications from Pre-Conception to the Postnatal Period*. Nice Clinical Guideline 63. NICE, London

Peppard HR, Marfori J, Iuorno MJ, Nestler JE (2001) Prevalence of polycystic ovary syndrome among premenopausal women with type 2 diabetes. *Diabetes Care* **24**: 1050–2

Richardson AC, Carpenter MW (2007) Inflammatory mediators in gestational diabetes mellitus. *Obstet Gynecol Clin North Am* **34**: 213–24

Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Hum Reprod* **19**: 41–7

Scott DA, Loveman E, Mcintyre L, Waugh N (2002) Screening for gestational diabetes. *Health Technol Assess* **6**: 1–161

Tomlinson J, Millward A, Stenhouse E, Pinkney J (2010) Type 2 diabetes and cardiovascular disease in polycystic ovary syndrome. *Diabet Med* **27**: 498–515

Tomlinson JA, Pinkney JH (2007) Diabetes and polycystic ovary syndrome. *Practice Nurse* **34**: 43–7

Toulis KA, Goulis DG, Kolibianakis EM et al (2009) Risk of gestational diabetes mellitus in women with polycystic ovary syndrome. *Fertil Steril* **92**: 667–77

Zawadski JK, Dunaif A (1992) Diagnostic criteria for polycystic ovary syndrome. In: Dunaif A, Givens JR, Haseltine FP, Merriam GE, eds. *Polycystic Ovary Syndrome*. Blackwell Scientific Publications, Boston

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