Diabetologia (2012) 55:3173–3181
DOI 10.1007/s00125-012-2726-7

ARTICLE

A two-step screening algorithm including fasting plasma glucose measurement and a risk estimation model is an accurate strategy for detecting gestational diabetes mellitus

C. S. Göbl · L. Bozkurt · P. Rivic · G. Schernthaner · R. Weitgasser · G. Pacini · M. Mittlböck · D. Bancher-Todesca · M. Lechleitner · A. Kautzky-Willer

Received: 8 July 2012 / Accepted: 6 August 2012 / Published online: 22 September 2012

Abstract
Aims/hypothesis It is currently not clear how to construct a time- and cost-effective screening strategy for gestational diabetes mellitus (GDM). Thus, we elaborated a simple screening algorithm combining (1) fasting plasma glucose (FPG) measurement; and (2) a multivariable risk estimation model focused on individuals with normal FPG levels to decide if a further OGTT is indicated.
Methods A total of 1,336 women were prospectively screened for several risk factors for GDM within a multicentre study conducted in Austria. Of 714 women (53.4%) who developed GDM using recent diagnostic guidelines, 461 were sufficiently screened with FPG. A risk prediction score was finally developed using data from the remaining 253 women with GDM and 622 healthy women. The screening algorithm was validated with a further 258 pregnant women.
Results A risk estimation model including history of GDM, glycosuria, family history of diabetes, age, preconception dyslipidaemia and ethnic origin, in addition to FPG, was accurate for detecting GDM in participants with normal FPG. Including an FPG pretest, the receiver operating

Electronic supplementary material The online version of this article (doi:10.1007/s00125-012-2726-7) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

C. S. Göbl · D. Bancher-Todesca
Department of Gynecology and Obstetrics,
Division of Feto-Maternal Medicine, Medical University of Vienna,
Vienna, Austria

C. S. Göbl · L. Bozkurt · P. Rivic · A. Kautzky-Willer (✉)
Department of Internal Medicine III,
Division of Endocrinology and Metabolism,
Unit of Gender Medicine, Medical University of Vienna,
Waehringer Guertel 18–20,
1090 Vienna, Austria
e-mail: alexandra.kautzky-willer@meduniwien.ac.at

G. Schernthaner
Department of Internal Medicine I, Rudolfstiftung,
Vienna, Austria

R. Weitgasser
Department of Internal Medicine I,
Paracelsus Private Medical University,
Salzburg, Austria

R. Weitgasser
Department of Internal Medicine, Diakonissen-Hospital,
Salzburg, Austria

G. Pacini
Institute of Biomedical Engineering, Metabolic Unit,
National Research Council,
Padua, Italy

M. Mittlböck
Center of Medical Statistics, Informatics and Intelligent Systems,
Section for Clinical Biometrics, Medical University of Vienna,
Vienna, Austria

M. Lechleitner
Department of Internal Medicine, University of Innsbruck,
Innsbruck, Austria

characteristic AUC of the screening algorithm was 0.90 (95% CI 0.88, 0.91). A cut-off value of 0.20 was able to differentiate between low and intermediate risk for GDM with a high sensitivity. Comparable results were seen with the validation cohort. Moreover, we demonstrated an independent association between values derived from the risk estimation and macrosomia in offspring (OR 3.03, 95% CI 1.79, 5.19, $p<0.001$).

Conclusions/interpretation This study demonstrates a new concept for accurate but cheap GDM screening. This approach should be further evaluated in different populations to ensure an optimised diagnostic algorithm.

Keywords Gestational diabetes · Glucose tolerance test · Risk assessment · Screening

Abbreviations

AGDS	Austrian Gestational Diabetes Study
FPG	Fasting plasma glucose
GDM	Gestational diabetes mellitus
HAPO	Hyperglycemia and Adverse Pregnancy Outcome (study)
IADPSG	International Association for Diabetes in Pregnancy Study Groups
LASSO	Least absolute shrinkage and selection operator
LGA	Large for gestational age
ROC	Receiver operating characteristic

Background

Diabetes in pregnancy carries a great number of complications for children and mothers. In addition to obstetric complications from delivering a large for gestational age (LGA) child [1–3], women affected by gestational diabetes mellitus (GDM) are at high risk for developing overt type 2 diabetes [4–10].

Although the appropriate criteria for diagnosing GDM have been debated for a long time, it is now well established that early identification and treatment of the disease can improve perinatal outcomes by reducing modifiable risk factors [11]. Recently, Tieu et al discussed different screening strategies for GDM [12]. While the OGTT is accepted as the diagnostic 'gold standard', it is currently not clear whether general screening and cost-intensive examination are preferable to the selective screening of individuals at particularly high risk. In the past, we and others have identified several risk factors for the occurrence of GDM, such as maternal age, obesity, history of GDM, family history of type 2 diabetes and ethnicity [5, 13, 14]. Used separately, these proposed risk indicators have shown limited diagnostic accuracy [15, 16]. Some researchers have further suggested that GDM screening based on risk factors might be more effective with the use of appropriate prediction models that include statistical combinations of several risk factors [16–18]. However, the design of a sufficient risk score requires an adequate number of cases and, moreover, additional validation to assess if the risk estimation model is effective in routine clinical use.

