Fasting glucose measurement as a potential first step screening for glucose metabolism abnormalities in women with anovulatory polycystic ovary syndrome

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STUDY QUESTION: Is routine screening by oral glucose tolerance test (OGTT) needed for all women with polycystic ovary syndrome (PCOS)?

SUMMARY ANSWER: Screening for glucose metabolism abnormalities of PCOS patients by an OGTT could potentially be limited to patients who present with a fasting glucose concentration between 6.1 and 7.0 mmol/l only.

WHAT IS KNOWN ALREADY: Women with PCOS are at increased risk of developing diabetes. This study proposes a stepwise screening strategy for (pre)diabetes for PCOS patients based on risk stratification by fasting plasma glucose.

STUDY DESIGN, SIZE, DURATION: A cross-sectional study of 226 women diagnosed with anovulatory PCOS.

PARTICIPANTS AND SETTING: A consecutive series of 226 patients, diagnosed with PCOS at the University Medical Centre Utrecht, the Netherlands, were screened for glucose metabolism abnormalities by OGTT (75 g glucose load).

MAIN RESULTS AND ROLE OF CHANCE: The majority of the 226 women (mean age: 29.6 ± 4.3 years; BMI: 27.3 ± 6.7 kg/m²; 81% Caucasian) presented with a normal OGTT (169 women (75%)). Of the 57 (25%) women presenting with mild to moderate glucose abnormalities, 53 (93%) could be identified by fasting glucose concentrations only. Diabetes was diagnosed in a total of eight women (3.5%). In six women, the diagnosis was based on fasting glucose ≥7.0 mmol/l. The other two cases of diabetes initially presented with fasting glucose between 6.1 and 7.0 mmol/l and were diagnosed by OGTT assessment. No women diagnosed with diabetes presented with fasting glucose levels below 6.1 mmol/l. We therefore conclude that all diabetes patients could potentially be found by initial fasting glucose assessment followed by OGTT only in patients with fasting glucose between 6.1 and 7.0 mmol/l.

LIMITATIONS, REASONS FOR CAUTION: Before general implementation can be advised, this screening algorithm should be validated in a prospective study of a similar or greater number of PCOS women.

WIDER IMPLICATIONS OF THE FINDINGS: Our study comprised of a mostly Caucasian (81%) population, therefore generalization to other ethnic populations should be done with caution.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a reported prevalence up to 12% (March et al., 2010). The syndrome is characterized by hyperandrogenism, anovulation and polycystic ovaries (PCO; The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004). Although not part of the diagnostic criteria for PCOS, insulin resistance is considered to play a key role in the aetiology of PCOS. Moreover, insulin resistance is associated with metabolic abnormalities (Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012) such as metabolic syndrome (Essah et al., 2007), dyslipidaemia (Westerveld et al., 2008), gestational diabetes (Boomsma et al., 2006) and type 2 diabetes (Legro et al., 1999). Debate continues whether women with PCOS, despite their adverse cardiometabolic profile, are indeed at increased risk of cardiovascular disease later in life (Fauser and Bouchard, 2011).

Insulin resistance in PCOS is caused by a distinct mechanism involving insulin signalling-transduction defects (Dunaif, 1997). The compensatory hyperinsulinaemia, which worsens with concomitant obesity (Bhathena, 2011), contributes to the clinical and metabolic presentation of PCOS. Ultimately, glucose tolerance can be affected. Indeed, impaired glucose tolerance (IGT) and type 2 diabetes are observed more frequently in women with PCOS compared with weight matched controls (Moran et al., 2010). Furthermore, accelerated conversion from IGT to diabetes has been reported in PCOS (Ehrmann et al., 1999; Norman et al., 2001; Legro et al., 2005; Pesant and Baillargeon, 2011).

Diabetes is considered a major health risk (WHO). In women with PCOS, diabetes may indeed contribute to mortality (Pierpoint et al., 1998). Early detection and treatment of glucose abnormalities by lifestyle intervention and pharmacotherapy has been reported to reduce progression to type 2 diabetes (Gillies et al., 2007). Therefore, regular screening for diabetes and IGT is recommended for all women diagnosed with PCOS (American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Writing Committee, 2005; Ledger et al., 2007; ACOG Committee on Practice Bulletins-Gynecology, 2009; Wild et al., 2010; Teede et al., 2011; Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012).

