Human Reproduction, Vol.29, No.6 pp. 1327–1336, 2014
Advanced Access publication on April 28, 2014 doi:10.1093/humrep/deu077

human reproduction

ORIGINAL ARTICLE ***Reproductive epidemiology***

Preconception predictors of gestational diabetes: a multicentre prospective cohort study on the predominant complication of pregnancy in polycystic ovary syndrome

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Submitted on December 20, 2013; resubmitted on January 31, 2014; accepted on February 18, 2014

STUDY QUESTION: Can we develop an adequate preconception prediction model to identify those women with polycystic ovary syndrome (PCOS) who have an increased risk of developing gestational diabetes mellitus (GDM) during subsequent pregnancy?

STUDY ANSWER: The risk of developing GDM in women with PCOS can be adequately predicted prior to conception by a prediction model.

WHAT IS KNOWN ALREADY: Women with PCOS are at increased risk of pregnancy complications, especially GDM. GDM has serious short-term and long-term effects on mother and baby.

STUDY DESIGN, SIZE, DURATION: This study is a part of a multicentre prospective cohort study, which was conducted between April 2008 and April 2012. A total of 326 women with PCOS were included.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with PCOS and a wish to conceive were included prior to conception and followed until 6 weeks after delivery. Maternal, neonatal and birth complications were reported. A multivariate model was developed to predict the most common pregnancy complication, GDM, by using univariate and multivariate logistic regression of preconception patient characteristics. The area under the curve (AUC) of the receiver-operating characteristic was used to test the performance of the model.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 189 women (58%) achieved an ongoing pregnancy (8% multiples) and delivered a live-born neonate. One or two maternal complications occurred in 62 (33%) pregnant women, mainly GDM ($n = 41$; 22%) and pregnancy-induced hypertension ($n = 14$; 7%). In children, one or two complications were observed in 49 (26%) of 206 children born, e.g. premature delivery ($n = 23$; 12%) and small for gestational age ($n = 15$; 8%). The preconception prediction model for GDM performed well (AUC 0.87, 95% CI 0.81–0.93). First-degree relatives with type 2 diabetes mellitus, serum levels of fasting glucose, fasting insulin, androstenedione and sex hormone-binding globulin before conception were identified as predictors.

LIMITATIONS, REASONS FOR CAUTIONS: The prediction model has not yet been externally validated in another group of patients. Also, there were missing data for some of the determinants, which were accounted for by multiple imputation.

WIDER IMPLICATIONS OF THE FINDINGS: Women with PCOS who achieve a pregnancy have an increased risk of GDM. The prediction model can be used to identify women particularly at risk for GDM who should be monitored closely to enable preventative measures that may reduce the risk of developing GDM and its adverse consequences.

STUDY FUNDING/COMPETING INTEREST(S): No external funding was used for the study. M.A.W., S.M.V.V., A.J.G., A.F. and M.P.H.K. have nothing to disclose. C.B.L has received fees and grant support from the following companies (in alphabetic order): Auxogen, European Society of Human Reproduction and Embryology and MSD. J.S.E.L. has received fees and grant support from the following companies (in alphabetic order): Ferring, Gennovum, Merck-Serono, MSD, Organon, Schering Plough, Sharp & Dome and Serono. M.J.C. has received grant support from the following companies (in alphabetic order): Illumina and MSD. B.C.J.M.F. has received fees and grant support from the following companies (in alphabetic order): Ferring, Ova-Science, PregLem SA, Roche and Watson Laboratories.

TRIAL REGISTRATION NUMBER: NCT00821379 [Clinicaltrials.gov].

Key words: polycystic ovary syndrome / gestational diabetes / pregnancy complications

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder worldwide in women of reproductive age, with a reported prevalence between 6 and 15% (Norman *et al.*, 2007; Fauser *et al.*, 2012). PCOS is a heterogeneous reproductive disorder, which is diagnosed when at least two out of the three following criteria are present: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism and polycystic ovaries (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). Associated features include obesity, impaired glucose tolerance, dyslipidaemia and metabolic dysfunction (Moran *et al.*, 2010; Wild *et al.*, 2011; Diamanti-Kandarakis and Dunaif, 2012). Women with PCOS exhibit classical risk factors for cardiovascular disease (CVD) such as metabolic syndrome, type 2 diabetes, elevated CVD risk markers and are at increased risk of developing CVD at later age (de Groot *et al.*, 2011; Toulis *et al.*, 2011; Diamanti-Kandarakis and Dunaif, 2012; Fauser *et al.*, 2012).

In the past, multiple pregnancies frequently occurred due to multiple follicle development in women with PCOS during ovulation induction strategies. Multiple pregnancies exhibit an inherent increased risk of pregnancy complications compared with singletons (Fauser *et al.*, 2005). This problem, however, has been largely overcome with current low-dose ovulation induction regimens along with the introduction of single embryo transfer policies in IVF.

