Diagnosis and follow-up of type 2 diabetes in women with PCOS: a role for OGTT?

Marianne Andersen and Dorte Glintborg

Department of Endocrinology, Odense University Hospital, Odense, Denmark

Correspondence
should be addressed
to M Andersen

Email
msa@rsyd.dk

Abstract

Polycystic ovary syndrome (PCOS) is common in premenopausal women. The majority of women with PCOS have insulin resistance and the risk of type 2 diabetes mellitus (T2D) is higher in women with PCOS compared to controls. In non-pregnant women with PCOS, glycemic status may be assessed by oral glucose tolerance test (OGTT), fasting plasma glucose (FPG) or HbA1c. OGTT has been reckoned gold standard test for diagnosing T2D, but OGTT is rarely used for diagnostic purpose in other non-pregnant individuals at risk of T2D, apart from PCOS. OGTT has questionable reproducibility, and high sensitivity of the 2-h glucose value is at the expense of relatively low specificity, especially regarding impaired glucose tolerance (IGT). Furthermore, lean women with PCOS are rarely diagnosed with T2D and only few percent of normal-weight women have prediabetes. Glycemic status is necessary at diagnosis and during follow-up of PCOS, especially in women with high risk of T2D (obesity, previous gestational diabetes (GDM)). We suggest that OGTT should be used in the same situations in PCOS as in other patient groups at risk of T2D. OGTT is indicated for diagnosing GDM; however, OGTT during pregnancy may not be indicated in lean women with PCOS without other risk factors for GDM.

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Introduction

Polycystic ovary syndrome (PCOS) is the most frequent endocrine condition in women, but the diagnosis of PCOS is only possible during premenopausal years (1). The Rotterdam Criteria are used to establish the diagnosis of PCOS when other causes of the clinical phenotype are excluded (1). PCOS is characterized by insulin resistance and hyperinsulinemia and insulin resistance is closely associated with obesity in PCOS (2). The prevalence of type 2 diabetes mellitus (T2D) is increased in PCOS. Recently, we reported that the hazard ratio of T2D in Danish women with PCOS was 4 compared to controls (3), which corresponded to findings from previous meta-analyses in mixed study populations of women with PCOS (4, 5, 6, 7). Validated diagnostic criteria are necessary to diagnose T2D in PCOS, but which diagnostic tool should be preferred is currently debated: Circulating glucose

(fasting plasma glucose (FPG) or during oral glucose challenge, 2-h glucose) or hemoglobinA1c (HbA1c).

The aim of assessing glycemic status in PCOS is to diagnose T2D or prediabetes. Furthermore, determination of glycemic status can be a measure of insulin resistance in PCOS and glycemic status may help selecting which women need closer prospective follow-up regarding cardiometabolic risk (Fig. 1). It is important to notice that prediabetes is neither normal glucose metabolism or an actual disease, but rather a risk factor for future T2D and cardiovascular disease (CVD). In PCOS, a diagnosis of prediabetes can also be used as an indication for metformin therapy (8). Glycemic status is included in the various definitions of metabolic syndrome. In PCOS, metabolic syndrome is defined as impaired glucose tolerance (prediabetes), waist circumference ≥ 88 cm, blood

Figure 1

Glycemic status in PCOS is influenced by various factors, and treatment of PCOS will modify risk of type 2 diabetes mellitus, cardiovascular disease and mortality..

pressure >130/85 mmHg, high-density lipoprotein (HDL) <1.3 mmol/L and triglyceride (TG) >1.7 mmol/L (9). It has been estimated that about 33% of women with PCOS fulfill one or more criteria of the metabolic syndrome (10) and international guidelines recommend that all newly

referred women with PCOS are screened for the elements of the metabolic syndrome to detect women with high cardiometabolic risk (10), but the best marker for glycemic status in PCOS is debated (11). Recommendations regarding oral glucose tolerance test (OGTT) at the time of PCOS diagnosis and follow-up vary between PCOS professionals. At one end of the spectrum, the Australian guideline recommends OGTT at diagnosis of PCOS and annually during follow-up, whereas European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) only recommends OGTT if BMI is $\geq 27 \text{ kg/m}^2$, and there is no mentioning of OGTT during follow-up (Table 1) (11). Should OGTT be recommended in all women with newly diagnosed PCOS and what are the pros and cons regarding OGTT during follow-up in PCOS (Table 2)?

Pre-pregnancy and pregnancy are times, where glycemic status is very important for the developing offspring and for the individual woman. The risk of gestational diabetes mellitus (GDM) was significantly increased in women with PCOS (12, 13). In general, OGTT is gold standard for diagnosing GDM, but the optimal cut-off value for 2-h glucose during OGTT in pregnancy and alternatively for FPG are debated (14, 15). Furthermore, should all women have an OGTT performed already when pregnancy is planned?

Table 1 International guidelines regarding OGTT upon diagnosis of PCOS.