Another approach to reduce the absolute number of individuals to be screened includes using information based on the fasting plasma glucose (FPG) measurement to decide if it is necessary to continue with the full OGTT [19]. This seems to be conclusive in the light of the recently developed IADPSG (International Association for Diabetes in Pregnancy Study Groups) guidelines, which recommend that at least one of three measurements during the 2 h OGTT must exceed the thresholds to make a diagnosis [20]. Thus, an FPG level of 5.1 mmol/l or higher is a diagnostic marker for GDM and there is no indication for a further examination.

Taking this into account, we can conclude that an optimal screening algorithm for GDM should consist of two simple steps: (1) general FPG screening as a pretest; and (2) a risk factor examination in individuals with normal fasting glucose levels based on appropriately designed prediction models to detect women with low risk for GDM. The OGTT remains the diagnostic test for individuals with intermediate or high risk.

Thus, this study aimed to elaborate and finally validate a two-step screening algorithm exclusively focused on identifying the risk for GDM by using combined information from a universal pretest measuring FPG and a multivariable risk estimation model focused on individuals with normal FPG. As a secondary objective, we assessed the association of the algorithm with the risk of delivering LGA offspring.

Methods

This report is part of the Austrian Gestational Diabetes Study (AGDS), which aims to evaluate the predictive value of GDM-specific risk factors and to assess the efficacy of different criteria to diagnose GDM, with a prospective cohort study design as previously reported [14]. In short, we conducted an open multicentre study in five hospitals in different parts of Austria (Vienna, Salzburg, Steyr and Innsbruck) during 2001–2004.

All participants underwent a broad risk evaluation at the initial contact, including: history of GDM, impaired fasting glucose (FPG ≥5.6 mmol/l) or impaired glucose tolerance (2 h OGTT ≥7.8 mmol/l) before pregnancy, previous recurrent abortions, glycosuria (>2.22 mmol/l), previous birthweight above 4,500 g, age (years), overweight or obesity (BMI >27 kg/m^2) before pregnancy, first- or second-degree relative with type 2 diabetes, previous preterm delivery (<37 weeks' gestation), ethnicity with a high risk for

diabetes (i.e. Hispanic, African, Asian or Indian), weight gain of 10 kg or more during pregnancy, hypertension (BP ≥140/90 mmHg) and anamnesis of preconception dyslipidaemia (triacylglycerol >1.70 mmol/l or total cholesterol >5.18 mmol/l). LGA was defined by using population-based birthweight percentile charts (>90th percentile, adjusted for sex and age of the Austrian population).

Participants underwent a 2 h 75 g OGTT and detailed metabolic characterisation (including a routine blood examination, as well as fasting insulin and markers for subclinical inflammation, such as ultrasensitive C-reactive protein and active plasminogen activator inhibitor-1 in subgroups) beginning at 24 weeks' gestation, with follow-up for the duration of the pregnancy. For this report, the presence of GDM was re-evaluated using the newly defined IADPSG criteria as a reference standard (FPG ≥5.1 mmol/l, 1 h OGTT glucose ≥10.0 mmol/l or 2 h OGTT glucose ≥8.5 mmol/l) [20]. Women with a positive FPG examination were identified in a first step and the risk prediction model was elaborated on the remaining participants. If more than one OGTT was performed during the study period (i.e. in case of positive symptoms for GDM), we used the first diagnostic visit if further evaluation was unremarkable. A total of 181 women underwent a 2 h 75 g OGTT before 24 weeks' gestation. However, participants with negative OGTT results before 24 weeks' gestation were only included if they were verified by a second OGTT in the second or third trimester. Of a total of 1,466 participants included in the AGDS, 130 women were excluded because of missing data (missing risk factors [n=6], OGTT values [n=3] or negative OGTT screening before 24 weeks' gestation, but missing verification of these results afterwards [n=121]). Women with known preconceptional diabetes were not included.

Of the remaining 1,336 women who were screened for the above-defined risk factors, 714 (53.4%) developed GDM. A total of 330 women with GDM (46.2%) were treated with insulin. Four participants with primarily negative OGTT screening were referred for insulin therapy during follow-up and were thus also classified as having GDM. FPG screening was sufficient in 64.6% of GDM women (461/714). Thus, the sample for evaluating the multivariable risk estimation model in cases of normal FPG consisted of 253 women with GDM and 622 women with normal glucose. A total of 147 of these participants (16.8%) presented with none of the above-described risk factors for GDM.

A further sample of pregnant women attending the diabetes outpatient clinic of the Medical University of Vienna between 2007 and 2010 for routine GDM screening was prospectively compiled as a validation cohort. All participants underwent a detailed risk evaluation followed by a 2 h 75 g OGTT using the IADPSG criteria to diagnose GDM.

The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. All prospective investigated individuals gave written informed consent to participate.

Statistical analysis Continuous variables were summarised by mean ± SD and categorical variables by counts and percentages, with comparisons using one-way analysis of variance or Fisher's exact test.

Logistic regression models were used to assess the probability of GDM by different risk factors in participants with normal FPG. Quantitative variables were included as continuous variables if not otherwise indicated. The effects were expressed as ORs. Tests of significance and 95% CIs were computed by using the likelihood ratio statistic. The goodness of fit of the final model was also evaluated (logistic link function, Hosmer–Lemeshow and the le Cessie and van Houwelingen statistic).