Even singleton pregnancies in women with PCOS are at increased risk for adverse outcomes as demonstrated by two recent meta-analyses and a large sample size population-based cohort study (Boomsma *et al.*, 2006; Kjerulff *et al.*, 2011; Roos *et al.*, 2011). These studies all disclosed increased complication rates in women with PCOS: e.g. gestational diabetes mellitus (GDM) [odds ratio (OR) 2.32–3.66], pre-eclampsia (OR 1.45–4.23) or pregnancy-induced hypertension (OR 3.67–4.07) (Boomsma *et al.*, 2006; Kjerulff *et al.*, 2011; Roos *et al.*, 2011). Moreover, infants born from women with PCOS are at increased risk: e.g. premature birth (OR 1.75–2.20), small for gestational age (OR 2.62) or large for gestational age (OR 1.39) (Boomsma *et al.*, 2006; Kjerulff *et al.*, 2011; Roos *et al.*, 2011).

The majority of studies included in the aforementioned meta-analyses were retrospective. The sample size of eight prospective studies undertaken so far was small ($n \leq 93$) and included only pregnant women (Kjerulff *et al.*, 2011). It is therefore impossible to draw any conclusions from those studies with regard to preconception characteristics in relation to complications during pregnancy or delivery. To date, the only report relating preconception features to complications of pregnancy in women with PCOS was a recent preliminary report from our own group, demonstrating sex hormone-binding globulin (SHBG) concentrations as a predictor of GDM (Veltman-Verhulst *et al.*, 2010).

Feto-maternal healthcare would benefit from a tool able to predict GDM in women with PCOS before conception. Apart from PCOS, GDM has serious short-term and long-term effects on mother (e.g. metabolic syndrome, type 2 diabetes) and baby (large for gestational age, childhood obesity, metabolic syndrome) (Reece *et al.*, 2009). Women with PCOS could be classified in risk groups in order to offer them personalized periconception care. This could reduce unnecessary burden of intensified antenatal care and costs for low-risk women and focus screening programmes on women with PCOS, at high risk for pregnancy complications. Therefore, we aimed to develop a prediction model for GDM in women with PCOS before pregnancy.

Materials and Methods

Study design

This study is a part of the Copper study. The Copper study was conducted in four hospitals in the Netherlands between April 2008 and April 2012. Women diagnosed with PCOS, who visited the hospital because of a fertility disorder and who wish to get pregnant, were included in the study before conception. PCOS was diagnosed according to the Rotterdam 2003 consensus criteria following standardized phenotyping (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004; Goverde *et al.*, 2009; Fauser *et al.*, 2012). Women were excluded in case of age <18 years or >45 years, language barrier and type 1 or type 2 diabetes mellitus.

Ethical approval

This study was approved by the institutional review boards of all our participating centres. All women who participated in the study gave written informed consent. This study was registered with Clinicaltrials.gov, number NCT00821379.

Clinical assessments

All women underwent standardized preconception screening upon inclusion. This screening included a questionnaire concerning lifestyle, socio-economic status, mental state and family history of CVD and/or type 2 diabetes. Standard anthropometry (height, weight, waist and hip circumference), blood pressure and a transvaginal ultrasound scan of the uterus and ovaries (including antral follicle count) were performed by trained medical doctors. Metabolic and endocrine measurements, as previously described, were performed and analysed in each centre separately (Goverde *et al.*, 2009). All women underwent an oral glucose tolerance test (OGTT) according to our standard preconception protocol (75-g glucose load, 2 h follow-up).

Subsequently, most women started fertility treatment by ovulation induction because of oligo- or anovulation. In case of concurrent male factor infertility, intrauterine insemination, IVF or ICSI was performed. When pregnancy was achieved, patients were followed by antenatal care visits at 6–8, 10–12, 16–18, 20–22, 24–26, 28–30, 32–34, 36–38, 38–40 and 40–42 weeks of pregnancy and at 6 weeks *post-partum*. At each visit maternal blood pressure, body weight and a venous blood sample were obtained.

At 6–8 weeks of gestation, a transvaginal ultrasound examination was performed to detect fetal heart activity and to measure the crown-rump length. Gestational age was determined by the best estimate according to the crown-rump length, or the first day of the last menstrual period. At 24–26 weeks of pregnancy, an OGTT (100-g glucose load, 3 h follow-up) was performed according to standard pregnancy protocol. Pregnancy outcome data were collected by a medical doctor after delivery.

Study outcomes

The aim of this study was to develop a prediction model for GDM. Secondary outcomes were other maternal complications and complications of labour and delivery.