However, current guidelines on glucose assessment in PCOS differ in relation to screening methods, population characteristics and frequency (Table I). In general, the oral glucose tolerance test (OGTT) is recommended as the preferred screening method. Measuring the 2 h post-load glucose concentration is believed to better diagnose prediabetes, as it also identifies IGT (American Diabetes Association, 2012). Such an

<table>
<thead>
<tr>
<th>Table I Screening recommendations of international organizations for glucose assessment in PCOS patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCOS-specific recommendations</strong></td>
</tr>
<tr>
<td>AACE (American Association of Clinical Endocrinologists)</td>
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<tr>
<td>ACE (American College of Endocrinology)</td>
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<tr>
<td>RCOG (Royal College of Obstetricians and Gynaecologists)</td>
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<tr>
<td>ACOG (American College of Obstetricians and Gynecologists)</td>
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<tr>
<td>AE-PCOS (Androgen Excess and Polycystic Ovary Syndrome Society)*</td>
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<tr>
<td>PCOS Australian Alliance</td>
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<tr>
<td>ASRM (American Society for Reproductive Medicine)</td>
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<tr>
<td><strong>General population recommendations: PCOS included as non-modifiable risk factor</strong></td>
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<tr>
<td>ADA</td>
</tr>
<tr>
<td><strong>OGTT for all PCOS patients aged ≥ 30 year. Periodically reassess</strong></td>
</tr>
<tr>
<td><strong>Screen all by fasting glucose regularly. If fasting glucose &gt;5.6 mmol/l or BMI &gt; 30 kg/m² or positive family history, screen by OGTT</strong></td>
</tr>
<tr>
<td><strong>OGTT for all women with PCOS</strong></td>
</tr>
<tr>
<td><strong>OGTT for PCOS women with a BMI &gt; 30 kg/m², or alternatively in lean PCOS women with advanced age (≥40 year), personal history of gestational diabetes or family history of type 2 diabetes</strong></td>
</tr>
<tr>
<td><strong>OGTT for all women with PCOS. Repeat every 2 years</strong></td>
</tr>
<tr>
<td><strong>Screen by OGTT when following conditions are present: Hyperandrogenism with anovulation, acanthosis nigricans, obesity (BMI &gt; 30 kg/m² or &gt;25 in Asian populations), in women with a family history of type 2 diabetes or gestational diabetes.</strong></td>
</tr>
</tbody>
</table>

OGTT, Oral glucose tolerance test (75 g glucose load, baseline and 2 h plasma glucose measure).
*A minority of the Androgen Excess Society Board members, however, recommend screening for IGT and type 2 diabetes only in obese PCOS patients with BMI ≥ 30 kg/m², or lean women with ≥ 1 additional risk factor for diabetes.*
approach allows for early intervention aiming to prevent progression from IGT to type 2 diabetes (Teede et al., 2011). Insulin resistance is predominantly present in the hyperandrogenic PCOS phenotypes (Shroff et al., 2007; Moran and Teede, 2009). Therefore, this subgroup of women with PCOS is recognized as particularly at risk for developing diabetes, as well as those women with higher age, obesity or positive family history of diabetes. According to several organizations, these women should therefore be targeted for diabetes screening (American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Writing Committee, 2005; Ledger et al., 2007; Paulweber et al., 2010; Wild et al., 2010; Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012; American Diabetes Association, 2012). In contrast, others suggest that all women with PCOS should be screened, regardless of specific phenotypic characteristics (ACOG Committee on Practice Bulletins—Gynecology, 2009; Teede et al., 2011). However, evidence to sustain these recommendations is mostly derived from retrospective studies (Cibula et al., 2000; Wild et al., 2000), and observations in highly obese American PCOS cohorts (with reported prevalence of 12% for diabetes and 40% for IGT; Ehrmann et al., 1999; Legro et al., 1999; Talbott et al., 2001).

