Screening for glycaemic abnormalities in PCOS: an ongoing controversy

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In the current issue of Human Reproduction, Veltman-Verhulst et al. (2013) have explored a controversial area of clinical importance screening of young women with polycystic ovary syndrome (PCOS) for diabetes abnormalities. In a cross-sectional study of 229 women with PCOS attending an infertility service, the authors evaluate a two-step screening process for the detection of diabetes. They conclude that diabetes patients could potentially be found by initial fasting glucose assessment followed by an oral glucose tolerance test (OGTT) only in patients with fasting glucose between 6.1 and 7.0 mmol/l. This commentary on the study by Veltman-Verhulst et al. highlights the need to consider levels of dysglycaemia lower than that of frank diabetes and emphasizes the need for further research into the metabolic impact of PCOS and into optimal screening approaches for glycaemic abnormalities in this high-risk group of reproductive age women.

PCOS is the commonest endocrinopathy affecting reproductive aged women with a reported prevalence of 6–21%, depending on the diagnostic criteria applied and population studied (Azziz et al., 2004; March et al., 2010). Whilst reproductive features are the most recognized in PCOS and underpin diagnosis, significant metabolic complications are well established, present across all phenotypes (Azziz et al., 2009) and are independent of obesity (Teede et al., 2011). These metabolic abnormalities are underpinned by insulin resistance which occurs in 60–95% of (lean to obese) women with PCOS (Moran and Norman, 2004); and whilst its occurrence is independent of, it can be exacerbated by, excess weight (Legro et al., 2004; Stepto et al., 2013). Metabolic complications include dyslipidemia, prediabetes, gestational diabetes (GDM), type II diabetes (DM2) amongst other cardiovascular conditions (Boomsma et al., 2006; Moran et al., 2010). Women with PCOS have an earlier onset of glycaemic abnormalities and a more rapid conversion to DM2 (Ehrmann et al., 1999). Even lean and younger women with PCOS have glycaemic abnormalities, although conventional risk factors, including age and higher BMI, do significantly contribute to this increased risk.

The increased risk of glycaemic abnormalities in PCOS is clinically relevant and should be actively screened for and identified, not only DM2 but also prediabetes, for four key reasons. First, absolute risk of glycaemic abnormalities is high and a further 3–4-fold greater risk with PCOS will result in a large increase in total cases (as observed in the study by Veltman-Verhulst et al., where 25% of the young women screened had glycaemic abnormalities). Secondly, the implications of glycaemic abnormalities (both prediabetes and DM2) for reproductive aged women seeking pregnancy are profound, given the well-established adverse maternal health impacts in pregnancy including pre-eclampsia, induced labour and Caesarean delivery, and neonatal health risks, including shoulder dystocia, hypoglycaemia, respiratory distress and neonatal care admissions (Metzger et al., 2008). This has prompted the urgent call for preconception screening, detection and optimization of both blood glucose levels and of body weight in reproductive aged women. Thirdly, recognizing those with increased risks (including those with prediabetes and GDM) mandates more aggressive or ‘higher dose’ lifestyle intervention. Whilst in the ideal world intensive lifestyle intervention would be offered equally to women with PCOS and/or obesity, the reality of high costs, limited availability and access necessitates lifestyle dose adjustment and mandates prioritization for those most at risk. Case in point, women with PCOS who also have prediabetes are a vital target group for intensive lifestyle programmes, which are proven to prevent diabetes onset (Diabetes Prevention Program Research Group, 2002). Finally, as women with PCOS are also more prone to obesity, dyslipidemia and potentially hypertension, the additive effect of glycaemic abnormalities (both prediabetes and DM2) to these other risk factors, augments overall metabolic risk and mandates more aggressive screening and intervention.

Moving forward, one of the key challenges in establishing screening approaches for glycaemic abnormalities in PCOS is the lack of good quality prospective longitudinal studies assessing outcomes across the range of BMIs, PCOS phenotypes and ethnic groups to inform recommendations. As highlighted in the recent National Institutes of Health evidence-based workshop on PCOS, these studies are vital to determine the natural history of the disease (including glycaemic status in PCOS) (NIH, 2012). In spite of this, the majority of international recommendations suggest regular testing with an OGTT, as outlined by Veltman-Verhulst et al. (2013). Veltman-Verhulst et al., in the accompanying publication, propose an alternative practical two-step approach for screening fasting glucose followed by targeted OGTT in those with fasting blood glucose levels between 6.1 and 7 mmol/l, after studying a mostly Caucasian population of young women with PCOS. However, before this more convenient and potentially cost-saving approach can be advocated for use in clinical practice, further evaluation is required. This should include the (i) assessment of the discriminatory power of screening approaches using area under the receiver operating characteristic curves (and comparisons with other approaches such as screening...
fasting glucose level alone and combination of screening fasting glucose level and clinical risk prediction scores); (ii) calculation of the integrated discrimination improvement statistics to measure the change in discrimination when an extra step was added; (iii) statistical testing at different thresholds of glucose [i.e. fasting blood glucose (mmol/l) < 5 versus ≥5; <5.6 versus ≥5.6; < 6.1 versus ≥6.1 and < 7 versus ≥7]; (iv) external validation in longitudinal prospective cohorts of diverse groups of women with PCOS and (v) assessment of cost-effectiveness.

PCOS is common and related to the obesity epidemic. Diagnosing PCOS identifies women at high risk of glycaemic abnormalities (including clinically relevant prediabetes, GDM and DM2) at a young age. Diagnosis of glycaemic abnormalities facilitates targeted more intensive intervention. Moving forward we need prospective longitudinal studies across the range of BMIs, PCOS phenotypes and ethnic groups to determine the natural history of glycaemic abnormalities in this population and to inform the optimal method and frequency of screening. Application of sophisticated statistical modelling techniques is then required to ascertain which is the best screening approach. Until that time consensus statements and recommendations on screening for glycaemic abnormalities are in principal important in PCOS, but will largely continue to be based on insufficient evidence.

References