Anticipated maternal complications besides GDM were pregnancy-induced hypertension, pre-eclampsia and the haemolysis elevated liver enzymes low platelets (HELLP) syndrome. GDM was defined as two or more plasma glucose levels exceeding a given threshold after a 100-g glucose load: fasting glucose $\geq$5.3 mmol/l, 1 h glucose $\geq$10.0 mmol/l, 2 h glucose $\geq$8.6 mmol/l and 3 h glucose $\geq$ 7.8 mmol/l (American Diabetes Association, 2003). Pregnancy-induced hypertension was defined as a systolic blood pressure $\geq$140 mmHg and/or a diastolic blood pressure $\geq$90 mmHg. Pre-eclampsia was defined as pregnancy-induced hypertension and proteinuria ($\geq$300 mg/24 h). Neonatal outcomes were (spontaneous or induced) premature birth which was defined as gestational age $<$37 weeks, small for gestational age as birthweight $<$10th percentile for gestational age and gender, large for gestational age as birthweight $>$90th percentile for gestational age and gender and hypoglycaemia as a glucose value $<$2.6 mmol/l. Complications of labour and delivery were assisted vaginal delivery (vacuum extraction or forceps), Caesarean section, *post-partum* haemorrhage, signs of intrauterine infection during delivery, shoulder dystocia and placental retention. *Post-partum* haemorrhage was defined as $>$1000 ml blood loss per 24 h within 6 weeks *post-partum* and placental retention as a situation after delivery in which placental delivery does not occur within 1 h. A shoulder dystocia was defined as a situation after delivery of the head of the neonate, when the indentation of the shoulder within the maternal pelvis prevents further delivery.

Statistical analysis

All data were collected in a database using SPSS Statistics (IBM SPSS, Inc., Chicago, IL, USA version 20.0). In the dataset, several women had missing data at random and for some laboratory measurements selective missing (up to 60%) may have occurred, due to insufficient compliance to the study protocol of some hospitals. To avoid any potential bias that might have occurred, multiple imputation (10 times) was applied using observed baseline characteristics and the outcome data, though the outcome itself was not imputed. Missing baseline data were imputed using a logistic regression model that included the variables given in Table I (Sterne *et al.*, 2009). We compared baseline characteristics in women who developed GDM with women who did not, χ^2 tests were used to calculate *P*-values for the categorical variables and Mann–Whitney *U*-tests were performed on the continuous variables. Associations between baseline characteristics and GDM were calculated by univariate and multivariate logistic regression analyses. After univariate regression, variables with $P \leq 0.15$ were put in a multivariate logistic regression model using backward elimination with $P > 0.15$ to determine the predictive strength of these variables for GDM. For a single model parameter, a critical *P* value of 0.15 is equivalent to using the broadly accepted Akaike's information criterion as model selection method (Akaike, 1973). The prediction model was tested using the area under the curve (AUC) of the receiver-operating characteristic (ROC). To assess the amount of overfitting, inherently present in analyses such as these, bootstrapping with 200 replications was used, which produced a shrinkage factor on the regression coefficients (Van Houwelingen and Le Cessie, 1990). Moreover, the optimism in the AUC was determined and an optimism-corrected AUC was subsequently calculated. For ease of use, the prediction model was presented as a score chart. The score chart was developed in R 3.0.0 by the normogram function in the RMS library.

Results

A total of 326 women with PCOS were included, of which 214 women got pregnant. The pregnancies of 189 (88%) women continued beyond a gestational age of 20 weeks and were followed intensively. Their features and outcomes are summarized in Table I. The remaining 25 pregnant women miscarried and were excluded from further analysis. The 189 women delivered 206 children, since there were 15 twins and 1 triplet pregnancy. A total of 62 (33%) women experienced 1 or 2 maternal complication(s). GDM alone occurred in 41 (22%) women, pregnancy-induced hypertension in 14 (7%) and pre-eclampsia in 8 (4%) women. Neonatal complications occurred in 49 (26%) infants. Ninety-one (48%) women had a complication of labour.

Table I shows differences in features comparing women who developed GDM versus women who did not; among other changes preconception BMI, waist circumference, systolic blood pressure and fasting glucose were significantly higher and SHBG was significantly lower in women who developed GDM.

After univariate and multivariate logistic regression analyses, the following variables turned out to be statistically significant independent predictors for GDM (Table II): type 2 diabetes in first-degree relatives (OR 3.87, 95% CI 1.21–12.38), fasting glucose (mmol/l) (OR 3.58, 95% CI 1.28–10.03), fasting insulin (mU/l) (OR 1.16, 95% CI 1.05–1.28), androstenedione (nmol/l) (OR 0.77, 95% CI 0.66–0.90) and SHBG serum concentration (nmol/l) (OR 0.98, 95% CI 0.96–1.00). The ROC curve in Fig. 1 shows the predictive strength of these preconception risk factors for GDM, with an AUC of 0.87 (95% CI 0.81–0.93).

The probability of developing GDM can be calculated using Table III and Fig. 2. A total score can be calculated by adding the subscores for the five screening predictors in Table III. The total score can be matched to a probability of developing GDM in Fig. 2.

The shrinkage factor on the regression coefficients after bootstrapping was 0·81 and the optimism corrected AUC was 0.83 (95% CI 0.77–0.89). The histogram and boxplot in Fig. 3 show the distribution of the predicted probabilities of our model for women with PCOS to develop GDM.

Discussion

The current study represents the largest prospective follow-up regarding pregnancy complications in anovulatory infertile women diagnosed with PCOS. Since women with PCOS were screened in a standardized fashion before conception, we were able to assess whether features upon initial screening could predict GDM. Such an approach may have relevant

Table I Epidemiological and clinical features and outcomes of pregnant women with PCOS who delivered according to their GDM status.