It seems justified to critically consider current guideline recommendations in other populations and investigate alternative strategies including step-wise risk assessment and selection of those women with PCOS particularly at risk (and thus eligible for diabetes screening by OGTT). The aim of this study was to evaluate the prevalence of glucose abnormalities in a large series of women diagnosed with anovulatory PCOS. We also investigated whether a single fasting glucose measurement could be used as a tool to select high-risk women for whom screening by OGTT is required.

### Materials and Methods

Between January 2008 and August 2011, 229 consecutive women who had been diagnosed with anovulatory PCOS underwent an OGTT after an overnight fast as part of the routine workup at our tertiary outpatient clinic for Reproductive Medicine (University Medical Centre Utrecht, the Netherlands). PCOS was diagnosed according to the Rotterdam 2003 consensus (The Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004) following a standardized screening protocol (Broekmans et al., 2006). Approval of the local Medical Ethical Review Board of the University Medical Centre Utrecht and written informed consent of the participants was obtained. This trial is registered at the clinical trials register (www.clinicaltrials.gov, registration number: NCT00821379).

Details of the diagnostic assessment are described previously (Broekmans et al., 2006; Goverde et al., 2009). Plasma glucose and insulin concentrations were both assessed at baseline and at 2 h post-glucose-load. Women were instructed not to eat, drink or smoke during the test, and not to perform any physical exercise. All blood samples were immediately processed by the laboratory of the University Medical Center Utrecht. Plasma glucose levels were measured using the Beckman DxC clinical chemistry analyser and insulin concentration was quantified using an Immulite platform (Diagnostic Products Corporation, Los Angeles, CA, USA).

Three women did not complete the OGTT (one due to illness of the participant and two due to laboratory failure). Further evaluation was therefore performed on the remaining 226 women.

The included patients were subdivided into four categories based on fasting plasma glucose concentrations:

- (i) $< 5.6 \text{ mmol/l} (< 100 \text{ mg/dl})$: normal fasting glucose (NFG).
- (ii) $5.6 – 6.1 \text{ mmol/l} (100 – 110 \text{ mg/dl})$: impaired fasting glucose group-1 (IFG-1).
- (iii) $6.1 – 7.0 \text{ mmol/l} (110 – 126 \text{ mg/dl})$: IGT group-2 (IFG-2).
- (iv) $\geq 7.0 \text{ mmol/l} (\geq 126 \text{ mg/dl})$: diabetes.

Two IFG subgroups were created in order to minimize confusion about terminology. It should be noted that the IFG-2 subgroup corresponds to the definition of IGT as defined by the World Health Organization (WHO). Both IFG groups combined (IFG-1 and IFG-2) correspond to the definition of IFG in use by the American Diabetes Associations (ADA; American Diabetes Association, 2012).

The 2 h post-load glucose was defined according to the ADA and WHO criteria:

- (i) IGT: $7.8 – 11.0 \text{ mmol/l} (140 – 200 \text{ mg/dl}).
- (ii) Diabetes: $\geq 11.1 \text{ mmol/l} (\geq 200 \text{ mg/dl}).

### Statistical analysis

Fasting glucose categories were compared by one-way analysis of variance (ANOVA) using SPSS for windows (SPSS Inc., Chicago, IL, USA, version 17.0.2). Data are presented as the mean with standard deviation (SD) except if stated otherwise. Analysis of distribution of PCOS phenotype in fasting glucose categories was performed by $\chi^2$ analysis. For both IFG cut-off levels the positive predictive values (PPVs) and the negative predictive values (NPVs) were calculated for an abnormal OGTT outcome and diabetes separately.

### Results

In this study group of 226 women presenting with infertility and oligo/amenorrhea and diagnosed with PCOS, three PCOS phenotypes were distinguished. In 148 PCOS patients (65%) all three diagnostic criteria, anovulation, hyperandrogenism and PCO, were present. Anovulation in combination with PCO was found in 28% and the combination of anovulation with hyperandrogenism in 6%. The majority of included women was Caucasian ($n = 182$ (81%), the remaining non-Caucasian population [$n = 44$ (19%)] was of mixed (mostly Arabic) origin.