To optimise the predictability of the final model, we used the least absolute shrinkage and selection operator (LASSO) method [21, 22]. The tuning parameter was fitted by 100-fold cross-validation.

The final prediction model was calculated for each participant and the performance was estimated using receiver operating characteristic (ROC) curves with and without the information of the FPG pretest. The ROC-AUC and 95% CIs were estimated by non-parametric methods.

Statistical analysis was performed with R (V2.13.1) [23]. A two-sided p value of ≤0.05 was considered statistically significant and there were no considerations to adjust for multiplicity. Full data were available for the statistical analyses, except where otherwise stated.

Results

Development of the multivariable risk estimation model in participants with normal FPG Characteristics of the study population are given in Table 1. Table 2 describes the association between GDM risk factors and incident GDM in participants with normal FPG, and also reports the test accuracy of the specific risk factors. If univariable analysis indicated an association with GDM then the respective variable was further included in a multiple logistic regression model. As lower FPG levels indicate a lower risk for GDM, this variable was further included in the multivariable model, which significantly improved the model fit. Being overweight or obese preconception missed significance in the multivariable model (OR 1.12, 95% CI 0.78, 1.61, p= 0.542) and was therefore excluded. The excluded variables showed no significant model improvement when they were re-entered into the final multivariable model. Comparable independent predictors were observed by using automatic variable selection procedures (forward, backward or

Table 1 Characteristics of the evaluation cohort

Characteristic	NGT (n=622)	GDM with NFG (n=253)	GDM with IFG (n=461)	p value
FPG, mmol/l	4.34±0.42	4.42±0.44	5.73±0.77	<0.001
1 h OGTT, mmol/l	7.18±1.53	10.6±1.36	10.1±2.22	<0.001
2 h OGTT, mmol/l	5.77±1.23	8.11±1.71	7.85±2.25	<0.001
History of GDM	19 (3.1)	26 (10.3)	54 (11.7)	<0.001
History of IFG or IGT	5 (0.8)	6 (2.4)	15 (3.3)	0.010
Previous recurrent abortions	78 (12.5)	30 (11.9)	65 (14.1)	0.647
Glycosuria (>2.22 mmol/l)	71 (11.4)	67 (26.5)	122 (26.5)	<0.001
Previous birthweight ≥4,500 g	32 (5.1)	9 (3.6)	40 (8.7)	0.012
Age, years	28.6±5.8	31.3±5.1	31.6±5.6	<0.001
Preconception overweight/obesity	135 (21.7)	72 (28.5)	210 (45.6)	<0.001
Relative with type 2 diabetes	195 (31.4)	105 (41.5)	168 (36.4)	0.013
Previous preterm delivery <37 weeks	31 (5.0)	17 (6.7)	31 (6.7)	0.390
High-risk ethnicity	42 (6.8)	32 (12.6)	48 (10.4)	0.011
Weight gain ≥10 kg during pregnancy	45 (7.2)	23 (9.1)	43 (9.3)	0.395
Preconception hypertension	30 (4.8)	13 (5.1)	45 (9.8)	0.004
Preconception dyslipidaemia	5 (0.8)	10 (4.0)	16 (3.5)	0.001

Data are n (%) or means ± SD

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NFG, normal fasting glucose; NGT, normal glucose tolerance

stepwise). Logistic link function and model calibration behaved satisfactorily. An interaction of FPG and preconception dyslipidaemia (p=0.016) was not included because of the low prevalence of preconception dyslipidaemia in the study population (n=15).

Regression coefficients of the remaining variables as well as penalised regression coefficients using the LASSO method (λ=1.60) are given in Table 2. The probability of incident GDM in participants with FPG below 5.1 mmol/l can be computed as:

$$P[GDM] = \exp[x \times b]/[1 + \exp(x \times b)]$$

where x×b=−5.72+history of GDM×1.16+glycosuria×0.94+age×0.08+relative with type 2 diabetes×0.46+preconception dyslipidaemia×1.38+ethnic origin×0.63+FPG [mmol/l]×0.48

A more user-friendly GDM calculator is provided as electronic supplementary material (ESM).

ROC analysis of the risk estimation model applied to participants with normal FPG The AUC from the ROC analysis of the risk estimation model applied to the evaluation cohort was 0.71 (95% CI 0.67, 0.75) and thus showed a fair accuracy for detecting GDM in participants with FPG below 5.1 mmol/l (Fig. 1a; ROC-AUC of 1.00 represents a perfect test and 0.50 a worthless test). The test accuracy of the multivariable risk model appeared superior to the ROC-AUC of the individual risk factors shown in Table 2.