	All women (n = 189)[a]	Without GDM (n = 148)	With GDM (n = 41)	P-value
Demographic characteristics				
Maternal age (years)	29 [27–31]	29 [27–31]	30 [26–33]	0.234
Ethnicity				0.041
European descent	172 (91)	138 (93)	34 (83)	
Non-European descent	17 (9)	10 (7)	7 (17)	
Occupational class				0.094
Low	19 (10)	12 (8)	7 (17)	
Medium	67 (35)	50 (34)	17 (41)	
High	103 (54)	86 (58)	17 (41)	
Smoking				0.794
Never	127 (67)	100 (68)	27 (66)	
Quit	40 (21)	32 (22)	8 (20)	
Current	22 (12)	16 (11)	6 (15)	
Cycle disorder				0.606
No cycle disorder	6 (3)	4 (3)	2 (5)	
Oligomenorrhoea	140 (74)	110 (74)	30 (73)	
Amenorrhoea	43 (23)	34 (23)	9 (22)	
Miscarriage prior to inclusion	20 (11)	15 (10)	5 (12)	0.704
Cause of infertility				0.874
PCOS	155 (82)	122 (82)	33 (80)	
PCOS and malefactor	30 (16)	23 (16)	7 (17)	
PCOS and other	4 (2)	3 (2)	1 (2)	
Primary or secondary fertility disorder				0.151
Primary	149 (79)	120 (81)	29 (71)	
Secondary	40 (21)	28 (19)	12 (29)	
Complications in previous pregnancies (eclampsia, haemorrhage etc.)			0.010	
Maternal	4 (2)	3 (2)	1 (2)	
Neonatal	10 (5)	4 (3)	6 (15)	
Type 2 diabetes in first-degree relatives				0.004
No relatives	155 (82)	128 (86)	27 (66)	
1 relative	34 (18)	20 (14)	14 (34)	
CVD in first-degree relatives				0.134
No relatives	139 (74)	110 (74)	29 (71)	
1 relative	40 (21)	32 (22)	8 (20)	
Clinical measures (preconception)				
BMI (kg/m^2)	24 [21–28]	24 [21–28]	27 [23–34]	0.001
Waist circumference (cm)	84 [76–95]	83 [74–92]	92 [83–104]	0.000
Waist/hip ratio	0.82 [0.76–0.88]	0.80 [0.75–0.87]	0.86 [0.80–0.91]	0.007
Polycystic ovaries	182 (96)	141 (95)	40 (98)	0.817
Acne	56 (30)	55 (37)	14 (34)	0.647
Hirsutism[b]	23 (12)	27 (18)	4 (10)	0.166
Systolic blood pressure (mmHg)	117 [110–125]	116 [109–122]	121 [113–134]	0.021
Diastolic blood pressure (mmHg)	74 [70–82]	73 [69–81]	80 [71–88]	0.005
Fasting glucose (mmol/l)	4.9 [4.7–5.2]	4.9 [4.7–5.2]	5.2 [4.9–5.6]	0.004
Fasting insulin (mU/l)	6 [4–10]	5 [3–8]	10 [7–16]	0.000