Fasting glucose concentrations were normal in the great majority of cases [$n = 173$ (77%); NFG ($< 5.6 \text{ mmol/l}$)]. IFG was present in 47 women (21%), 32 (14%) of whom had IFG-1 (5.6 – 6.1 mmol/l) and 15 (7%) had IFG-2 (6.1 – 7.0 mmol/l). In six patients (3%) diabetes was diagnosed by elevated fasting plasma glucose ($\geq 7.0 \text{ mmol/l}$) alone. As expected, there were significant differences between the women presenting with normal fasting glucose, IFG-1, IFG-2 and diabetes (Table II). Increasing BMI, waist circumference, HOMA-IR and insulin levels and decreasing sex hormone-binding globulin (SHBG) concentrations were all found with increasing fasting glucose category.

Subsequent post-glucose load measurements performed in all women revealed IGT in 10 non-diabetic women (4%) (8 of whom had fasting glucose $< 6.1 \text{ mmol/l}$) and diabetes was diagnosed in two additional women based on abnormal 2 h plasma glucose levels ($\geq 11.1 \text{ mmol/l}$). Thus, in total, eight women (3.5%) were diagnosed with diabetes. Of note, 11 out of the 15 women with IFG-2 (73%) had normal 2 h glucose levels at OGTT, whereas four women with normal fasting glucose levels showed IGT (2%). Prediabetes, defined by the ADA as IFG and/or IGT (24), was present in 49 patients (22%), 45 (20%) women having IFG and IGT in addition to the 4 women (2%) with IGT while having normal FG. Figure 1 shows the relationship between fasting plasma glucose and the 2 h post-load glucose concentrations.
The eight women diagnosed with diabetes presented with all three phenotypic criteria of PCOS. χ² analysis of the phenotype groups did not reveal a significant difference for the distribution into fasting glucose categories (P = 0.09). The BMI of the women diagnosed with diabetes ranged from 30.8 to 41.4 kg/m² (35.0 ± 3.6 kg/m²) with a mean waist circumference of 109 ± 11 cm.

Since fasting glucose alone may be insufficient to diagnose IGT and diabetes properly, we investigated a step-wise screening model using the fasting glucose concentration (IFG-1 and IFG-2) as a criterion to additionally perform an OGTT. Both approaches were able to identify all women with diabetes. Based on the IFG-2 cut-off (≥ 6.1 mmol/l), a total of 15 patients would have been selected for OGTT assessment, resulting in the additional diagnosis of two cases with diabetes and two with IGT. The overall PPV of an abnormal 2 h concentration of the IFG-2 cut-off level was 26.7% and the NPV was 96.1%. The PPV of IFG-2 for diabetes was 13% and the NPV 100%. Based on the IFG-1 cut off level (≥ 5.6 mmol/l), 47 women would have been selected for OGTT. The PPV of this cut-off level was 17.0% and the NPV 97.7%. For diabetes the PPV of IFG-1 was 4.3%, with a NPV of 100%.

To control for the ethnic variation in our mostly Dutch Caucasian population, the performance of the step-wise screening model by IFG-2 was additionally assessed in the subgroups of Caucasian (n = 182) and non-Caucasian (n = 44) women. Diabetes was observed in 4 (2%), and IFG-2 in 11 (6%) Caucasian women. The PPV of the subsequent OGTT assessment was 18%, with a NPV of 97%. In non-Caucasian women, diabetes was observed in four (9%) and IFG in another four women (9%). The PPV, although only based on four OGTT’s was 50% and the NPV 81%.

A previous single fasting plasma glucose concentration measured within 6 months prior to the OGTT in the same hospital laboratory, was available for 187 of the included women for evaluation of the robustness of our proposed method of step-wise screening for diabetes in PCOS patients. First, we evaluated the OGTT outcome of those women who would be selected for OGTT screening based on the previous FG concentration. Secondly, we evaluated whether diabetes was present in those women who would not be advised to undergo an OGTT. Based on this prior fasting glucose level, 8 of the 187 women (4%) would at that time have been selected to undergo an OGTT. Six of these eight women presented with fasting glucose levels over 6.1 mmol/l at the OGTT assessment as well, two of whom were classified as diabetes at the repeat assessment. The remaining two women presented with fasting glucose levels just below 5.6 mmol/l at the time of OGTT assessment in this study. One woman with normal fasting glucose concentration of 5.5 mmol/l at initial assessment presented with a second fasting glucose concentration of 7.0 mmol/l. No other case of diabetes was identified among those women who screened <6.1 mmol/l on prior glucose assessment.

