Sex hormone-binding globulin concentrations before conception as a predictor for gestational diabetes in women with polycystic ovary syndrome

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BACKGROUND: Low plasma sex hormone-binding globulin (SHBG) concentrations during pregnancy have been associated with the risk of developing gestational diabetes mellitus (GDM). Women presenting with polycystic ovary syndrome (PCOS) often exhibit low plasma SHBG concentration and are at increased risk of developing GDM. In this study, we investigate whether SHBG levels before conception are predictive of GDM in women with PCOS.

METHODS: A total of 50 women with PCOS were enrolled and followed up during pregnancy. Initial endocrine, metabolic and physical features were assessed according to a standardized preconception screening program. At 24–26 weeks of gestational age a 100-g glucose tolerance test was performed to screen for GDM.

RESULTS: Of the 50 women, 21 (42%) were diagnosed with GDM by a 100-g glucose tolerance test. Waist circumference, BMI, blood pressure, plasma glucose, insulin, homeostasis model assessment-insulin resistance (HOMA-IR) and SHBG levels before conception were significantly different between women who did and did not develop GDM. Stepwise logistic regression analysis showed that SHBG was the most significant predictive parameter for GDM (odds ratio 0.92; 95% confidence interval 0.87–0.97), without significant contribution of waist circumference and HOMA-IR. Receiver operator characteristic (ROC) analysis indicated that plasma SHBG (area under the curve 0.86) had the highest predictive value for subsequent development of GDM, however, the limited group size did not allow for calculation of a threshold value of SHBG.

CONCLUSIONS: In women with PCOS, preconception SHBG levels are strongly associated with subsequent development of GDM. Regression and ROC analysis show that preconception SHBG levels may be a better predictor for GDM in PCOS women compared with waist circumference or HOMA-IR.

Clinical trial registration number: NCT00821379

Key words: polycystic ovary syndrome (PCOS) / sex hormone-binding globulin (SHBG) / gestational diabetes mellitus (GDM) / pregnancy complication / oral glucose tolerance test (OGTT)

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy characterized by oligo- or anovulation, hyperandrogenism and polycystic ovaries (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The syndrome affects ~12% of women of reproductive age (March et al., 2010). PCOS is increasingly recognized for its metabolic abnormalities. Besides its reproductive implications, PCOS is associated with obesity, insulin resistance (IR) and dyslipidemia (Essah et al., 2007). Women presenting with PCOS are known to exhibit an increased risk for pregnancy complications such as gestational diabetes mellitus (GDM), and an increased risk for developing type 2 diabetes (Legro et al., 1999; Boomsma et al., 2006). Low sex hormone-binding globulin (SHBG) levels are
commonly observed in PCOS (Pugeat et al., 1991). Low SHBG results in a larger fraction of unbound testosterone and therefore in hyperandrogenism, one of the key components of PCOS (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Hyperandrogenism itself tends to further reduce SHBG levels (Pugeat et al., 1991).

Previous studies have shown an inverse relation between plasma SHBG concentrations and the risk of developing type 2 diabetes in pre- and post-menopausal women (Ding et al., 2006, 2009). The mechanism of this association is not fully understood since IR or obesity do not explain this association completely (Pugeat et al., 2010). A recent study of different SHBG polymorphisms showed evidence of a genetic correlation between SHBG levels and type 2 diabetes, independent of BMI (Ding et al., 2009). This could indicate a possible causal role of SHBG in the glucose regulation pathway. A relationship was also found between SHBG and GDM. Several case–control studies have reported lower plasma SHBG levels in the first trimester of pregnancy in women who developed GDM (Bartha et al., 2000; Thadhani et al., 2003; Spencer et al., 2005).

Although pregnant women with PCOS are more than three times as likely to develop GDM when compared with pregnant women without PCOS (Boomsma et al., 2006), to our knowledge no data are available concerning a possible association between SHBG levels and GDM in PCOS. SHBG concentrations are usually assessed as part of the diagnostic work up in women with oligo- or amenorrhoea. It could therefore easily be included as a predictive measure for GDM, beyond the predictive value of traditional risk factors such as BMI and IR.