ROC analysis of the combined information of risk estimation model and FPG (two-step algorithm) on all available 1,336 women Figure 1b shows the combined information of this algorithm in addition to the FPG pretest applied to all included 1,336 women (participants with a pathological FPG pretest [≥5.1 mmol/l] were diagnosed as having GDM and thus received a score value of 1). The ROC-AUC of the FPG measurement alone (0.82, 95% CI 0.81, 0.84) was significantly increased to 0.90 (95% CI 0.88, 0.91) by including information from the multivariable risk estimation model. Youden's index revealed a cut-off value of 0.54 (sensitivity 74.4%, 95% CI 71.0, 77.4; specificity 94.2, 95% CI 92.1, 95.8). However, a score value of 0.20 or higher with a maximum sensitivity was chosen to decide between low and intermediate/high risk for GDM (sensitivity 96.5%, 95% CI 94.9, 97.6; specificity 30.9%, 95% CI 27.4, 34.6). Thus, 192 of 622 participants (30.9%) were correctly defined as glucose-tolerant normals, while 25 of 714 women with GDM (3.5%) were misclassified.

Adjusted ORs of additional predictive variables for GDM, which were evaluated in subgroups, are given in Table 3. Some predictors showed a significant contribution to the combined information of the risk estimation model in addition to FPG using the likelihood ratio test. However, the ROC-AUC remained similar. We observed a significant linear association between FPG and preconception BMI (r=0.28, p<0.001) in the studied population. Moreover, women with FPG levels of 5.1 mmol/l or higher had significantly higher preconception BMI (mean difference 3.4 kg/m^2, 95% CI 2.7, 4.0, p<0.001).

Validation of the risk prediction algorithm Of a total of 258 pregnant women, 59 (22.9%) developed GDM. A total of 29

Table 2 Analysis of different predictors for GDM in participants with normal fasting glucose (<5.1 mmol/l)

Predictor	Univariable analysis						Multivariable analysis[a]				
	OR	95% CI	*p* value	Specificity	Sensitivity	ROC-AUC	OR	95% CI	*p* value	Log_e(OR)	LASSO
History of GDM	3.64	1.98, 6.78	<0.001	97.0	10.3	53.6	3.31	1.74, 6.38	<0.001	1.20	1.16
History of prediabetes[b]	3.00	0.89, 10.5	0.074	99.2	2.4	50.8					
Previous recurrent abortions	0.94	0.59, 1.46	0.780	87.5	11.9	50.3					
Glycosuria (>2.22 mmol/l)	2.80	1.92, 4.06	<0.001	88.6	26.5	57.5	2.61	1.76, 3.87	<0.001	0.96	0.94
Previous birthweight ≥4,500 g	0.68	0.30, 1.39	0.301	94.9	3.6	50.8					
Age, years	1.09	1.06, 1.12	<0.001	38.3	84.2	63.5	1.08	1.05, 1.11	<0.001	0.08	0.08
Preconception overweight/obesity	1.43	1.03, 2.00	0.035	78.3	28.5	53.4					
Relative with type 2 diabetes	1.55	1.15, 2.10	0.004	68.7	41.5	55.1	1.63	1.18, 2.25	0.003	0.49	0.46
Previous preterm delivery <37 weeks	1.37	0.73, 2.50	0.316	95.0	6.7	50.9					
High-risk ethnicity	2.00	1.22, 3.24	0.006	93.3	12.7	53.0	1.93	1.14, 3.25	0.014	0.66	0.63
Weight gain ≥10 kg during pregnancy	1.28	0.75, 2.15	0.359	92.8	9.1	50.9					
Preconception hypertension	1.07	0.53, 2.04	0.846	95.2	5.1	50.2					
Preconception dyslipidaemia	5.08	1.79, 16.4	0.002	99.2	4.0	51.6	4.30	1.38, 14.96	0.012	1.46	1.38
FPG (mmol/l)	1.55	1.09, 2.21	0.014	60.3	50.2	56.1	1.66	1.14, 2.43	0.008	0.51	0.48
Intercept							0.003			−5.93	−5.72

Sensitivity and specificity for age and fasting glucose were assessed for their specific Youden's index

[a] Included primarily significant variables from univariable analysis and was thereafter reduced to significant multivariable predictors

[b] Impaired glucose tolerance or impaired fasting glucose

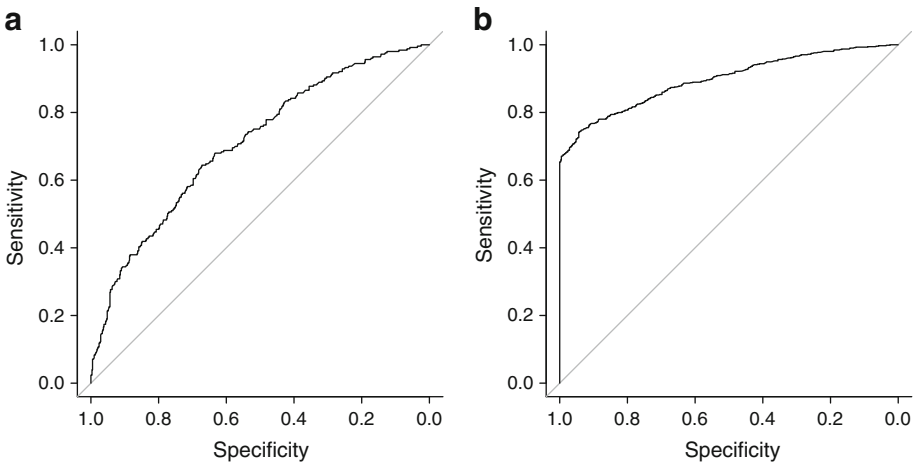

Fig. 1 ROC curves for (**a**) detecting GDM in 875 participants with normal FPG; and (**b**) for the combined information of risk score and FPG pretest, including 1,336 participants