Guidelines	OGTT recommended upon diagnosis in all women with PCOS?	Follow up OGTT
Joint AACE/ACE and AE-PCOS society	Yes	Yearly in women with IGT Every 1–2 years based on BMI (not specified) and family history of T2D
Australian NHMRC	Yes	Every 2 years Annually if additional risk factors for T2D*
Endocrine Society	Yes	Every 3–5 years Sooner if additional risk factors for T2D** Annually in women with IGT or IFG
Royal College of Obstetricians and Gynecologists	No Recommended if one or more: BMI $\geq 25 \text{ kg/m}^2$, age ≥ 40 years, previous gestational diabetes, or family history of T2D	
AE-PCOS Society	No Recommended if one or more: BMI $\geq 30 \text{ kg/m}^2$, age ≥ 40 years, previous gestational diabetes, or family history of T2D	Every 2 years in women with risk factors*** Sooner if additional risk factors for T2D develop***
ESHRE and ASRM	No Recommended if BMI $\geq 27 \text{ kg/m}^2$	Not specified

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*Age, gender, ethnicity, parental history of diabetes, history of high blood glucose levels, use of antihypertensive medications, smoking, physical inactivity, waist circumference; **central adiposity, substantial weight gain, and/or symptoms of diabetes; ***obesity, cigarette smoking, dyslipidemia, hypertension, IGT or subclinical vascular disease.

AACE, Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AE-PCOS society, Androgen Excess and PCOS society; ASRM, American Society for Reproductive Medicine; ESHRE, European Society of Human Reproduction and Embryology; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NHMRC, National Health and Medical Research Council; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

Table 2 Arguments for OGTT in PCOS and corresponding counter-arguments.

Argument for OGTT	Counter-argument
OGTT is important for diagnosing T2D and prediabetes in women with PCOS – at PCOS diagnosis and during follow up	HbA1c or FPG may be used for assessing glycemic status in most cases, however the setting needs to be considered
Considered gold standard test for T2D	OGTT as gold standard test may be questioned due to high variability of the test
ADA and WHO agree about the cut-off for IGT	95 percentile is used as cut-off for IGT, resulting in a high number of false positive patients
Can be performed in various settings (hospital, private clinic, at home)	High variability – two tests needed for diagnosis of T2D. HbA1c is more robust
Costs can be kept low (e.g. only measure 2 h CBG e.g. India)	HbA1c and FPG are cheaper than OGTT in many countries
FPG and HbA1c are not widely available	HbA1c could be superior to OGTT regarding metabolic risk and CVD
Standardized test – easy to perform	Dependent of height – one size does not fit all? Risk of over-diagnosis of T2D and IGT in women with low height?
High sensitivity compared to FPG and HbA1c regarding diagnosis of IGT and T2D	Over-diagnosis of IGT, T2D? Quality of life may be negatively influenced by a diagnosis of IGT
Can be applied in patients with iron deficiency, sickle cell trait etc.	Not recommended after bariatric surgery
Diagnosis of T2D and prediabetes important for risk of future CVD	HbA1c, sCD36, IL-6 or other markers could be superior to OGTT as screening markers for risk of future CVD
Diagnosis of IGT could determine treatment with metformin	Treatment with lifestyle modification and metformin is not dependent of OGTT, but should be considered in the majority of women with PCOS
OGTT can be used to determine insulin resistance in PCOS	Waist and BMI are the best markers of insulin resistance in PCOS
Can be used to determine metabolic status during metformin and oral contraceptive treatment	There are insufficient data to recommend prospective OGTTs during medical treatment in PCOS
Prediabetes screening is important before pregnancy in PCOS	Screening for metabolic risk before pregnancy could include HbA1c, BMI and waist measurements
Gold standard for diagnosing GDM	The cut-off for CBG in OGTT to diagnose GDM is not settled. The risk for GDM in PCOS is dependent of BMI

CBG, capillary blood glucose; CVD, cardiovascular disease; FPG, fasting plasma glucose; GDM, gestational diabetes; IGT, impaired glucose tolerance; T2D, type 2 diabetes.

The case in favor of OGTT in PCOS

OGTT as a diagnostic method for T2D

OGTT has been used for more than 40 years and the test is available worldwide. The test is usually considered gold standard for diagnosing diabetes. The international definition of T2D during a 2-h 75 g OGTT is a 2-h glucose value ≥ 11.1 mmol/L (16). The OGTT can be performed at a hospital setting, at a laboratory or may be performed at the patient's home by a health professional. In some countries, only 2-h glucose is assessed in capillary blood using a small portable device, and hence, the cost of the OGTT can be kept low. Alternative methods for diagnosing T2D are FPG and/or HbA1c. The cut-off for FPG is ≥ 7.0 mmol/L (16). The use of FPG for determining glycemic status has drawbacks and advantages compared to OGTT. FPG requires fasting for 8 h (17) in line with OGTT, and the glucose analysis should be performed in venous plasma (17). FPG has less sensitivity but increased specificity compared to 2-h glucose (18, 19).