**Discussion**

The current study assessed the frequency of glucose abnormalities in an anovulatory PCOS population and aimed to evaluate whether a single fasting glucose measurement could be used to identify women with a low risk for diabetes. We found a 3.5% prevalence of diabetes in our studied group. In addition, prediabetes was commonly observed (22%), to which IGT without increased fasting glucose contributed only slightly (2% of study group). Therefore, a considerable proportion

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**Table II** Clinical and endocrine characteristics of 226 PCOS women categorized by fasting plasma glucose.

<table>
<thead>
<tr>
<th></th>
<th>Total n = 226</th>
<th>Normal fasting glucose &lt;5.6 mmol/l n = 173</th>
<th>IFG-1 5.6–6.1 mmol/l n = 32</th>
<th>IFG-2 6.1–7.0 mmol/l n = 15</th>
<th>Diabetes ≥ 7.0 mmol/l n = 6</th>
<th>P-value of between group analyses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.6 ± 4.3</td>
<td>29.3 ± 4.2</td>
<td>30.3 ± 4.1</td>
<td>31.1 ± 5.0</td>
<td>29.0 ± 5.3</td>
<td>0.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.3 ± 6.7</td>
<td>26.2 ± 6.3</td>
<td>29.8 ± 7.1</td>
<td>30.8 ± 6.3</td>
<td>36.1 ± 3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>89.3 ± 16.0</td>
<td>86.6 ± 14.8</td>
<td>95.4 ± 16.9</td>
<td>97.7 ± 17.3</td>
<td>113.5 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCOS phenotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AO + HA + PCO</td>
<td>148 (66%)</td>
<td>112 (65%)</td>
<td>18 (56%)</td>
<td>12 (80%)</td>
<td>6 (100%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>AO + HA</td>
<td>14 (6%)</td>
<td>8 (5%)</td>
<td>5 (16%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>AO + PCO</td>
<td>64 (28%)</td>
<td>53 (31%)</td>
<td>9 (28%)</td>
<td>2 (14%)</td>
<td>0 (0%)</td>
<td>n.a.</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>2.2 ± 1.0</td>
<td>2.2 ± 1.0</td>
<td>2.0 ± 0.9</td>
<td>1.8 ± 0.7</td>
<td>2.7 ± 1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>50.6 ± 30.0</td>
<td>54.9 ± 31.0</td>
<td>41.7 ± 20.7</td>
<td>33.8 ± 22.3</td>
<td>17.5 ± 6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, fasting (mmol/l)</td>
<td>5.3 ± 0.7</td>
<td>5.0 ± 0.3</td>
<td>5.8 ± 0.1</td>
<td>6.4 ± 0.3</td>
<td>8.2 ± 1.5</td>
<td>–</td>
</tr>
<tr>
<td>Glucose, 2-h post-load (mmol/l)</td>
<td>5.5 ± 2.0</td>
<td>5.1 ± 1.2</td>
<td>5.7 ± 1.5</td>
<td>7.0 ± 2.5</td>
<td>12.8 ± 4.5</td>
<td>–</td>
</tr>
<tr>
<td>Insulin, fasting (mU/l)</td>
<td>9.4 ± 8.1</td>
<td>7.8 ± 5.8</td>
<td>12.5 ± 10.1</td>
<td>15.1 ± 13.2</td>
<td>24.3 ± 12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin, 2-h post-load (mU/l)</td>
<td>51.3 ± 55.7</td>
<td>43.8 ± 38.7</td>
<td>68.7 ± 100.0</td>
<td>76.7 ± 68.5</td>
<td>109.3 ± 58.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 ± 14</td>
<td>126 ± 14</td>
<td>126 ± 13</td>
<td>130 ± 17</td>
<td>141 ± 20</td>
<td>0.07</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>82 ± 11</td>
<td>81 ± 11</td>
<td>84 ± 8</td>
<td>83 ± 10</td>
<td>89 ± 16</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD and available for all 226 women.

*One way ANOVA.