women (49.2%) with GDM had FPG levels of 5.1 mmol/l or higher. Comparable with the evaluation cohort, the ROC-AUC for the multivariable risk estimation model was 0.74 (95% CI 0.65, 0.83) in women with normal FPG and 0.87 (95% CI 0.81, 0.92) for the two-step screening algorithm. The ROC-AUC for the FPG pretest alone was 0.75 (95% CI 0.68, 0.81). By using the cut-off value of 0.20 or higher, 33 women (16.6%) were correctly defined as glucose-tolerant normals, whereas one participant (1.7%) was classified as a false negative (sensitivity 98.3%, 95% CI 91.0, 99.7; specificity 16.6%, 95% CI 12.1, 22.4).

Association of the risk prediction algorithm with LGA infants A total of 125 LGA offspring were reported from all 1,336 pregnancies. The probability of GDM (estimated by the two-step scoring algorithm) was closely related to the risk of delivering an LGA infant (OR 3.03, 95% CI 1.79, 5.19, $p<0.001$). This association remained significant after adjusting for GDM status (OR 2.28, 95% CI 1.07, 5.11, $p=0.032$) and after accounting for 1 and 2 h OGTT values (OR 1.97, 95% CI 1.06, 3.65, $p=0.031$) and other predictors of LGA such as log-transformed triacylglycerol (OR 3.38, 95% CI 1.75, 6.62, $p<0.001$) and preconception BMI (OR 1.97, 95% CI 1.11, 3.50, $p=0.020$).

Discussion

The purpose of the present study was to develop a screening algorithm for GDM combining simple and routinely available clinical variables. A multivariable risk estimation model was designed to predict alterations in the OGTT by absence of pathologies in FPG and was thus suited for integration into a multistage procedure for diagnosing GDM following a simple fasting blood examination. However, the OGTT remains the final diagnostic test in pregnant women with normal FPG levels but with intermediate or high risk of GDM. This strategy could significantly reduce the number of invasive and expensive OGTT examinations, with a particularly low number of false-negative participants. A pragmatic explanation of how the proposed algorithm could be used in clinical practice is shown in Fig. 2.

In the past, several research groups have focused on clinical risk equations for GDM in different ethnic groups

Table 3 Implication of further variables on the two-step screening concept

Variable	GDM/NGT, *n*	aOR	95% CI	*p* value	ROC-AUC
HbA_{1c} (%)	533/419	1.95	1.34, 2.89	<0.001	88.7
Fasting insulin (pmol/l)	246/198	1.18	1.00, 1.40	0.057	86.0
Log_e(triacylglycerol [mmol/l])	460/397	2.27	1.43, 3.70	<0.001	89.2
Total cholesterol (mmol/l)	461/397	1.23	1.06, 1.43	0.006	89.2
HDL-cholesterol (mmol/l)	441/393	0.86	0.56, 1.30	0.470	88.3
Preconception BMI (kg/m^2)	677/555	1.02	0.99, 1.05	0.197	89.5
PAI (ng/ml)	243/230	1.02	1.01, 1.03	0.004	87.4
usCRP (nmol/l)	220/194	0.98	0.76, 1.08	0.756	85.4
Polyhydramnios on ultrasound	714/622	3.24	1.15, 9.00	0.026	89.8
Macrosomia on ultrasound	714/622	2.73	1.50, 4.93	<0.001	89.9

To compute the adjusted (a)OR, fasting insulin and usCRP were divided by 100

PAI, plasminogen activator inhibitor; usCRP, ultrasensitive C-reactive protein

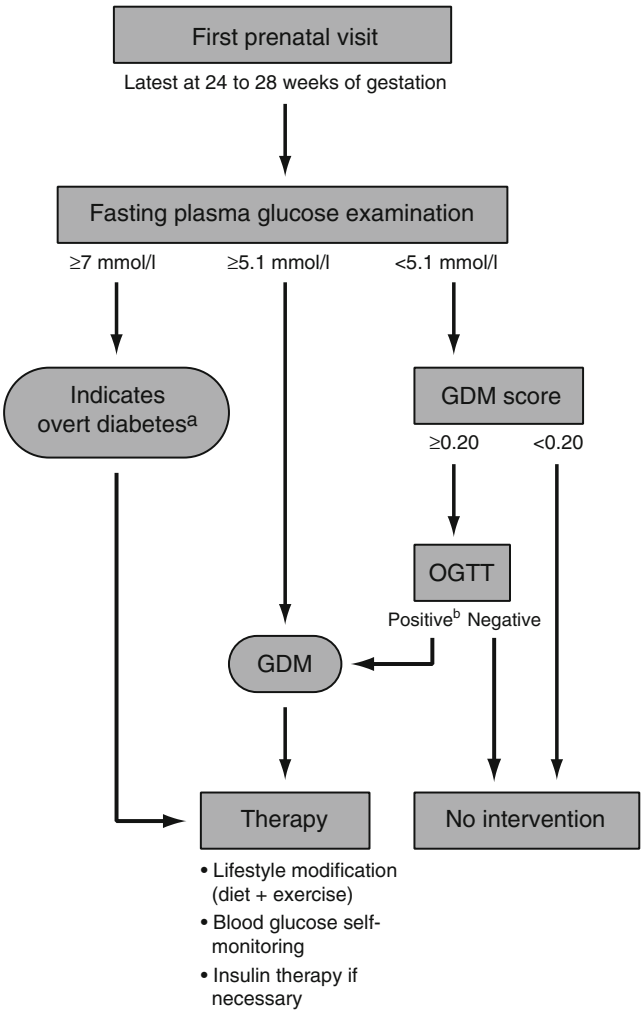

Fig. 2 Flow diagram of the two-step decision process. [a]Preconceptional diabetes is assumed; [b]positive if plasma glucose after 60 min is ≥10 mmol/l and after 120 min is ≥8.5 mmol/