International guidelines support that values of HbA1c >48 mmol/mol ($\geq 6.5\%$) can be applied for diagnosing T2D in asymptomatic patients (20), whereas HbA1c levels between 6 and 6.4% (42–47 mmol/mol) should be followed by an OGTT and HbA1c levels below 6% require no further tests (20). The cut-off point for HbA1c is largely based on the established association between HbA1c and microvascular disease (20). HbA1c reflects the average blood glucose levels during a 2- to 3-month period in persons a normal erythrocyte life cycle (20). When OGTT is considered the gold standard for diagnosing T2D, HbA1c may not be appropriate for diagnosing T2D. In PCOS, we found that 20 women out of 208 had T2D according to OGTT, whereas only 7/208 women had elevated HbA1c (21). The sensitivity of HbA1c $\geq 6.5\%$ as a diagnostic test for T2D compared to OGTT was only 35%, whereas the specificity of HbA1c was 99%, and the more severe cases of T2D diagnosed by OGTT were also identified by HbA1c (21). Low diagnostic performance of HbA1c compared to OGTT for the diagnosis of T2D was also reported in non-

PCOS populations (22, 23, 24). Previous studies evaluated the consequence of reducing the HbA1c cut-off to 6.0% (24) and reported that the sensitivity of HbA1c compared to the OGTT increased from 35 to 50%, however, specificity only decreased from 99 to 96%.

The prevalence of impaired glucose tolerance (IGT) in PCOS was up to 36% and the odds ratio for IGT was 2.48 (95% CI 1.63–3.77) in women with PCOS compared with controls (25). In the general population, around 5–10% individuals with prediabetes convert to diabetes per year and up to 70% individuals with prediabetes will develop T2D (26). Prediabetes may be diagnosed by IGT, IFG or HbA1c in the gray zone. However, the cut-offs for glucose and HbA1c are unsettled. American Diabetes Association (ADA) and World Health Organization (WHO) have consensus regarding cut-off limits for IGT, whereas the cut-offs for IFG are 5.6 mmol/L (ADA) and 6.0 mmol/L (WHO) (27). The cut-off for prediabetes, using HbA1c, is 42 mmol/mol (6.0%), according to WHO and the International Expert Committee, whereas the cut-off according to ADA is 39 mmol/mol (5.7%) (27). In our previous study in PCOS, all patients with IGT during OGTT had HbA1c levels <6.5% and the sensitivity for HbA1c $\geq$ 6.5% as diagnostic test for abnormal glucose tolerance compared to the OGTT was only 13% (21). HbA1c therefore seems to be a poor marker of IGT and 2-h glucose is the most sensitive test for diagnosing prediabetes.

OGTT as a marker of insulin resistance

Central obesity is associated with insulin resistance and predicts the development of T2D and CVD (28). MRI is considered gold standard for measurement of regional fat mass, but is not generally available in a clinical setting (29). Weight and BMI are the simplest methods for the establishment of total body fat, and waist circumference is a good estimate of abdominal fat (30). Therefore, weight, BMI and waist measurements should be applied in all newly referred women with PCOS (31). In addition, whole-body DXA scans make it possible to estimate abdominal and extremity fat mass (32). This method does not distinguish intra-abdominal fat mass from subcutaneous fat mass, but subcutaneous abdominal and intra-abdominal fat could have similar adverse effects on insulin resistance (33). BMI was the most important predictive factor for the development of T2D in prospective studies in PCOS (34). We recently compared fat distribution in women with PCOS vs controls and established the best measure of fat mass to predict insulin resistance in PCOS (35). Women with PCOS had higher central fat mass (waist, waist-to-

hip ratio (WHR) and upper/lower fat ratio) compared to controls. Trunk fat, waist and BMI were the best predictors of homeostatis model of insulin resistance (HOMA-IR) in PCOS (35). These findings supported that BMI and waist measurements could predict insulin resistance in women with PCOS. Insulin sensitivity is most reliably measured by a hyperinsulinemic-euglycemic glucose clamp method. However, in favor of OGTT – also in PCOS, Abdul-Ghani *et al.* (36) showed that IGT showed closer association with total glucose disposal during a hyperinsulinemic-euglycemic clamp than IFG. Furthermore, the 2-h glucose level during OGTT is less fluctuating than FPG, as OGTT is a standardized challenge test. IGT is an important predictor of future T2D in patients with PCOS (37, 38) and a diagnosis of IGT may be used in the daily clinic to identify patients who may benefit the most from lifestyle and medical intervention.

OGTT during preconception and pregnancy

In pregnancy, maternal insulin sensitivity changes to accommodate fetal glucose needs and insulin resistance prevail in the third trimester (39). GDM complicates 2–3% of pregnancies in Denmark (40). Maternal hyperglycemia is associated with excessive fetal growth and increased need for cesarean delivery (41). The intrauterine environment in women with PCOS is influenced by maternal obesity, hyperinsulinemia, androgen excess and elevated fat mass in the offspring at birth (42) and later in life (43). Therefore, women with T2D or IGT should be identified as early as possible for example during preconception care and during fertility treatment (44). Individual screening for metabolic risk and initiation of lifestyle intervention and metformin treatment should be considered in all women with PCOS, who are seeking advice for fertility treatment. The time during preconception care could indeed be a window of opportunity to investigate and treat adverse metabolic risk in PCOS.