We hypothesized that women with PCOS who develop GDM can be identified before pregnancy by their low SHBG level. The identification of patients at risk for GDM prior to pregnancy is of clinical importance because preventive interventions such as weight reduction can be started in a timely fashion. This preventive strategy may also be important for health of PCOS women at a later age, since women who have had GDM are at increased risk of developing type 2 diabetes within 5–10 years after pregnancy (Kim et al., 2002). We therefore prospectively studied the predictive value of SHBG concentrations before conception, in relation to the risk of developing GDM in PCOS women.

Materials and Methods

As part of a large ongoing follow-up study of PCOS women, 50 infertile women, diagnosed with PCOS, who conceived following fertility treatment were enrolled prior to conception and were followed up during pregnancy at the University Medical Centre Utrecht (Utrecht, The Netherlands) between April 2008 and April 2010. PCOS was diagnosed according to the Rotterdam 2003 consensus criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). All women underwent standardized screening at study inclusion, including a physical examination, transvaginal ultrasound scan of the ovaries and metabolic and endocrine laboratory measurements, as previously described (Goverde et al., 2009). Waist circumference was measured in fasting state and normal standing position, halfway between the lower ribs and the superior anterior iliac spine of the pelvis; Agarwal et al. showed a high inter- and intra-observer agreement (0.983 and 0.982) for the performed measure method (Agarwal et al., 2009). Laboratory measurements were repeated annually until pregnancy was achieved. This study is part of a large ongoing follow-up study of PCOS women for which approval of the Medical Ethical Committee of the University Medical Centre Utrecht was obtained. All subjects gave written informed consent before inclusion in the study. This trial is registered at the clinical trials register (www.clinicaltrials.gov; NCT00821379).

Pre-existing diabetes was ruled out by an oral glucose tolerance test (75 g glucose load) at study inclusion. All couples received ovulation induction treatment except four couples (three in the GDM group and one in the non-GDM group) for whom IVF or ICSI treatment was indicated for concomitant severe male factor. Type and duration of treatment were not influenced by study participation. During pregnancy, patients received obstetric care according to national guidelines (NVOG, 2002). An oral glucose tolerance test (100-g glucose load, 3 h follow-up), was performed between 24 and 26 weeks of gestational age. GDM was diagnosed if two or more glucose values were increased (Metzger and Coustan, 1998).

All blood samples were analysed at the laboratory of the University Medical Centre Utrecht, The Netherlands. SHBG was quantified using the Modular E170 (Roche Diagnostics, Mannheim, Germany), calibrated using the international standard preparation 95/560. The within run coefficient of variation was 1.0% (at 21 nmol/l). Glucose levels were measured using the Beckman DxC clinical chemistry analyzer and insulin was quantified using an Immulite® platform (Diagnostic Products Corporation, Los Angeles, CA, USA).

The homeostasis model assessment (HOMA) was used as the measure for IR (formula HOMA-IR: glucose (mmol/l) × insulin (mU/l)/ 22.5 (Matthews et al., 1985).

Power analysis

To detect a difference of 0.80 standard deviation (Cohen’s d) in SHBG between women with and without GDM, 50 patients had to be included (power = 80% at α = 0.05). Cohen’s d of 0.80 is at the upper limit of what may be considered as a medium size effect.

Statistical analysis

All analyses were performed using SPSS for windows (SPSS Inc., Chicago, IL, USA, version 15.0). Log transformation was performed for SHBG and HOMA-IR. The preconception parameters were compared between women with GDM and those without GDM by analysis of variance with adjustment for BMI when appropriate. Dichotomous data were evaluated by Chi-square analysis. Correlation coefficients were calculated for BMI, HOMA-IR, SHBG, insulin and glucose to check the magnitude of the relation between these parameters.

Logistic regression analysis was performed by forward stepwise method (inclusion if P < 0.05) to determine the strength of the association of the different variables with the occurrence of GDM.

In order to maintain a statistically valid model, a maximum of three candidate variables was entered. To evaluate the additive effect of the HOMA-IR and waist circumference in a model with SHBG, the odds ratio’s (OR) and confidence intervals (CI) of the variables were calculated by separately entering them in the model.

To assess the predictive value of different variables, receiver operator characteristic (ROC) curves were determined. The area under the curve (AUC) of the ROC represents the accuracy with which the test predicts the outcome, in this case GDM.