[16–18, 24]. While most of these studies were technically well performed, they reflect the inconsistency of strategies and thresholds for diagnosing GDM [11]. The IADPSG Consensus Panel recently revised its recommendations for the diagnosis of GDM, particularly based on the results of the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study, aiming to close the 'lack of international uniformity in the approach to ascertainment and diagnosis of GDM' [20, 25]. Although OGTT screening is recommended for all pregnant women, the Consensus Panel stated that more cost-effective strategies that do not require an OGTT should be developed. However, clinical prediction models exclusively based on these recent diagnostic guidelines are still missing [20]. Furthermore, the discomfort of the OGTT might present an additional barrier to GDM screening among pregnant women, again highlighting the need for alternatives to universal OGTT screening in this group [11].

In contrast, FPG measurement is a well tolerated and inexpensive routine examination [26]. The requirement for an overnight fast might be a limitation; however, FPG measurement has been suggested to have a better test accuracy as a random plasma glucose test with reproducible values throughout the entire pregnancy [11, 27]. The HAPO study further estimated that FPG measurement identifies about 50% of all affected women without additional 1 and 2 h OGTT values [25]. This is comparable to our findings, where 40–65% of women with GDM were diagnosed by an FPG level of 5.1 mmol/l or above in both the validation and evaluation cohorts. As other recent studies have proposed that low FPG levels might help to rule out incident GDM [19, 26], this continuous variable was additionally included to improve the final risk equation. Furthermore, Black et al recently demonstrated that the risk for adverse pregnancy outcomes differs between women with impaired fasting glucose and abnormal glucose values during the OGTT, providing evidence that women with elevated fasting levels particularly suffer from delivering LGA infants [28]. Our results might corroborate this important observation as the presented risk algorithm, which uses a maximum of information from the FPG measurement, was strongly associated with postnatal macrosomia, even when the model was adjusted for other OGTT values and moreover for GDM status as well as other variables associated with macrosomia of the offspring, such as preconception BMI [29] or maternal triacylglycerol levels [30, 31].

The other variables in the risk estimation model included history of GDM, glycosuria, first- or second-degree relative with type 2 diabetes, preconception dyslipidaemia, age at gestation and high-risk ethnicity for GDM. While these predictors are in accord with the literature [4, 12, 32, 33], it is of interest that maternal overweight/obesity gave almost no contributing information and was therefore not included in the final model. The first clinical scoring system for GDM prediction, presented by Naylor et al, was based on preconception BMI in addition to maternal age and ethnicity [17]. In addition, other risk scores have revealed a contributing effect of BMI in GDM prediction [16, 18, 24]. It is, however, striking that in contrast to our model, none of the above-mentioned prediction algorithms included data on FPG. However, it has been stated that the combined effect of preconception BMI and FPG in the prediction of GDM has no additional effect on sensitivity and specificity [26]. In addition, higher rates of overweight were observed in participants with impaired fasting glucose in our study; this might explain the marginal contribution of BMI in our study and its exclusion from the multivariable model.

Savvidou et al have demonstrated that several biochemical measurements in the first trimester of pregnancy can improve the discrimination of high- and low-risk individuals, in addition to simple anamnestic variables using the

WHO criteria for diagnosing GDM [34]. However, inclusion of some novel risk variables did not improve test accuracy in our analysis; therefore, and to optimise the cost-effectiveness of the algorithm, these biochemical variables were not included in our prediction model, which was primarily based on cheap and simple variables that are ubiquitously available in an obstetric setting. Nevertheless, women with negative test results should be re-evaluated if clinical signs of GDM such as macrosomia on ultrasound [35] or glycosuria occur during pregnancy.

Regarding the cost-effectiveness of various procedures, a randomised cost-minimisation analysis found that one-step screening (2 h OGTT, Canadian Diabetes Association criteria) was more expensive than two-step approaches including a glucose challenge test based on time expenditure and analyses of multiple blood samples [36]. Another very recent decision analysis suggested that the IADPSG criteria are cost-effective, if post-delivery care is accomplished aiming to reduce diabetes incidence at follow-up. The authors recommended an FPG test at the first prenatal visit and a 2 h OGTT at 24–28 weeks' gestation in all women with early FPG levels lower than 5.1 mmol/l [37]. This approach is in accordance with our algorithm and argues for its cost-effectiveness.