OGTT is considered gold standard test to diagnose GDM. At present, there is conflicting evidence whether PCOS *per se* increases the risk of GDM or whether obesity is the key factor (15). We recently reviewed 30 studies regarding GDM in PCOS and found that the prevalence of GDM in PCOS and controls varied widely (1.1–55.7% in PCOS and 0.6–30.4% in controls) (15). Data were not uniform and study cohorts varied widely, but higher BMI, higher age, Asian ethnicity and fertility treatment were associated with increased risk of GDM in PCOS. In a relatively lean Danish cohort, the prevalence of GDM was similar in women with PCOS and controls independent

of applied diagnostic criteria for GDM (15). Pregnancy in PCOS is characterized by factors known to increase risk of GDM, especially high BMI and fertility treatment, whereas PCOS may not be an individual risk factor for GDM. Criteria for individual risk assessment are not available in PCOS, and until then, OGTT should be performed during pregnancy in all women with PCOS.

OGTT as a marker of long-term metabolic risk and CVD

Insulin resistance, low-grade inflammation and central obesity in PCOS could be associated with increased risk of development of CVD. Coronary artery calcification and echocardiographic abnormalities were more common in women with PCOS compared to controls (45), but the risk for hard cardiovascular endpoints such as coronary heart disease and stroke in PCOS is debated. The OR for CVD in PCOS varied from 1.3 to 2.0 in recent meta-analyses (4, 5, 6, 7), but the association between CVD and PCOS was not significant in all studies (4, 5). In a Danish study population of women with PCOS, we found a hazard ratio (95% CI) for development of CVD including hypertension and dyslipidemia of 1.7 (1.6–1.8) and the total event rate of CVD was 22.6 per 1000 person years in women with PCOS vs 13.2 per 1000 person years in controls ($P < 0.001$) (46). When we excluded hypertension and dyslipidemia from the study outcome, the incidence rate for CVD was reduced to 6.4 per 1000 person years in PCOS vs 4.5 per 1000 person years in controls ($P < 0.001$) (46). Included women in the study were aged 29 (23–35) years (median (quartiles) at study inclusion and the follow-up was 11.1 (6.9–16.0) years (46). These findings supported that the risk for CVD should be considered also in young women with PCOS (46), but the absolute risk for CVD in premenopausal women with PCOS was low. The best glycemic marker for future CVD in PCOS is debated. In non-PCOS study populations, several studies suggested that HbA1c could be a better predictor of CVD and overall mortality than fasting or 2-h glucose during OGTT (47, 48). Population-based studies found that higher HbA1c levels within the reference range were associated with higher risk for CVD (49, 50, 51) and the lowest risk for CVD was observed in individuals with HbA1c levels $< 5\%$ (50, 51). Furthermore, HbA1c was more strongly associated with risk of CVD and death from any cause than fasting glucose (49). In agreement with this hypothesis, we previously performed OGTT and HbA1c in 208 premenopausal women with PCOS and found that HbA1c showed closer correlation with waist, BMI and lipid profile than 2-h BG during OGTT

(21). These results could be in favor of measuring HbA1c instead of performing OGTT to determine cardiovascular risk in PCOS (21). We further evaluated this hypothesis in 1165 women with PCOS and no previous diagnosis of CVD, dyslipidemia or hypertension (46). We found that HbA1c, fasting insulin and HOMA-ir were higher at baseline evaluation in women with PCOS who were diagnosed with CVD later on compared to women not diagnosed with CVD. In multiple regression analyses, 2-h glucose, fasting insulin and HOMA-ir predicted development of CVD after adjusting for age and BMI, whereas HbA1c did not predict CVD risk. Therefore, these study findings did not support that HbA1c was a better predictor of CVD than 2h or fasting glucose (49). In our national study cohort of women with PCOS, a baseline diagnosis of diabetes, without considering diagnostic assessment method, increased the risk of CVD more than threefold, confirming that women with PCOS and diabetes need special attention regarding risk of CVD (46). Furthermore, the risk of CVD is closely associated with age, and the absolute risk for cardiovascular events in young women with PCOS is low. Medical treatment with statins, antihypertensives and blood diluting agents are rarely indicated in reproductive aged women with PCOS as there are limited safety data regarding treatment with the drugs during pregnancy (52). The prevalence for myocardial infarction was 27% in women with PCOS aged > 65 years and the OR for myocardial infarction were 12.9 in women with PCOS aged > 65 years vs controls (53). Furthermore, the risk for stroke was significantly increased in PCOS when only studies in women of average age > 45 years were included (5). Increasing age in PCOS was associated with higher blood pressure, more adverse lipid profile, and impaired beta cell function (54). These findings suggest that the metabolic screening program in PCOS should be adjusted to take increasing age into account. Menopause status could be an important confounder when looking at the association between metabolic risk and age in PCOS. After menopause, levels of adrenal and ovarian androgens decrease, which could affect cardio-metabolic risk in PCOS. Decreased estrogen levels during menopause could be associated with metabolic dysfunction and deposition of visceral (and ectopic) fat (55). Testosterone has, previously, been associated with unfavorable metabolic factors in premenopausal women (56, 57). However, whether high androgens have a protective or unfavorable influence on the manifestation of CVD in women with PCOS has not been settled (58, 59). Interestingly, metabolic health may be better than expected in postmenopausal women with previous PCOS, as no strong positive associations were