Results

Of the 50 PCOS women who conceived while participating in this prospective study, 21 developed GDM (42%). The mean duration between preconception assessment and pregnancy was 35 weeks.
Women with or without GDM were similar in terms of age, smoking and PCOS characteristics (Table 1). Forty-six women were of Caucasian ethnicity. Two Arabic women were included, one in each group, and two women of South-Asian origin were present in the GDM group. Five women with GDM had a first degree family member with type 2 diabetes, compared with one in the non-GDM group. Three twin pregnancies were included, one of which was complicated by GDM. An abnormal glucose tolerance test prior to pregnancy was also performed since these women may have a stronger predisposition for developing GDM for SHBG of 0.92 (95% CI 0.87–0.97).

SHBG concentrations were significantly different between the PCOS women who did and those who did not develop GDM (P < 0.001; Fig. 1). A good predictive accuracy of SHBG as marker for GDM was found by ROC analysis [AUC 0.86 (95% CI 0.75–0.97; Fig. 2)]. An SHBG threshold of 58.5 nmol/l had a sensitivity of 81.0% and a specificity of 82.8%. The AUC of the ROC analysis for waist circumference, BMI and HOMA-IR revealed a less predictive accuracy (AUC 0.72, 0.68 and 0.83, respectively; Table III).

Because twin pregnancies give rise to an increased risk of developing gestational diabetes the analyses were also performed excluding these women. Similar results were found for all analyses, again showing significantly lower SHBG in the women who developed GDM (P < 0.001). Regression analysis with SHBG, waist circumference and HOMA-IR as candidate variables revealed an OR for developing GDM of 0.92 (P = 0.002, 95% CI 0.87–0.97). The ROC analysis remained similar with an AUC for SHBG of 0.86 (95% CI 0.75–0.97).

A sensitivity analysis with exclusion of the women with an abnormal glucose tolerance test prior to pregnancy was also performed since these women may have a stronger predisposition for developing GDM than the preconceptionally normoglycemic PCOS women. The patient characteristics were similar to those found in the main group analyses. SHBG was again significantly lower in the GDM group (P < 0.001). The OR of developing GDM was 0.91 for every unit SHBG increase (95% CI 0.86–0.97). The AUC of the ROC analysis gave similar results (AUC 0.87, 95% CI 0.75–0.99).

Table I Preconception characteristics of PCOS women who did and those who did not develop GDM.

<table>
<thead>
<tr>
<th></th>
<th>Gestational diabetes (n = 21)</th>
<th>No gestational diabetes (n = 29)</th>
<th>P-value</th>
<th>P-value BMI adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>26.6 ± 3.5</td>
<td>25.6 ± 3.0</td>
<td>0.25</td>
<td>—</td>
</tr>
<tr>
<td>Smoker</td>
<td>2 (10%)</td>
<td>6 (21%)</td>
<td>0.29</td>
<td>—</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 ± 5.8</td>
<td>24.7 ± 5.7</td>
<td>0.04</td>
<td>—</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94.7 ± 15.3</td>
<td>84.0 ± 12.6</td>
<td>0.01</td>
<td>0.10</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130 ± 14</td>
<td>123 ± 13</td>
<td>0.10</td>
<td>0.24</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86 ± 12</td>
<td>78 ± 10</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Polycystic ovaries</td>
<td>18 (86%)</td>
<td>28 (97%)</td>
<td>0.16</td>
<td>—</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>5 (24%)</td>
<td>5 (17%)</td>
<td>0.57</td>
<td>—</td>
</tr>
<tr>
<td>Testosterone (nmol/l)a</td>
<td>2.1 ± 0.9</td>
<td>2.3 ± 1.2</td>
<td>0.67</td>
<td>0.39</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)b</td>
<td>7.9 ± 2.6</td>
<td>7.9 ± 3.3</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>Glucose—fasting (mmol/l)</td>
<td>5.4 ± 0.6</td>
<td>5.0 ± 0.3</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Glucose—2 h post 75 g glucose load (mmol/l)</td>
<td>5.8 ± 2.0</td>
<td>4.7 ± 1.4</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>Insulin—fasting (mU/l)</td>
<td>11.5 ± 6.2</td>
<td>6.0 ± 3.0</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.45 (0.85–6.36)</td>
<td>1.17 (0.40–2.93)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>40 (16–77)</td>
<td>63 (40–170)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD, median (range) or number (%) if appropriate. Analyses: x² or analysis of variance with log transformation if appropriate; —, not applicable. SHBG, sex-hormone binding globulin; HOMA-IR, homeostatic model of insulin resistance.

