Improvement of selective screening strategy for gestational diabetes through a more accurate definition of high-risk groups

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Abstract

Objective: This study aimed to assess the predictive value of risk factors (RFs) for gestational diabetes mellitus (GDM) established by selective screening (SS) and to identify subgroups of women at a higher risk of developing GDM.

Design: A retrospective, single-center study design was employed.

Methods: Data of 1015 women screened for GDM at 24–28 weeks of gestation and diagnosed according to the International Association of Diabetes and Pregnancy Study Groups criteria were evaluated. Information on RFs established by SS was also collected and their association with GDM was determined. To identify distinct and homogeneous subgroups of patients at a higher risk, the RECURSIVE Partitioning and AMalgamation (RECPAM) method was used.

Results: Overall, 113 (11.1%) women were diagnosed as having GDM. The application of the SS criteria would result in the execution of an oral glucose tolerance test (OGTT) in 58.3% of women and 26 (23.0%) cases of GDM would not be detected due to the absence of any RF. The RECPAM analysis identified high-risk subgroups characterized by fasting plasma glucose values >5.1 mmol/l (odds ratio (OR) = 26.5; 95% CI 14.3–49.0) and pre-pregnancy BMI (OR = 7.0; 95% CI 3.9–12.8 for overweight women). In a final logistic model including RECPAM classes, previous macrosomia (OR = 3.6; 95% CI 1.1–11.6), and family history of diabetes (OR = 1.8; 95% CI 1.1–2.8), but not maternal age, were also found to be associated with an increased risk of developing GDM. A screening approach based on the RECPAM model would reduce by over 50% (23.0 vs 10.6%) the number of undiagnosed GDM cases when compared with the current SS approach, at the expense of 50 additional OGTTs required.

Conclusions: A screening approach based on our RECPAM model results in a significant reduction in the number of undetected GDM cases compared with the current SS procedure.

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Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). In the last few years, many screening and diagnostic criteria have been proposed (2, 3, 4, 5), and this is the main reason for the different prevalence rates of GDM being reported worldwide (6).

GDM is an important factor for determining adverse maternal and neonatal outcomes (7, 8, 9) and long-term consequences for both infants and mothers, such as predisposition to obesity, metabolic syndrome, cardiovascular diseases, and diabetes (10, 11, 12). For these reasons, GDM necessitates an early detection and

proper treatment. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel (3), reconsidering the results of the HAPO Study (13), proposed new diagnostic criteria, based on a universal diagnostic approach, which have been accepted by the American Diabetes Association (14). According to the universal screening criteria, all pregnant women not previously known to have diabetes have to be screened for GDM at 24–28 weeks of gestation, using a 75 g 2-h oral glucose tolerance test (OGTT), regardless of the presence of any risk factor (RF). Moreover, several International Diabetes Scientific Societies, including the British National Institute for Health and Clinical Excellence (NICE) and the Italian Guideline of Physiological Pregnancy (5, 15), have established that selective screening (SS) had to be conducted for GDM, based on the presence of specific RFs. According to the universal screening criteria, all pregnant women not previously known to have diabetes have to be screened in a first step for the presence of defined RFs.

Traditional RFs such as maternal age, pre-pregnancy BMI, fasting plasma glucose (FPG), previous GDM, previous macrosomia, family history of diabetes, and ethnicity were considered. In case of presence of even one RF, women have to be screened for GDM using a 75 g 2-h OGTT. However, there is still debate as to which RFs should be taken into account to make screening and diagnostic procedures cost effective.

The aim of this study was to assess, in a Caucasian population, the independent predictive value of RFs for GDM established by SS and to identify subgroups of women at a higher risk of developing GDM.

In particular, we retrospectively applied the SS criteria to our population to estimate the number of OGTTs that would have been required by these criteria and the proportion of diagnoses of GDM that would have been missed when compared with a universal screening approach. We also compared the yield of the SS criteria strategy with that of an alternative approach, based on risk stratification derived from the application of tree-growing regression techniques.