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found between testosterone levels and risk of CVD (59). All the above findings underline the need for prospective, well-phenotyped cohort studies in postmenopausal women with a former PCOS diagnosis.

Conclusion in favor of OGTT

Women with PCOS have significantly increased risk of T2D compared to women without PCOS (3). OGTT is reckoned gold standard test for diagnosing diabetes and prediabetes (27) and OGTT is recommended for assessing glycemic status at time of diagnosing PCOS and during follow-up, independently of BMI (8). Especially in countries where FPG cannot be handled correctly and HbA1c is not valid, OGTT is a necessity. OGTT is often used in pre-pregnancy and of course during pregnancy to diagnose GDM.

The case against OGTT in PCOS

No indication for OGTT in all women with PCOS

Glycemic status needs to be evaluated in PCOS due to increased risk of T2D (3). OGTT has been considered gold standard test for diagnosing diabetes and prediabetes (27), and the Australian guideline for PCOS recommends that OGTT should be performed by time of the PCOS diagnosis and then repeated annually (11). The prevalence of PCOS is estimated to be 10–15% in reproductive aged women and adhering to the Australian guideline would result in performing a considerable number of OGTTs. Performing such a high number of OGTTs may not balance the cost for the individual woman, lost income and time or general cost for society (60). The recommendation for performing OGTT according to the last guideline from 2013, was more modest: ‘Diagnosis and treatment of Polycystic Ovary Syndrome: An endocrine society clinical practice guideline: All women with PCOS should have an OGTT at time of PCOS diagnosis and every 3–5 years hereafter, unless the woman is unable or unwilling to complete an OGTT’ (8). In agreement, ESHRE/ASRM recommended that OGTT is only indicated in overweight women (11). This last recommendation reflects that T2D or IGT are mainly diagnosed in overweight women (11, 18) as no one (11) or very few normal-weight women with PCOS had impaired glycemic status (18). Ollila *et al.* (61) reported that none of 62 lean Finnish women with self-reported PCOS developed T2D by 46 years of age and suggested that OGTT screening should be targeted to overweight and obese women with PCOS. Recently, Pelanis *et al.* (11)

confirmed these results in a Nordic cohort of women with PCOS. No Nordic (0/298) woman was diagnosed with T2D using OGTT if BMI was below 25 kg/m². In agreement, other studies found very few patients with BMI <25 kg/m² and T2D during OGTT: 0/298 (0%) (62), 1/104 (0.9%) (63) and 1/57 (1.8%) (18).

Celik *et al.* (64) reported that obese women with PCOS were 4 times more prone to convert from normal glucose tolerance (NGT) to IGT than lean women with PCOS. Other papers confirmed that BMI was an independent risk factor (34, 65) for development of T2D in PCOS. Even in an Asian population, Li *et al.* (66) reported that impaired glucose metabolism with decreased insulin secretion was predominantly found in Chinese women with PCOS and BMI >25.5 kg/m². β -Cell function was not impaired in normal-weight patients with PCOS, but insulin resistance was common in lean Chinese women with PCOS (67). These studies question the necessity for OGTT in lean women with PCOS.

Metabolic risk could be modified according to PCOS phenotype. Women fulfilling the National Institute of Health (NIH) criteria for PCOS could have higher metabolic risk than patients with milder phenotypes (68) and metabolic disturbances were more pronounced in women with PCOS and hyperandrogenism as compared to women with no hyperandrogenism (69). However, high testosterone and PCOS phenotype did not predict glycemic status in three studies, two recent Nordic studies (3, 11) and one Chinese study (70). It is important to recognize that BMI differed between different Rotterdam phenotypes (11). Therefore, studies regarding metabolic risk in different PCOS phenotypes need to adjust for BMI.

Problems with OGTT as a diagnostic method for T2D and IGT

OGTT is rarely used as a diagnostic tool for T2D (71), except during pregnancy and in women with PCOS (11). A previous study on reproducibility of a standard 75 g 2-h OGTT concluded that the intra-individual variation in 2-h glucose determinations was so high that the continued use of an OGTT for a diagnostic purpose could be questioned (72). Therefore, a second OGTT is required in order to establish a diagnosis of diabetes mellitus if the first test is abnormal (27).