Continued

Table I *Continued*

	All women ($n = 189$)[a]	Without GDM ($n = 148$)	With GDM ($n = 41$)	*P*-value
Total cholesterol (mmol/l)	4.8 [4.3–5.3]	4.7 [4.3–5.5]	5.0 [4.6–5.2]	0.835
Triglycerides (mmol/l)	0.7 [0.5–1.2]	0.7 [0.5–1.2]	1.1 [0.6–2.0]	0.003
Low-density lipoprotein cholesterol (mmol/l)	2.9 [2.5–3.4]	1.5 [1.2–1.8]	1.2 [1.0–1.5]	0.254
High-density lipoprotein cholesterol (mmol/l)	1.4 [1.1–1.7]	2.8 [2.4–3.5]	3.1 [2.7–3.4]	0.002
Androstenedione (nmol/l)	8.6 [6.5–11.7]	9 [7–12]	7 [6–10]	0.009
Testosterone (nmol/l)	2.0 [1.5–2.6]	2.0 [1.4–2.7]	1.9 [1.6–2.6]	0.802
LH (IU/l)	10.8 [6.4–14.9]	11.0 [6.3–15.0]	10.0 [7.1–12.0]	0.36
Prolactin (IU/l)	0.19 [0.14–0.25]	0.19 [0.14–0.25]	0.19 [0.13–0.25]	0.66
Sex hormone-binding globulin (nmol/l)	51 [38–73]	58 [41–84]	38 [25–50]	0.000
Thyroid Stimulating Hormone (mU/l)	1.7 [1.1–2.4]	1.7 [1.1–2.4]	1.7 [1.0–2.7]	0.938
Outcome variables				
Pregnant after treatment ($n = 181$)				
No treatment	22 (12)	15 (10)	7 (17)	0.014
Ovulation induction (clomiphene citrate, follicle-stimulating hormone)	126 (67)	102 (69)	24 (59)	
IVF/ICSI	30 (16)	20 (14)	10 (24)	
Other	3 (1.6)	3 (2)	0	
Single or multiple pregnancy ($n = 189$)				0.29
Single pregnancy	173 (92)	133 (90)	40 (98)	
Twin pregnancy	15 (8)	14 (9)	1 (2)	
Triplet pregnancy	1 (0.5)	1 (0.7)	0	
Gestational age at delivery ($n = 188$)	39.5 [38.3–40.4]	39.6 [38.3–40.4]	39.3 [38.4–40.3]	
Start of labour ($n = 189$)				0.00
Spontaneously	123 (65)	108 (73)	15 (37)	
Induction	52 (28)	31 (21)	21 (51)	
Elective Caesarean section	14 (7)	9 (6)	5 (12)	
Delivery outcome ($n = 189$)				0.73
Vaginal spontaneously	109 (58)	86 (58)	23 (56)	
Assisted vaginal delivery (vacuum, forceps)	35 (19)	29 (20)	6 (15)	
Caesarean section	45 (24)	33 (22)	12 (29)	
Maternal complications ($n = 189$)[c]				
Any maternal complication[d]	62 (33)	21 (14)	41 (100)[e]	0.00
Pregnancy-induced hypertension	14 (7)	9 (6)	5 (12)	
Pre-eclampsia	8 (4)	6 (4)	2 (5)	
GDM	41 (22)	0	41 (100)	
Other (infection, HELLP)	8 (4)	7 (5)	1 (2)	
Neonatal complications ($n = 184$)[c]				
Any neonatal complication[d]	49 (26)	35 (24)	14 (34)	0.11
Spontaneous premature birth	16 (8)	13 (9)	3 (7)	
Induced premature birth	7 (4)	5 (3)	2 (5)	
Large for gestational age	4 (2)	3 (2)	1 (2)	
Small for gestational age	15 (8)	14 (9)	1 (2)	
Hypoglycaemia	8 (4)	3 (2)	5 (12)	
Other (immature, congenital abnormalities)	8 (4)	6 (4)	2 (5)	
Birth complications ($n = 185$)[c]				
Any birth complication[d]	91 (48)	75 (51)	16 (39)	0.67

Continued

Table I *Continued*

	All women ($n = 189$)[a]	Without GDM ($n = 148$)	With GDM ($n = 41$)	*P*-value
Instrumental delivery (vacuum, forceps)	32 (17)	27 (18)	5 (12)	
Caesaean section	45 (24)	33 (22)	12 (29)	
Haemorrhage *post-partum*	13 (7)	10 (7)	3 (7)	
Other (placental retention, infection, shoulder dystocia)	6 (3)	6 (4)	0	

Data are median [IQR] or number (). The following variables are used for analysis, but not shown in the table: diet, alcohol, dehydroepiandrosterone, type 2 diabetes and CVD in second-degree relatives and age at menarche.
BMI, body mass index; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; IVF/ICSI, *in vitro* fertilisation/intracellular sperm injection; LH, lutenising hormone; PCOS, polysystic ovary syndrome.
[a]Miscarriages ($n = 25$) during the study period were excluded.
[b]Ferriman–Gallwey score >8.
[c]In some subjects ≥1 complication occurred.
[d]Total number of subjects with a complication.
[e]All women in this group had GDM as a complication.

clinical implications since an individualized periconception care plan can be developed.

The women participating in the current study were relatively lean (BMI 24 kg/m^2) compared with women with PCOS in other studies, possibly because obese women conceive less due to their overweight. Moreover, the general policy of our fertility outpatient clinic is that obese women with fertility problems must lose weight before starting fertility treatment; other prospective studies in women with PCOS reported a mean BMI between 24 and 28 (Bjercke *et al.*, 2002; Sir-Petermann *et al.*, 2005; Palomba *et al.*, 2010). The risk of pregnancy complications might be reduced due to the relatively low incidence of obesity; however, we found a remarkably high incidence (22%) of GDM in our study group. Obesity (BMI ≥ 30 kg/m^2) contributes to the high risk of GDM and one study showed a presence of 37% in the women diagnosed with GDM (Ghazeeri *et al.*, 2012), whereas only 20% of our total study group was obese.

The incidence of GDM in other prospective studies in women with PCOS reported so far varied from 8 to 16% (Bjercke *et al.*, 2002; Palomba *et al.*, 2010). However, these studies involved much smaller sample sizes, and other studies were retrospective (Kjerulff *et al.*, 2011). In healthy women, GDM occurred in 1–5% of all pregnancies (Shand *et al.*, 2008; Roberts *et al.*, 2011).

Multiple pregnancies occurred in 16 (8%) of the women. Multiple pregnancies have an increased risk of pregnancy complications compared with singleton pregnancies (Fauser *et al.*, 2005). We decided not to exclude multiple pregnancies in our study, because we aimed to develop a prediction model based on patient characteristics before conception, prior to knowledge about the occurrence of a multiple pregnancy. *Post hoc*, it appeared that only 1 of the 16 multiple pregnancies was complicated with gestational diabetes, thus it would not have made a large difference to exclude them from analysis.