The major advantage of our study is that the presented risk estimation is based on a large number of affected women using the new international diagnostic recommendations. It should be mentioned that both the evaluation and validation cohorts consisted of central Europeans and it is difficult to extrapolate the results to other populations. This is an important limitation of our study, as in a recent report of the HAPO study, Sacks et al observed considerable variations in GDM incidence between different centres and ethnic subgroups [38]. While FPG measurement was successful in diagnosing 55% of GDM cases in the total cohort and showed good test performance at most HAPO study sites, the accuracy was much lower in some Asian centres. The authors concluded that it might be reasonable to perform an initial FPG measurement followed by the full OGTT examination if this test is negative, particularly in populations with high FPG success rates. This is in agreement with the two-step algorithm presented in our study.

The high percentage of women with GDM in the evaluation cohort of this study (53.4%) is explained by the study design including more individuals with positive risk factors. It is not expected that this design per se is accompanied by a risk of bias for the model estimators. However, such a risk factor constellation could differ from that of the target population; this might have an impact on the selection of variables for the prediction score and thus underlines the need for a second validation cohort, which was included in this study. GDM incidence was still high in the latter cohort (23%), but comparable with incidences reported in some HAPO centres (e.g. 24.3% in Manchester, UK) [38]. However, it should be noted that the present study was performed in centres with intensive care units for neonates and thus the study population is a representative sample of tertiary care units. The lack of specificity of the risk estimation model (the second step) is another limitation. We chose a lower cut-off with high sensitivity for the second step to keep the number of false-negative results as low as possible. Consequently, this was accompanied by a higher proportion of individuals receiving an OGTT. Therefore, we recommend the FPG examination with high specificity (100%) as a first screening step. As shown in this study, the combination of both tests improves the overall accuracy.

In summary, we have developed a simple prediction algorithm for evaluating the risk of GDM that includes information from FPG results in addition to several anamnestic variables that can be easily assessed in a clinical setting. The proposed screening algorithm is based on the recent IADPSG recommendations and showed a high diagnostic accuracy, validated by a second cohort. The proposed cut-off value was also able to rule out GDM with high sensitivity. The predictive ability of the risk estimation for the delivery of a macrosomic offspring, which was also apparent after adjustment for GDM status and several covariables, underlines its clinical importance, in particular for a central European population. The proposed algorithm may be a further step in the development of an alternative to the OGTT, particularly in settings where the universal screening of all pregnant women with the full diagnostic OGTT is difficult or impossible. Further evaluation of this approach in different populations is necessary to ensure an optimised simple diagnostic algorithm for GDM.

Acknowledgements We thank T. Prikoszovich, MD, Department of Internal Medicine III, Division of Nephrology, Medical University of Vienna, Austria, for helping with data assessment. We particularly acknowledge Mr F. Ortag, Department of Geoinformation and Cartography, Vienna University of Technology, Austria, for help with preparing the manuscript.

Funding This study was supported by a clinical research project award from the Austrian Diabetes Association to AKW as well as in part by the Medical Scientific Fund of the Mayor of Vienna (No.: 09063) to AKW. There are no further competing financial interests to declare.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement AKW, DBT, GS, RW and ML conceived the study. Data assessment of the validation cohort was performed by PR and LB. Statistical analysis, calculations and data interpretation were performed by CSG, GP and MM. The manuscript was written by CSG, LB and AKW. GP, AKW, PR, GS, MM, RW, DBT and ML reviewed and edited the manuscript. All authors gave final approval of the manuscript to be published.