Furthermore, body composition may affect the result of OGTT along with genetics, diet and lifestyle (73, 74). South Asians tend to have significantly shorter stature, and reduced height could explain the higher incidence of IGT in women as compared to men, whereas more

men more often have IFG (73). In contrast to negative associations between height and 2-h glucose, FPG and HbA1c were not significantly related to height (73). It is possible that the glucose load during an OGTT should be adjusted according to height and/or ethnicity (73). However, what is the real gold standard test for T2D? The cut-off level for 2-h blood glucose to diagnose diabetes was initially defined in a very high-risk group of individuals, the Pima Indian population, where glucose values were bi-modally distributed (75). In contrast to Pima Indians, other populations usually have a unimodal distribution of 2-h glucose values (75). In general, it is difficult to separate patients from healthy individuals in a unimodal distribution (75), whereas bimodal distributions enable a cut-off between healthy individuals and patients with T2D. A cut-off rarely ensures 100% sensitivity and 100% specificity, but in a bimodal distribution, it is possible to estimate sensitivity and specificity of various cut-offs. Cut-off limits are usually defined as the lower and upper boundaries of a 95% reference interval. Regarding risk of T2D or prediabetes, only the upper cut-off limit is of interest. The cut-off limit would correspond to the 97.5 percentile and by definition, 2.5% of healthy individuals would be false-positive individuals (76). WHO (16), actually, applied the 95 percentile for diagnosing IGT and thereby accepted 5% false-positive tests (76). A change of cut-off limit will impact the sensitivity and specificity of a test. Clinicians may prioritize high sensitivity of diagnostic tests to avoid skipping a single patient, but false-positive and false-negative diagnoses matter differently in various situations (60). A false-negative test result should be avoided when donor blood is screened for human immunodeficiency virus (HIV) infection, but diagnosing T2D or prediabetes is a different situation. If sensitivity should be close to 100%, it would be at the expense of diagnosing healthy individuals with T2D or prediabetes. Receiver-operating characteristic (ROC) curves summarize accuracy of various cut-offs of f.x. 2-h glucose (60), and the graphical ROC curve may be very informative (60). ROC curves require a gold standard test. OGTT is reckoned a gold standard test to diagnose T2D, but considering the low reproducibility of 2-h glucose levels (72), the OGTT may disqualify for a gold standard status? Furthermore, ROC curves do not take disease prevalence into account.

It is important to notice that there is no accurate diagnostic test for prediabetes (27). The OGTT is more sensitive to diagnose prediabetes than FPG or HbA1c; however, this increased sensitivity may be at the expense of decreased specificity (76). In addition, cut-off limits for prediabetes differ between ADA (United States) and

WHO (27). Diagnosing an individual with prediabetes has large implications for many patients. Time consumed with testing, medication and especially stigma and worries should be considered before recommending the OGTT. Women with PCOS have lower scores for good quality of life compared to healthy controls (77) and higher prescription rate of antidepressants compared to controls (78). Importantly, many women with PCOS and IGT could have continued living relatively healthy normal lives without ever having either T2D and perhaps without increased risk of CVD (27). Therefore, performing an OGTT may not be needed even in women with an elevated risk of T2D, and measurement of FPG or HbA1c may be applied instead.

Glycemic status and CVD, OGTT is not necessary

The risk of T2D is low in most women with PCOS, but the risk for T2D increases along with BMI (3, 11, 18, 61), and central obesity is associated with insulin resistance and increased levels of adipokines and inflammatory markers. High levels of inflammatory markers could predict the development of type 2 diabetes mellitus and CVD (79, 80). The foam cell formation process is initiated and enhanced by the binding of oxLDL to CD36 receptors, therefore making CD36 activity a risk factor of CVD (81). Women with PCOS had higher soluble CD36 levels than weight-matched controls (82) and soluble CD36 was inversely associated with insulin sensitivity and positively associated with lipid oxidation during insulin stimulation (83). Other promising cardiovascular risk markers in PCOS are hsCRP and IL-6 (31). Measurement of these markers has not been implemented in everyday clinic, and it remains to be established whether one or more of these markers could be better predictors of long-term cardiometabolic risk in PCOS than glycemic status established by OGTT.

Prediabetes may be an indication for metformin therapy. Furthermore, a diagnosis of prediabetes may focus the attention on other metabolic risk factors for CVD such as BP and lipid status (84). Lipid status should be assessed by the time of PCOS diagnosis (46), but statin treatment is rarely indicated in women with PCOS <35 years (52) as there is no evidence for treating all women with PCOS and a diagnosis of IGT as strict as patients with T2D (84). Data are needed to support an additional effect of knowing IGT status for the motivation and performance regarding weight loss and physical activity of the individual woman with PCOS. No data exist from large international studies regarding prediabetes and

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risk of CVD in PCOS. A recent study in ageing women and men reported that prediabetes defined by HbA1c was associated with a worse prognosis than prediabetes defined by FPG or 2-h glucose. However, the excess risk among individuals with prediabetes is mainly explained by the clustering of other cardiometabolic risk factors associated with hyperglycemia (85).