Subjects and methods

This is a retrospective study approved by the local ethics committee, involving a total of 1015 Caucasian pregnant women consecutively referred to the Clinic of Diabetes and Pregnancy of the University of Messina, Italy, from 1st May 2010 to 31st October 2011. All the participants gave informed consent.

All the participants underwent a 75 g 2-h OGTT between 24 and 28 weeks of gestation and the diagnosis of GDM was made according to the IADPSG recommendations (3). Briefly, the IADPSG suggests conducting a 75 g OGTT, with plasma glucose measurements at fasting and at 1 and 2 h, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes. The diagnosis of GDM is made when any of the following plasma glucose values are exceeded: fasting: ≥ 5.1 mmol/l, 1 h: ≥ 10.0 mmol/l, and 2 h: ≥ 8.5 mmol/l. First-trimester FPG values and information on the RFs established by SS (13) were also collected from clinical records. The following RFs were considered: maternal age ≥ 35 years, pre-pregnancy BMI ≥ 25 kg/m², FPG values between 5.6 and 6.9 mmol/l during pre-pregnancy or in the first trimester of pregnancy, previous GDM, previous macrosomia (birth weight ≥ 4500 g), family history of diabetes (first-degree relative with diabetes), and origin of family from areas with a high prevalence of diabetes. Data of 1028 singleton consecutive pregnancy cases in the study period were evaluated. Twelve of them had no complete information on the RFs or the first-trimester FPG values; one was diagnosed as having pre-pregnancy diabetes on the basis of the first-trimester FPG values. Therefore, 13 patients were excluded from the study.

Statistical analyses

Data are reported as means $\pm$ s.d. for continuous variables and percentages for categorical variables. The characteristics of the study population were categorized by GDM (yes/no) and were compared using the χ^2 statistic for categorical variables and the Mann–Whitney *U* test for continuous variables.

A multivariate logistic regression analysis was carried out to evaluate the association between the RFs considered in SS and GDM. The following baseline covariates were tested: FPG values between 5.6 and 6.9 mmol/l (yes or no), previous macrosomia (birth weight ≥ 4500 g) (yes or no), pre-pregnancy BMI ≥ 25 kg/m² (yes or no), family history of diabetes (yes or no), and maternal age ≥ 35 years (yes or no). The results of the logistic models are expressed as adjusted odds ratios (aORs) with their 95% CIs.

Furthermore, to identify distinct and homogeneous subgroups of patients at a higher risk of developing GDM, the REcursive Partitioning and AMalgamation (RECPAM) method was used (16, 17, 18). This tree-based method integrates the advantages of main effects of standard logistic regression and tree-growing techniques. At each partitioning step, the method chooses the covariate and

its best binary split to maximize the difference in the risk of developing GDM. The algorithm stops when user-defined conditions (stopping rules) are met. In our RECPAM analysis, a minimum set of 20 GDM cases and 50 women per node was considered. In the RECPAM model, we tested the same set of variables used in the multivariate logistic regression analysis, without categorizing continuous variables, to allow the algorithm to choose the natural cutoff points. A final backward logistic regression analysis with the RECPAM classes forced in was carried out to highlight the role of additional variables acting as global correlates. A sensitivity analysis comparing the SS criteria and RF-based screening (according to our RECPAM model) criteria with respect to the universal screening criteria was carried out. The number of OGTTs to be carried out and that of undetected GDM cases resulting from the application of the current and RECPAM-based selective criteria, when compared with the universal screening criteria, were calculated. A *P* value <0.05 was considered for statistical significance. The analyses were carried out using SAS version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Overall, 1015 pregnant women were evaluated and GDM was diagnosed in 113 cases (11.1%). By applying the SS criteria to the study population, we found that only 591 patients (58.3%) would have undergone the diagnostic OGTT because of the presence of at least one RF. The number of patients with GDM according to the IADPSG criteria but not having any RF, and therefore not considered for SS, was 26. When compared with women having a normal glucose tolerance (NGT) value during the OGTT, women with a GDM diagnosis made by a universal screening approach were older and had a higher pre-pregnancy BMI, a higher BMI during the OGTT, and a higher FPG value in the first trimester of pregnancy; furthermore, they more often had a family history of diabetes, previous GDM, and previous macrosomia (Table 1). Women with GDM did not differ from those with NGT for gestational age, parity, weight gain during pregnancy, and percentage aged ≥ 35 years (Table 1). The results of logistic regression indicated a higher risk of developing GDM in the presence of FPG values between 5.6 and 6.9 mmol/l (aOR 66.3; 95% CI 8.0–548.1), previous macrosomia (aOR 6.1; 95% CI 2.1–17.3), pre-pregnancy BMI ≥ 25 kg/m² (aOR 2.2; 95% CI 1.4–3.4), and family history of diabetes (aOR 2.0; 95% CI 1.3–3.1). An increased risk was not found to be associated with maternal age ≥ 35 years (aOR 1.0; 95% CI 0.6–1.6).