The observed pregnancy-induced hypertension rate in the current study was relatively low (7%). Previous studies in women with PCOS reported an increased incidence of pregnancy-induced hypertension ranging from 8 to 27% (Bjercke *et al.*, 2002; Sir-Petermann *et al.*, 2005; Hu *et al.*, 2007; Palomba *et al.*, 2010). In contrast, pregnancy-induced hypertension occurred in 4–9% of healthy pregnant women (Bhattacharya *et al.*, 2007; Shand *et al.*, 2008; Liu *et al.*, 2011; Roberts *et al.*, 2011). The broad range of the reported incidence of pregnancy-induced hypertension in studies in women with PCOS could be explained by the bias which may have occurred because of the small sample sizes, the inclusion of women who were already pregnant or the retrospective designs.

Our study was unable to identify an increased incidence of pregnancy-induced hypertension in women suffering from PCOS, which may be related to the relatively low BMI in our study population.

The most common neonatal complication in this study was premature birth (12%), a third of which (4%) was due to induction, possibly reflecting the high GDM rate in this population. The incidence of preterm birth reported in a meta-analysis on pregnancies in women with PCOS was 14%; however, no differentiation was made between spontaneous and induced premature birth (Kjerulff *et al.*, 2011). The reported undifferentiated premature delivery incidence in neonates of healthy women ranged from 5 to 8% (Bhattacharya *et al.*, 2007; Shand *et al.*, 2008; Roberts *et al.*, 2011).

Despite the high number of women with GDM in our study, only 2% of the neonates were large for gestational age, although 16% of neonates in a meta-analysis regarding pregnancies in women with PCOS were large for gestational age (Kjerulff *et al.*, 2011). In healthy women, 10–12% of the neonates were large for gestational age (Shand *et al.*, 2008; Liu *et al.*, 2011). A possible explanation for the low number of large for gestational age neonates observed in our study group might be that glucose levels were better regulated compared with other studies. In the Netherlands, women with GDM are intensively monitored and adequately treated (by e.g. diet, insulin, metformin). Moreover, the definition of GDM has always been a subject of discussion. WHO criteria from 1999 and older were used by some studies, which described higher threshold values for diagnosing GDM compared with the criteria we used as postulated by the American Diabetes Association (American Diabetes Association, 2003; Palomba *et al.*, 2010). Another explanation might be that our study population was relatively lean.

We aimed to develop a prediction model for one of the most common pregnancy complications in women with PCOS, GDM. Predictors in our multivariate prediction model were first-degree relatives with type 2

Table II Univariate and multivariate logistic regression analysis of possible predictor variables for GDM.

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Demographic characteristics		
Maternal age (years)	1.07 (0.97–1.18)	
Ethnicity		
European descent	Ref	
Non-European descent	2.84 (1.01–8.01)	
Occupational class		
Low	Ref	
Medium	0.66 (0.20–2.18)	
High	0.38 (0.12–1.21)	
Smoking		
Never	Ref	
Quit	0.97 (0.40–2.34)	
Current	1.59 (0.56–4.53)	
Cycle disorder		
No cycle disorder	Ref	
Oligomenorrhea	0.42 (0.07–2.62)	
Amenorrhea	0.41 (0.06–2.81)	
Primary or secondary fertility disorder		
Primary	Ref	
Secondary	1.77 (0.81–3.90)	
Cause of infertility		
PCOS	Ref	
PCOS and malefactor	1.13 (0.45–2.87)	
PCOS and other	1.79 (0.16–20.37)	
Any miscarriage prior to inclusion versus none	1.22 (0.42–3.59)	
Complications in previous pregnancies (eclampsia, haemorrhage etc.)		
Maternal	1.38 (0.14–13.70)	
Neonatal	6.22 (1.66–23.30)	
Type 2 diabetes in first-degree relatives		
No relatives	Ref	
1 relative	4.37 (1.83–10.40)	3.87 (1.21–12.38)
CVD in first-degree relatives		
No relatives		
1 relative	0.86 (0.33–2.19)	
Clinical measures (preconception)		
BMI (kg/m^2)	1.13 (1.05–1.20)	
Waist circumference (cm)	1.05 (1.02–1.07)	
Waist/hip ratio[a]	1.85 (1.17–2.92)	
Polycystic ovaries	1.45(0.17–12.40)	
Acne	1.16 (0.50–2.7)	
Hirsutism[b]	0.46 (0.10–2.18)	
Systolic blood pressure (mmHg)	1.03 (1.01–1.06)	
Diastolic blood pressure (mmHg)	1.05 (1.02–1.09)	
Fasting glucose (mmol/l)	3.24 (1.52–6.92)	3.58 (1.28–10.03)
Fasting insulin (mU/l)	1.13 (1.06–1.21)	1.16 (1.05–1.28)
Total cholesterol (mmol/l)	1.01 (0.72–1.42)	
Triglycerides (mmol/l)	2.20 (1.26–3.84)	
Low-density lipoprotein cholesterol (mmol/l)	0.98 (0.65–1.48)	
High-density lipoprotein cholesterol (mmol/l)	0.31 (0.11–0.87)	
Androstenedione (nmol/l)	0.87 (0.77–0.99)	0.77 (0.66–0.90)
Testosterone (nmol/l)	0.94 (0.64–1.38)	
LH (IU/l)	0.96 (0.91–1.02)	
Prolactin (IU/l)	0.5 (0.01–17.88)	
SHBG(nmol/l)	0.96 (0.95–0.98)	0.98 (0.96–1.00)
Thyroid stimulating hormone (mU/l)	1.04 (0.96–1.13)	