a Normal value: 0.5–2.0 nmol/l.
b Normal value: 3–7 nmol/l.
Discussion

We observed a strong association between preconception SHBG levels and subsequent development of GDM. This association was partially independent of BMI, waist circumference and IR at preconception screening. Since logistic regression analysis showed that the predictive value of SHBG is stronger than the predictive value of BMI, waist circumference or HOMA-IR, preconception SHBG may be the preferred predictive screening marker for the risk of developing GDM in women with PCOS. Unfortunately, the limited group size of our study did not allow for a calculation of a clinically useful threshold value of SHBG.

To our knowledge, this is the first prospective study to investigate the association of plasma SHBG concentrations before conception with GDM in PCOS women. Our novel findings may help to improve the early identification of women with PCOS at risk of GDM and type 2 diabetes.

Women with PCOS have a 3-fold increased risk of developing GDM compared with women without PCOS (Boomsma et al., 2006). The increased risk for GDM in PCOS has been related to both IR and obesity (Paradisi et al., 1998). We did indeed find more pronounced IR, expressed as higher HOMA-IR values, and obesity in PCOS women who developed GDM. The difference in HOMA-IR between women with and without GDM remained significant after statistical
Preconception SHBG levels and GDM in PCOS

Table III  ROC curve analysis of possible predictive parameters for developing GDM in PCOS women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHBG (nmol/l)</td>
<td>0.86</td>
<td>0.75–0.97</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.83</td>
<td>0.72–0.94</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.72</td>
<td>0.60–0.87</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.68</td>
<td>0.53–0.84</td>
</tr>
<tr>
<td>Glucose (fasting) (mmol/l)</td>
<td>0.73</td>
<td>0.56–0.89</td>
</tr>
<tr>
<td>Insulin (fasting) (mU/l)</td>
<td>0.78</td>
<td>0.66–0.91</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>0.70</td>
<td>0.56–0.84</td>
</tr>
</tbody>
</table>

Data presented as area under the curve and 95% CI.

Conflict of interest: B.C.J.M.F. has received fees and grant support from the following companies (in alphabetic order); Andromed, Ardana, Ferring, Genomuv, Glycotope, Merck Serono, Organon, Pantheari Bioscience, Philips, PregLem, Schering, Schering Plough, Serono and Wyeth. T.W.H. has received fees from Merck, Sharpe & Dohme, GlaxoSmithKline, NovoNordisk and Eli Lilly.

Funding

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References


correction for BMI. Women who subsequently developed GDM had significantly lower plasma SHBG levels compared with those who did not. Interestingly, since a contributing effect of BMI, waist circumference or HOMA-IR disappeared when SHBG was entered in the stepwise regression model, we conclude that SHBG has an independent effect on the development of GDM in PCOS women. The biologically relevant pathways of this effect are currently unknown. In particular it remains unclear whether the association between GDM and SHBG is direct or indirect; lower SHBG results in higher free androgens and that it could be this has a direct association with GDM rather than the SHBG itself, and this warrants further investigation.

In conclusion, we find that preconception SHBG is a strong predictor for GDM in women with PCOS, independently of obesity and measures of IR. The present study suggests that assessment of SHBG levels before conception is a useful tool to identify PCOS patients at risk for GDM during pregnancy. Larger cohort studies are needed to define a clinically useful threshold value for SHBG in women with PCOS.

Authors’ roles

S.M.V.: study coordination, data collection, analysis and interpretation and writing of the manuscript; T.W.v.H.: data interpretation, drafting and writing of the manuscript; H.W.d.V.: data collection, study design, reviewing the manuscript; M.J.C.E.: data analysis and design of tables and figures; B.C.J.M.F.: study design and manuscript writing; A.J.G.: study design, manuscript drafting, writing, data interpretation, table and figure lay-out.