Table 1 Clinical characteristics of the participants according to their glucose tolerance status.

	NGT (n=902)	GDM (n=113)	<i>P</i> ^a
Age (years)	30.5 ± 5.4	32.0 ± 4.8	0.0076
Women aged ≥ 35 years (n (%))	212 (23.5)	35 (31.0)	0.0811
Gestational age (weeks)	25.9 ± 1.8	25.6 ± 2.0	0.128
Pre-pregnancy BMI (kg/m ²)	23.7 ± 6.8	25.7 ± 4.7	<0.0001
Women with pre-pregnancy BMI ≥ 25 (kg/m ²)	243 (26.9)	56 (49.0)	<0.0001
Women with pre-pregnancy BMI ≥ 30 (kg/m ²)	68 (7.5)	19 (16.8)	<0.0001
BMI during the OGTT (kg/m ²)	26.6 ± 9.4	28.6 ± 4.2	<0.0001
Family history of diabetes (n (%))	199 (22.1)	46 (40.7)	<0.0001
Parity > 1 (n (%))	429 (47.6)	49 (43.4)	0.399
Previous GDM (n (%))	0 (0)	10 (8.8)	<0.0001
Previous macrosomia (n (%))	11 (1.2)	7 (6.2)	0.0002
FPG values between 5.6 and 6.9 mmol/l (n (%))	1 (0.1)	12 (10.6)	<0.0001
FPG values during the first trimester (mmol/l)	4.3 ± 0.4	4.8 ± 0.6	<0.0001
Glycemia T0 during the OGTT (mmol/l)	4.3 ± 0.4	4.9 ± 0.5	<0.0001
Glycemia T60 during the OGTT (mmol/l)	6.8 ± 1.4	9.8 ± 1.6	<0.0001
Glycemia T120 during the OGTT (mmol/l)	5.8 ± 1.2	7.8 ± 1.4	<0.0001
Weight gain during pregnancy (kg)	7.1 ± 3.9	7.5 ± 3.8	0.246

NGT, normal glucose tolerance; GDM, gestational diabetes mellitus.

^aMann-Whitney *U* test for continuous variables and χ^2 statistic for categorical variables.

RECPAM analysis

The RECPAM analysis led to the identification of four classes at different risks of developing GDM (Fig. 1). The reference category was represented by the subgroup of women with the lowest prevalence of GDM. Thus, the ORs for all the other subgroups were estimated with respect to the reference class. The most important variable for differentiating the risk of GDM was represented by FPG, with patients with a FPG value ≤ 4.4 mmol/l having the lowest prevalence. Therefore, this group served as the reference category. On the opposite side of the regression tree, patients with a FPG value >5.1 mmol/l represented the subgroup with the highest prevalence of GDM (OR 26.5; 95% CI 14.3–49.0). In women with FPG values between 4.5 and 5.1 mmol/l, the risk of GDM was further differentiated on the basis of pre-pregnancy BMI values.