Of note, two women in this category were diagnosed with diabetes based on a 2 h post-load Glucose concentration > 11.1 mmol/l.

AO, anovulation; HA, hyperandrogenism, either clinical, biochemical or both; PCO, polycystic ovaries on ultrasound.

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**Table II** Clinical and endocrine characteristics of 226 PCOS women categorized by fasting plasma glucose.
of our relatively young and on average only overweight population is at increased risk of developing diabetes. We also demonstrated that if women present with fasting plasma glucose below 6.1 mmol/l, they have a very low risk of being diagnosed with diabetes since we did not observe a single case of diabetes among our 205 PCOS patients with a fasting glucose below 6.1 mmol/l at OGTT. Consequently, we propose a step-wise screening for glucose metabolism abnormalities by fasting glucose for all women with PCOS and subsequent OGTT screening for diabetes in the small proportion of women with PCOS with fasting glucose concentration between 6.1 and 7.0 mmol/l only. To validate this step-wise screening algorithm the hypothesis that the maximum proportion of women with diabetes missed by this algorithm is $< 1.5\%$ (exact Clopper Pearson confidence interval of 0 – 1.5%) should be tested. Such a validation study would need a group of 225 women with a similar distribution of women with normal and abnormal glucose concentrations.

It is increasingly recognized that not all PCOS patients have a similar adverse metabolic profile (Moran and Teede, 2009; Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group, 2012). As awareness grew that the risk of metabolic abnormalities and diabetes in women with PCOS varies with age, BMI, ethnicity and lifestyle (Dahlgren et al., 1992; Legro et al., 1999; Ehrmann et al., 2005), the justification of OGTT screening of all PCOS women, as proposed by some (ACOG Committee on Practice Bulletins-Gynecology, 2009; Teede et al., 2011), was debated (Inder, 2011; Stovall et al., 2011). Previous studies revealed a diabetes prevalence up to 10% in PCOS women but with on average a much higher BMI than those included in this study (mean BMI $\sim 33$ kg/m$^2$ compared with 27.3 kg/m$^2$ in) (Ehrmann et al., 1999; Legro et al., 1999). However, although the prevalence of diabetes in our group of women with anovulatory PCOS was much lower (3.5%), it remains distinctly increased when compared with the reported 0.5% in the general Dutch female population aged 20–40 years (CBS, 2010). We therefore propose a screening approach based on risk differentiation. Our findings suggest that fasting glucose assessment could be used as standard screening method for such purpose in a relatively low-risk PCOS population.

Many other investigators suggested that fasting glucose assessment alone does not suffice for screening of prediabetes in women with PCOS (Legro et al., 1999; Yildiz and Gedik, 2004; Barcellos et al., 2007; Gagnon and Baillargeon, 2007) because a single fasting blood level does not adequately identify those women in whom post-prandial glucose tolerance is impaired. Our results demonstrate that fasting glucose is already mildly affected in women who tested abnormal on post-load OGTT, which is in concordance with other reports (Gagnon and Baillargeon, 2007). In fact, fasting plasma glucose levels below 6.1 mmol/l (IFG-2) excluded the presence of diabetes in 100% of women. However, IGT was missed in four women who presented with a NFG concentration. The question arises whether it is clinically relevant to identify IGT when fasting glucose is normal, since this may not lead to any change in management, especially in the absence of obesity (Inder, 2011). This could also be said of the relevance of diagnosing prediabetes (present in 22% of our study population), since this is regarded as carrying an increased risk for developing diabetes (American Diabetes Association, 2012). One might argue that different levels of

![Figure 1](https://example.com/figure1.png)

**Figure 1** Scatter diagram of fasting plasma glucose versus 2 h post-load glucose. Lines on the X-axis reflect cut-off levels of IFG-1, IFG-2 and diabetes mellitus (DM); lines on the Y-axis reflect cut-off levels of IGT and DM. Note the two cases diagnosed with DM based on elevated 2 h glucose levels at OGTT (dark squares). IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
disruption of glucose metabolism require different levels of intervention. Indeed, diabetes requires intensive intervention whereas women with low-risk need less extensive intervention. However, life-style management aiming to reduce risk factors should be advised irrespective of glucose concentration. The presence of mild glucose abnormalities, such as fasting glucose levels between 5.6 and 6.1 mmol/l, found in 14% (n = 32) of our study population, might, however, lead to more stringent life-style interventions and follow-up for women with PCOS who try to achieve pregnancy, since even mild glucose elevations are associated with adverse pregnancy outcomes (Metzger et al., 2008).