For now, a diagnosis of IGT is not mandatory as part of the cardiometabolic risk assessment in PCOS.

OGTT during medical treatment?

Lifestyle intervention and metformin are first-line treatment in overweight and obese women with PCOS, whereas the use of lifestyle and metformin treatment in normal weight women is less established. The aim of these treatment modalities is to promote weight loss, increase insulin sensitivity and to regulate menstrual cycles (86, 87). Weight loss around 5% is often sufficient to improve menstrual cycles and ovulation rate (86). Metformin is often considered second-line treatment in PCOS and the PCOS guideline from 2013 recommended metformin in women with PCOS with T2D or IGT who failed lifestyle modification (8). The number of women with PCOS, who fail lifestyle intervention, is very high, and metformin therapy is indicated in many women with PCOS. Metformin is efficacious in reducing weight in women with PCOS also before a derangement in glycemic status (88). Therefore, metformin may be of benefit also in women with PCOS and NGT. Treatment with metformin in lean women with PCOS was associated with a significant weight loss (88) and improved menstrual cycles (89), but lifestyle intervention in lean women with PCOS may not be first choice unless the woman has a disadvantageous metabolic risk profile. The effect of lifestyle and metformin treatment can be monitored by decreased weight and improved cycle regularity. But how should effect of lifestyle and metformin treatment on glycemic status be monitored? – Is it relevant to monitor glucose tolerance prospectively by OGTT in normal weight women with PCOS treated with metformin? Long-term studies regarding the effect of metformin treatment on insulin sensitivity and outcomes of OGTT in PCOS are limited. We recently performed a randomized controlled trial in 90 women with PCOS randomized to 12-month treatment with metformin (2 g/day), oral contraceptives or metformin+oral contraceptives (90). Metformin treatment was associated with a significant weight loss of -3.0 (-10.3 ; 0.6) kg (median (quartiles) (88, 90). T2D at study entry was an exclusion criterion (88, 90), but three

women randomized to metformin treatment had IGT. During study intervention with metformin, two women with IGT converted to normal, but four women converted from normal glucose tolerance to IGT (unreported data) and area under the curve for glucose was unchanged (88). The study population was relatively lean with median BMI 25.1 (22.7 ; 29.4) kg/m² (median (quartiles)), which could have affected our study results. The study raises the question of the value of performing prospective OGTTs during medical treatment with metformin in lean women with PCOS. According to Tomlinson (91), no study has determined whether the incidence of T2D is reduced during treatment with metformin (91, 92). Small observational studies reported conflicting results regarding the effect of metformin on glucose tolerance in PCOS (93), and we are not aware of international guidelines concerning prospective OGTTs in women with PCOS on metformin treatment. In a similar way, the relevance of performing prospective OGTTs in women with PCOS treated with oral contraceptive treatment (OCP) has not been determined. Treatment with OCP was associated with increased body weight (88) and OCP could have an adverse effect on insulin resistance (87, 94). Prospective screening for T2D is therefore very relevant in women with PCOS on OCP, but the optimal screening modality has not been clarified.

OGTT may not be indicated during medical therapy in PCOS and development of T2D may be diagnosed by HbA1c and/or FPG.

Pregnancy and OGTT in PCOS

It is mandatory to diagnose impairment in glycemic status during pre-pregnancy and in pregnancy as hyperglycemia should be avoided, especially in early pregnancy. Glycemic status may be assessed by HbA1c, FPG or 2-h glucose before pregnancy. The indication for OGTT before pregnancy is debated, but there is no evidence regarding the superiority of OGTT in this situation. By definition, many women with PCOS have irregular menses and pregnancy may not be fully planned; hence, it is difficult to plan the timing of an OGTT, whereas HbA1c may be easier to assess consecutively. Furthermore, in many cases, a diagnosis of IGT during OGTT will not change the handling of the individual woman with PCOS as lifestyle modification, weight loss and physical activity should always be recommended during planning of pregnancy.

During pregnancy, the situation is different. OGTT has, historically, been the test of choice for GDM. However, even though the WHO2013 criteria (95) have been accepted in Europe, a recent European survey

reported that most European centers used risk factor assessment before an OGTT was performed (96). In accordance, The Danish Society for Obstetrics and Gynecology has endorsed the WHO2013 criteria (95), but the GDM diagnosis in Denmark follows the criteria stated by Jensen *et al.* (97). PCOS is a risk factor for GDM, but PCOS as a sole risk factor has not yet been implemented. In a prospective study in the Odense Child Cohort (98), we found no significant increase in GDM in women with PCOS compared to those without PCOS (15). The women in OCC were relatively lean, and the study included very few women of Asian origin.