Variable					P value
Age (years)	32.0 (29.0–36.0)	32.0 (28.0–35.0)	31.0 (28.0–35.0)	30.0 (27.0–34.0)	<0.0001
Gestational age (weeks)	25.0 (24.0–28.0)	25.0 (24.0–27.0)	26.0 (25.0–27.0)	26.0 (25.0–27.0)	0.0399
Pre-pregnancy BMI (kg/m ²)	25.9 (22.0–31.5)	27.3 (25.4–30.5)	21.7 (20.1–23.1)	22.5 (20.3–25.0)	<0.0001
Pre-pregnancy BMI ≥ 25 kg/m ² (%)	58.7	82.5	0	24.5	<0.0001
Family history of diabetes (%)	49.3	31.8	18.7	21.3	<0.0001
Parity >1 (%)	56.0	54.0	42.9	46.0	0.0903
Previous GDM (%)	2.7	0.8	2.0	0.5	0.1134
Previous macrosomia (%)	6.7	4.0	0.5	1.1	0.0007
FPG between 100 and 125 mg/dl (%)	17.3	0	0	0	<0.0001
FPG at first trimester (mmol/l)	5.3 (5.2–5.4)	4.8 (4.7–4.9)	4.7 (4.6–4.8)	4.2 (3.8–4.3)	<0.0001
Glycemia T0 at the OGTT (mmol/l)	4.9 (4.6–5.2)	4.6 (4.3–4.8)	4.4 (4.1–4.7)	4.3 (4.1–4.5)	<0.0001
Glycemia T60 at the OGTT (mmol/l)	9.2 (7.9–10.3)	7.1 (6.2–8.2)	6.9 (5.9–8.0)	6.7 (5.7–7.7)	<0.0001
Glycemia T120 at the OGTT (mmol/l)	7.2 (6.2–8.3)	5.9 (5.1–7.3)	5.8 (4.9–6.7)	5.8 (5.1–6.6)	<0.0001

Figure 1

Identification of subgroups at different risks of developing GDM: results of the RECPAM analysis. The RECPAM analysis identified subgroups of patients at different risks of developing GDM. The tree-growing algorithm modeled odds ratios (ORs) following a logistic regression with age, family history of diabetes, fasting plasma glucose (FPG), pre-pregnancy BMI and previous macrosomia as global variables. Splitting variables are shown between branches, whereas a condition sending patients to the left or right

sibling is on a relative branch. Class 4 with the lowest risk of developing GDM was the reference category (OR = 1). Circles indicate subgroups of patients; squares indicate the patient subgroup RECPAM classes. Numbers inside circles and squares represent the number of events (top) and the number of nonevents (bottom) respectively. An OR with the corresponding 95% CI (in parentheses) is shown for each class. The characteristics of the patients within each RECPAM class are presented.

Women with a pre-pregnancy BMI > 24.4 kg/m² exhibited a sevenfold higher risk of developing GDM compared with the reference class (OR 7.0; 95% CI 3.9–12.8) and a double risk compared with women with a pre-pregnancy BMI ≤ 24.4 kg/m² (class 3). Other RFs that were considered did not contribute to the identification of distinct subgroups at an increased risk of developing GDM. When examining the clinical characteristics of the RECPAM classes, the class at a higher risk of developing GDM (class 1) was found to have higher and statistically significant percentages of women with a family history of diabetes and women with previous macrosomia compared with the other classes

(Fig. 1). A final logistic regression model with RECPAM classes forced in, carried out to highlight the role of additional covariates, identified RECPAM classes 1, 2, and 3, previous macrosomia, and a family history of diabetes as predictive variables to be associated with an increased risk of developing GDM. Maternal age was not found to be associated with an increased risk (Table 2).

As shown in Table 3, the use of the most predictive RFs detected by the RECPAM model can help in the identification of women at a higher risk of developing GDM, when compared with the current SS criteria. Following the application of universal screening

Table 2 Backward logistic regression with the RECPAM classes forced in: odds ratios (ORs) and 95% CIs of the risk factors considered. Variables included in the model were RECPAM classes, previous macrosomia, family history of diabetes, and maternal age.