Variables with a *P*-value of ≤ 0.15 in the univariate logistic regression analysis were used in the multiple logistic regression model. The following variables are used for analysis, but not shown in the table: diet, alcohol, dehydroepiandrosterone, type 2 diabetes and CVD in second-degree relatives and age at menarche.
OR, odds ratio; SHBG, sex hormone binding globulin.
[a]Per 0.1 points.
[b]Ferriman Gallway score >8.

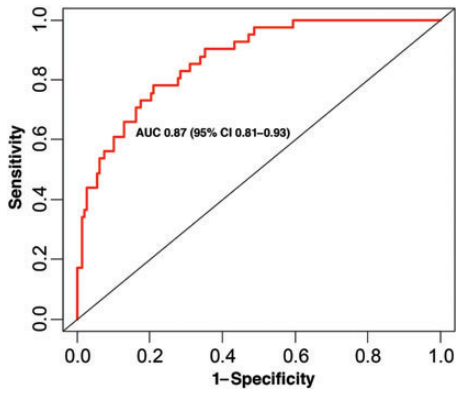

Figure 1 Receptor-operator characteristic curve for prediction of GDM by a model based on first-degree relatives with type 2 diabetes, fasting glucose, fasting insulin, androstenedione and SHBG (AUC = area under the curve).

diabetes, fasting glucose, fasting insulin androstenedione and SHBG serum concentrations. We were able to identify women at risk for GDM with an 83% precision. A score chart involving the above-mentioned screening characteristics has been designed to calculate the GDM risk for a given woman. Interventions were not performed in this study.

The predicting variables androstenedione and SHBG seem associated with the development of GDM (American Diabetes Association, 2003).

Table III Five screening parameters with subscores for the prediction of risk for GDM.

Screening parameters	Score[a]
Type 2 diabetes in first-degree relatives	
No relatives	0
1 relative	4
Fasting glucose (mmol/l)	
3.5	0
4.0	2
4.5	4
5.0	6
5.5	8
6.0	10
6.5	12
7.0	14
7.5	16
8.0	18
Fasting insulin (mU/l)	
0	0
5	2
10	5
15	7
20	9
25	12
30	14
35	16
Androstenedione (nmol/l)	
2	20
4	18
6	17
8	15
10	13
12	12
14	10
16	8
18	7
20	5
22	3
SHBG (nmol/l)	
0	13
20	12
40	10
60	9
80	7
100	6
120	4
140	3
160	1
180	0

Continued

Table III *Continued*

A total score can be calculated by adding the subscores for each screening parameter together. The score can be matched to the risk chart (Fig. 2) in order to obtain a predicted probability for a woman to get GDM. For example, a woman with PCOS had no first-degree relatives with type 2 diabetes, a glucose of 5.1 mmol/l, an insulin of 12.0 mU/l, an androstenedione of 8.3 nmol/l and a SHBG of 25.0 nmol/l. Scores are 0 for first-degree relatives with type 2 diabetes, 6 points for glucose, 5 for insulin, 15 for androstenedione and 12 for SHBG. The total score is 38, with a predicted probability to get GDM of 42%.

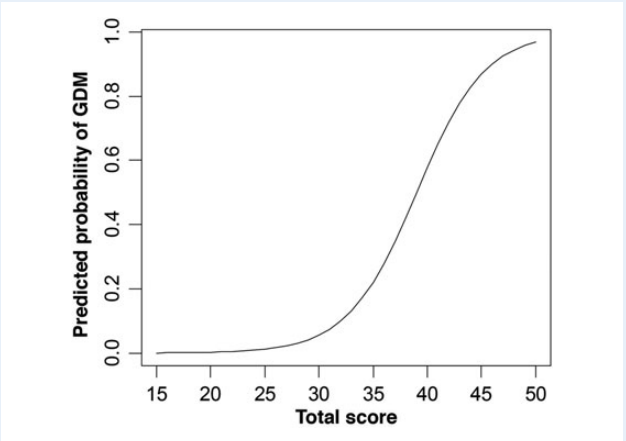

Figure 2 Score chart and the preconception probability for women with PCOS to get GDM.