There is a growing interest in FPG to determine glycemic status during pregnancy (14). However, a discussion of the cut-off for FPG is mandatory, as the number of pregnant women with GDM may be quite high in some populations. In accordance, we recently reported that applying the WHO2013 FPG threshold of ≥ 5.1 mmol/L (95) resulted in 40% women with GDM (14). Ethnicity predicts the risk of GDM as especially Asian women had a high prevalence of GDM (99). However, the use of 3 h 100 g OGTT and 1 h 50 g OGTT for diagnosing GDM (99) could lead to overdiagnosis of GDM due to low height in Asian populations (73, 74).

Bariatric surgery, GDM and OGTT

Bariatric surgery in PCOS is associated with high weight loss, increased insulin sensitivity and improved ovulation rate (100, 101). The phenotype of PCOS often totally disappears after bariatric surgery and therefore supports an emerging concept that, in the presence of massive obesity, a secondary PCOS may develop. In Denmark, PCOS is considered an individual risk factor for obesity, and women with BMI >35 kg/m² and a diagnosis of PCOS are bariatric surgical candidates. In a recent Danish study, the average weight loss in premenopausal women during the first postoperative year was 39.6 kg (102). Pregnancy should be avoided within 2 years after bariatric surgery and young fertile women should use safe birth control (103). Performing OGTT after bariatric surgery can trigger dumping syndromes and is generally not recommended (104). OGTT-induced dumping syndrome can lead to inaccurate results of the OGTT and the risk of reactive hypoglycemia was 55% in previous studies (105). Screening for GDM in women with previous bariatric surgery should therefore not involve the OGTT. Instead, HbA1c can be measured at the first antenatal visit to exclude pre-existing diabetes, but later in pregnancy there are no data to support use of HbA1c. Instead, fasting,

pre- and postprandial capillary blood glucose measurements are recommended to screen for GDM in pregnant women with previous bariatric surgery (104). The diagnostic or intervention thresholds for capillary blood glucose were >5.3 mmol/L before meals, >7.8 mmol/L 1 h after meals and >6.4 mmol/L 2 hours after meals according to National Institute for Health and Care Excellence (NICE) (<https://www.nice.org.uk/guidance/ng3/>).

Metformin during pregnancy in PCOS

Metformin may be applied as part of fertility treatment to improve pregnancy rate and the use of metformin may be continued during pregnancy to decrease risk of GDM and to improve pregnancy outcome. At present, metformin therapy in PCOS during pregnancy is considered experimental and metformin during pregnancy in PCOS is not yet generally recommended. A recent meta-analysis found that metformin improved live birth/ongoing pregnancy (RR, 1.28 (95% CI, 1.01–1.63)) and clinical pregnancy rates (RR, 1.26 (95% CI, 1.04–1.53)) when compared with placebo or no intervention (106), but the studies were of low quality and the effect of metformin was only modest. A randomized controlled trial in pregnant women with PCOS, comparing metformin to placebo, reported no significant difference in GDM prevalence 17.6% and 16.9%, respectively (107); however, the study could have been underpowered to detect change in GDM prevalence. Recent studies reported that the use of metformin during pregnancy in PCOS was associated with higher head circumference in the offspring at birth (108) and higher BMI and increased prevalence of overweight/obesity at 4 years of age (109).

At present, data are insufficient to decide if it is necessary to monitor glycemic status using OGTTs during metformin therapy in PCOS pregnancies, and it is too preliminary to apply the WHO2013 FPG threshold of ≥ 5.1 mmol/L (95) also in PCOS. Available data support that OGTT is probably not necessary in all pregnant women with PCOS whether untreated or on experimental metformin therapy.

Conclusion against OGTT

Glycemic status in PCOS may be evaluated by HbA1c, FPG or OGTT (71). BMI needs to be considered in PCOS as very few normal weight women are diagnosed with T2D. We need further data regarding prediabetes in PCOS and the impact of diagnosing IGT for future CVD, especially in young women with PCOS. At pre-pregnancy, glycemic

status may be assessed by other methods than OGTT. During pregnancy, OGTT may not be indicated in lean women with PCOS without other risk factors.

In general, the indication for OGTT in PCOS resembles the indication in other populations at risk for T2D (71). In most instances, HbA1c or FPG may be applied instead of OGTT.

Conclusion

Data are quite convincing against recommending OGTT in normal-weight, non-pregnant women with PCOS, including during planning of pregnancy. This statement is in line with the rare use of OGTT for diagnosing diabetes or prediabetes in other populations at risk of T2D. In overweight women with PCOS, an OGTT may be the test of choice, especially if OGTT is readily available. However, it is necessary to take the low reproducibility of 2-h glucose measurements in OGTT into account and the risk of a false-positive diagnosis of IGT or T2D. In pregnancy, normal-weight women with PCOS do not seem to have increased risk of GDM. Prospective OGTTs, during follow-up in PCOS, including metformin and OCP therapy, is a matter of discussion. In our opinion, glycemic status may be evaluated by HbA1c in many cases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this debate.

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Debate	M Andersen and D Glintborg	OGTT and T2DM	179:3	D14
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