The relevance of identifying mild fasting glucose abnormalities and the degree of women identified by our screening algorithm who eventually develop (gestational) diabetes, should be determined in time by other follow-up studies.

Our approach towards selective OGTT screening for PCOS patients with fasting glucose levels between 6.1 and 7.0 mmol/l only would markedly reduce the number of OGTT’s to be performed, without compromising early diagnosis of diabetes. The reduction would amount to 93% since only 15 women of our study group presented with fasting glucose between 6.1 and 7.0 mmol/l. In those women in whom IGT would have remained undiagnosed because they did not undergo OGTT based on a fasting glucose below 6.1 mmol/l [which would be in our study sample: 8 out of 197 women (4%)] further aggravation of glucose homeostasis will be identified at follow-up screening, which would still ensure early detection. However, the frequency of such follow-up screening still needs to be determined.

It has been suggested that HbA1c levels, recommended by the ADA as a screening tool for diabetes and prediabetes in the general population with cut-off levels of 6.5 and 5.6%, respectively (American Diabetes Association, 2012), might also be useful as a single or additional tool in screening women with PCOS (Hurd et al., 2011; Pesant and Baillargeon, 2011). A study performed in a setting with prevalences of diabetes and prediabetes in a PCOS group similar to ours, albeit more obese, demonstrated that HbA1c identifies a similar group of patients with IGT as does OGTT (Hurd et al., 2011). The use of repeated HbA1c is advocated especially because the relative ease with which it can be applied as screening tool in contrast to the OGTT. Unfortunately, we had not included HbA1c in our screening panel and therefore cannot corroborate these findings.

We have reported here a cross-sectional study performed as part of a relatively large prospective follow-up cohort of PCOS patients, of which the minimal drop-out rate (1%) strengthens our study results. Patients were diagnosed with PCOS by the revised Rotterdam ASRM/ESHRE criteria according to a predefined protocol. Since a majority of the women of our study group had previously undergone this assessment before the OGTT was performed, we were able to add retrospective data on fasting glucose concentrations of these cases to our evaluation. Moreover, this standardized assessment resulted in a well-defined though heterogeneous study group of anovulatory PCOS. By the nature of their anovulation these patients will generally seek medical help in order to conceive and are therefore easily identified as risk population for diabetes screening. A limitation of the study is that we have no follow-up assessment of the patients who were normal upon OGTT screening. However, data of a previous fasting glucose assessment in our study group are reassuring, since the second assessment led to a different diagnosis in only one woman. Although our screening approach seems valid for the complete studied population, due to the inclusion of mostly Caucasian women generalization to non-Caucasian ethnic populations should be done with caution. Future studies are encouraged to validate our algorithm for initial screening and follow-up screening by fasting glucose in other populations, as well as to determine the frequency of this screening proposal, with or without the addition of HbA1c measurement.

In conclusion, diabetes was observed in 8 of the 226 women with PCOS (3.5%), six of whom were diagnosed on the basis of their fasting glucose being ≥ 7.0 mmol/l. It is of note that the fasting glucose concentration of the additional two patients was over 6.1 mmol/l. Our study suggests that a fasting plasma glucose <6.1 mmol/l is reliable in identifying PCOS women with a low risk of diabetes. We therefore propose screening of all women with PCOS by fasting plasma glucose and additional screening by OGTT for those with IFG (6.1–7.0 mmol/l) instead of screening all women with PCOS by OGTT. Validation of this new screening algorithm is awaited.

Authors’ roles
S.M.V.-V., A.J.G. and B.C.J.M.F. designed the study. Data collection and analysis was primarily performed by S.M.V.-V.; S.M.V.-V., A.J.G. and T.W.H. conceptualized the article and took the lead in writing. B.C.J.M.F. revised several draft versions of the manuscript. All authors approved the final version of the article.

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Conflict of interest
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