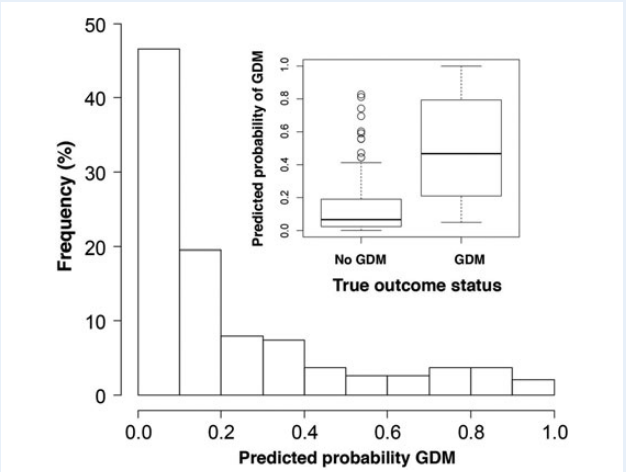

Figure 3 Histogram to show the distribution of predicted probabilities to get GDM based on first-degree relatives with type 2 diabetes, fasting glucose, fasting insulin, androstenedione and SHBG. Inset, boxplot of predicted probability of GDM by true GDM status.

As previously reported, SHBG could be a marker of insulin resistance *in vivo*, because of the inhibition of SHBG secretion in the human hepatoma cell line *in vitro* by insulin (Plymate *et al.*, 1988). In addition, earlier findings in a small subgroup of the current study (50 first included women) showed that GDM is associated with lower SHBG levels (OR 0.92, 95% CI 0.87–0.97) with a predictive precision of 86% (Veltman-Verhulst *et al.*, 2010). This study was based on a smaller number of patients and no internal validation was performed and so no correction for optimism was applied. Indeed, in the current data the corrected AUC for SHBG solely was 0.74 (95% CI 0.66–0.82), which is considerably lower than in the previous study, but also much lower than the AUC of the model with five predictors.

The association between low androstenedione concentrations and GDM remains unclear. However, hyperandrogenism is an important feature of PCOS and hyperinsulinaemia, observed in many women with PCOS, increases the bioavailability of androgens (Rajkhowa *et al.*, 1994).

The main points in the current study are its prospective design starting before conception, the considerable sample size and the standardized collection of determinants and outcomes. Another limitation is some missing data for the determinants, which were accounted for by multiple imputation. Multiple imputation is preferred over complete case analysis when missing data are at random (Donders *et al.*, 2006). Furthermore, we might have overestimated the incidence of GDM in a small proportion of women, since we used the preferred glucose load (100 g) for diagnosing GDM with the OGTT according to the American Diabetes Association in 2003 (American Diabetes Association, 2003). Shortly after this study ended, a new guideline of the American Diabetes Association appeared which recommended to use a 75-g OGTT with the same cut-off points as the 100-g OGTT (American Diabetes Association, 2012). With the 75-g OGTT women with moderate glucose intolerance will not be classified as GDM and so we speculate that the performance of our prediction model would then even improve. It would therefore be very interesting to perform an external validation of our prediction model in future studies in women with GDM based on the new ADA guidelines.

In conclusion, the current study confirms that women with PCOS exhibit an evident increased risk of developing GDM and premature delivery. In contrast to other studies in women with PCOS, the observed incidence of pregnancy-induced hypertension, pre-eclampsia and small for gestational age infants did not seem to be increased. We developed a prediction model able to identify accurately women with PCOS at risk for GDM before conception. Such women should be monitored closely during pregnancy, with frequent glucose evaluation and interventions if needed. This will enable preventive measures that may reduce the risk of developing GDM or enable early detection of GDM to reduce adverse consequences. For future research purposes, a combined prediction model for GDM could be created with a preconception prediction and an adjusted prediction during pregnancy in order to improve our prediction model. Moreover, further research is needed to determine intervention strategies based on the calculated risks for women with PCOS.

Authors' roles

S.M.V.-V., A.J.G., M.J.C.E. and B.C.J.M.F. designed the study. M.A.d.W., S.M.V.-V., C.B.L., J.S.E.L., A.F. collected the data. M.A.d.W., S.M.V.-V., A.J.G., C.B.L., J.S.E.L., A.F., M.P.H.K., M.J.C.E. and B.C.J.M.F. analysed and interpreted the data and wrote the manuscript. B.C.J.M.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding

No external funding was obtained for this study.

Conflict of interest

M.A.W., S.M.V.V., A.J.G., A.F. and M.P.H.K. have nothing to disclose. C.B.L has received fees and grant support from the following companies (in alphabetic order): Auxogen, European Society of Human Reproduction and Embryology and MSD. J.S.E.L. has received fees and grant support from the following companies (in alphabetic order): Ferring, Gennovum, Merck-Serono, MSD, Organon, Schering Plough, Sharp & Dome and Serono. M.J.C. has received grant support from the following companies (in alphabetic order): Illumina and MSD. B.C.J.M.F. has received fees and grant support from the following companies (in alphabetic order): Ferring, Ova-Science, PregLem SA, Roche and Watson Laboratories. The authors declare complete independence from funders.

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