References

1. Pedersen J (1967) The pregnant diabetic and her newborn: problems and management. William & Wilkins, Baltimore, pp 128–137
2. Pettitt DJ, Knowler WC, Bennett PH, Aleck KA, Baird HR (1987) Obesity in offspring of diabetic Pima Indian women despite normal birth weight. Diabetes Care 10:76–80
3. Catalano PM, Hauguel-De Mouzon S (2011) Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? Am J Obstet Gynecol 204:479–487
4. Metzger BE, Coustan DR (1998) Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care 21 (Suppl 2):B161–B167
5. Kjos SL, Buchanan TA (1999) Gestational diabetes mellitus. N Engl J Med 341:1749–1756
6. Kim C, Newton KM, Knopp RH (2002) Gestational diabetes and the incidence of type 2 diabetes. Diabetes Care 25:1862–1868
7. Bozkurt L, Göbl CS, Tura A et al (2012) Fatty liver index predicts further metabolic deteriorations in women with previous gestational diabetes. PLoS One 7:e32710
8. Retnakaran R (2009) Glucose tolerance status in pregnancy: a window to the future risk of diabetes and cardiovascular disease in young women. Curr Diabetes Rev 5:239–244
9. Bellamy L, Casas JP, Hingorani AD, Williams D (2009) Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta analysis. Lancet 373:1773–1779
10. Göbl CS, Bozkurt L, Prikoszovich T, Winzer C, Pacini G, Kautzky-Willer A (2011) Early possible risk factors for overt diabetes after gestational diabetes mellitus. Obstet Gynecol 118:71–78
11. Farrar D, Duley L, Lawlor DA (2011) Different strategies for diagnosing gestational diabetes to improve maternal and infant health. Cochrane Database Syst Rev, Issue 10, Art. no. CD007122
12. Tieu J, Middleton P, McPhe AJ, Crowther CA (2011) Screening and subsequent management for gestational diabetes for improving maternal and infant health. Cochrane Database Syst Rev, Issue 7, Art. no. CD007222
13. Metzger BE, Buchanan TA, Coustan DR et al (2007) Summary and recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. Diabetes Care 30:251–260
14. Kautzky-Willer A, Bancher-Todesca D, Weitgasser R et al (2008) The impact of risk factors and more stringent diagnostic criteria of gestational diabetes on outcomes in central European women. J Clin Endocrinol Metab 93:1689–1695
15. Griffin ME, Coffey M, Johnson H et al (2000) Universal vs. risk factor-based screening for gestational diabetes mellitus: detection rates, gestation at diagnosis and outcome. Diabet Med 17:26–32
16. van Leeuwen M, Opmer BC, Zweers EJ et al (2010) Estimating the risk of gestational diabetes mellitus: a clinical prediction model based on patient characteristics and medical history. BJOG 117:69–75
17. Naylor CD, Sermer M, Chen E, Farine D (1997) Selective screening for gestational diabetes mellitus. N Engl J Med 337:1591–1596
18. Phaloprakarn C, Tangjitgamol S, Manusirivithaya S (2009) A risk score for selective screening for gestational diabetes mellitus. Eur J Obstet Gynecol Reprod Biol 145:71–75
19. Agarwal MM, Dhatt GS, Shah SM (2010) Gestational diabetes mellitus: simplifying the international association of diabetes and pregnancy diagnostic algorithm using fasting plasma glucose. Diabetes Care 33:2018–2020
20. International Association of Diabetes and Pregnancy Study Groups Consensus Panel (2010) International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes Care 33:676–682
21. Goeman J (2010) L1 and L2 penalized regression models. Available from: http://cran.r-project.org/web/packages/penalized/vignettes/penalized.pdf. Accessed 19 November 2011
22. Goeman JJ (2010) L1 penalized estimation in the Cox proportional hazards model. Biom J 52:70–84
23. R Development Core Team (2011) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available from: www.R-project.org. Accessed 19 November 2011
24. Caliskan E, Kayikcioglu F, Öztürk N, Koc S, Haberal A (2004) A population-based risk factor scoring will decrease unnecessary testing for the diagnosis of gestational diabetes mellitus. Acta Obstet Gynecol Scand 83:524–530
25. Coustan DR, Lowe LP, Metzger BE, Dyer AR (2010) The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Am J Obstet Gynecol 202:654.e.1–6
26. Riskin-Mashiah S, Damti A, Auslender R (2010) First trimester fasting hyperglycemia as a predictor for the development of gestational diabetes mellitus. Eur J Obstet Gynecol Reprod Biol 152:163–167
27. Siegmund T, Rad NT, Ritterath C, Siebert G, Heinrich W, Buhling KJ (2008) Longitudinal changes in the continous glucose profile measured by the CGMS in healthy pregnant women and determination of cut-off values. Eur J Obstet Gynecol Reprod Biol 139:46–51
28. Black MH, Sacks DA, Xiang AH, Lawrence JM (2010) Clinical outcomes of pregnancies complicated by mild gestational diabetes differ by combinations of abnormal oral glucose tolerance test values. Diabetes Care 33:2524–2530
29. Boerschmann H, Pflüger M, Henneberger L, Ziegler AG, Hummel S (2010) Prevalence and predictors of overweight and insulin resistence in offspring of mothers with gestational diabetes mellitus. Diabetes Care 33:1845–1849
30. Schaefer-Graf UM, Graf K, Kulbacka I et al (2008) Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care 31:1858–1863
31. Göbl CS, Handisurya A, Klein K et al (2010) Changes in serum lipid levels during pregnancy in type 1 and type 2 diabetic subjects. Diabetes Care 33(9):2071–2073
32. Scott DA, Loveman E, McIntyre L, Waugh N (2002) Screening for gestational diabetes: a systematic review and economic evaluation. Health Technol Assess 6:1–161
33. Kjos S, Buchanan T, Langer O, Yariv Y, Most O, Xenakis EM (2005) Gestational diabetes: the consequence of not treating. Am J Obstet Gynecol 192:989–997
34. Savvidou M, Nelson SM, Makgoba M, Messow CM, Sattar N, Nicolaides K (2010) First-trimester prediction of gestational diabetes mellitus: examining the potential of combining maternal characteristics and laboratory measures. Diabetes 59:3017–3022
35. Kjos SL, Schaefer-Graf UM (2007) Modified therapy for gestational diabetes using high-risk and low-risk fetal abdominal circumference growth to select strict versus relaxed maternal glycaemic targets. Diabetes Care 30:S200–S205
36. Meltzer SJ, Snyder J, Penrod JR, Nudi M, Morin L (2010) Gestational diabetes mellitus screening and diagnosis: a prospective randomised controlled trial comparing costs of one-step and two-step methods. BJOG 117:407–415
37. Werner EF, Pettker CM, Zuckerwise L et al (2012) Screening for gestational diabetes mellitus: are the criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups cost effective? Diabetes Care 35:529–535
38. Sacks DA, Haden DR, Maresch M, HAPO Study Cooperative Research Group et al (2012) Frequency of Gestational Diabetes Mellitus at collaborating centers based on IADPSG Consensus Panel recommend criteria. Diabetes Care 35:526–528