Variables	OR	95% CI
RECPAM class 3 vs 4	3.9	2.1–7.0
RECPAM class 2 vs 4	6.4	3.52–11.7
RECPAM class 1 vs 4	22.0	11.7–41.2
Previous macrosomia (birth weight ≥ 4500 g)	3.6	1.1–11.6
Family history of diabetes	1.8	1.1–2.8

recommendations, all the women in our study underwent the diagnostic OGTT (i.e. 1015 OGTTs). Considering a screening strategy based on the most predictive RFs suggested by the RECPAM model, 641 women would be considered at risk, having at least one of these RFs. The use of OGTTs only in women at risk would result in the execution of 641 OGTTs, thus leading to a saving of $1015 - 641 = 374$ OGTTs (36.8%), when compared with the universal screening criteria. On the other hand, the application of the current SS recommendations would imply the execution of an OGTT in 591 women, because of the presence of at least one RF. Therefore, the application of the RECPAM approach would increase by only 50 the number of OGTTs required to be carried out (641 vs 591), when compared with the current recommendations.

Discussion

Our study allowed us to determine the independent predictive role of the suggested individual RFs for GDM in a Caucasian population of pregnant women. We also identified subgroups of women at a higher risk of developing GDM.

Our approach was similar to that of several studies designed with the aim to identify the best diagnostic approach for GDM (19, 20, 21, 22, 23). In the European countries, the nonconformity of screening and diagnostic procedures for GDM is responsible for the different reported prevalence rates of GDM (6). The attempt made by the IADPSG Consensus Panel to establish a common strategy triggered an international debate, still on-going, on its validity (24, 25). In the various national contexts, a divergence in the acceptance of the IADPSG recommendations was, therefore, observed and, in some cases, a reworking of the same was done. The Italian Institute of Health had elaborated a specific guideline that established, according to the NICE criteria, a two-step RF-based procedure for the detection of GDM (15).

Our study aimed, for the first time, to evaluate the relevance of each RF through the RECPAM model, the algorithm of which allowed us to choose the natural cutoff points of the continuous variables included in the model. Thus, the cutoff values chosen by the model are not defined a priori, but they represent the split effect that maximizes the difference in the risk of GDM. The big advantage of the RECPAM model, when compared with the classical multivariate analysis, is that it does not identify the risk of GDM associated with a specific variable but defines the subgroups of patients at a higher risk, according to the factors most capable of determining a high predictive value for GDM. In the RECPAM model, we tested a set of variables of the suggested RFs for GDM. FPG was confirmed to be the most important factor for differentiating the risk of GDM. It is worth noting that the highest risk of developing GDM was observed in the subgroup of women with a FPG value > 5.1 mmol/l, and this is exactly in line with the FPG diagnostic cutoff value proposed by the IADPSG. This could support the IADPSG Panel recommendations to consider a FPG value ≥ 5.1 mmol/l for the diagnosis of GDM. Furthermore,

Table 3 Comparison of GDM screening procedures according to the current selective criteria or the risk factors suggested by the RECPAM model, when compared with the universal screening criteria.

Risk factors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	OGTTs needed	Undetected GDM cases
Current selective screening	80	44	85	94	591	26 (23.0%)
FPG > 4.4 mmol/l	80	66	77	96	399	23 (20.3%)
FPG > 4.4 mmol/l or pre-pregnancy BMI ≥ 25 kg/m ²	87	50	82	96	550	15 (13.3%)
FPG > 4.4 mmol/l or pre-pregnancy BMI ≥ 25 kg/m ² or family history of diabetes	89	40	84	97	641	12 (10.6%)

PPV, positive predictive value; NPV, negative predictive value.

the reference class that we identified was characterized by a FPG value ≤ 4.4 mmol/l, the same FPG cutoff value for which the risk of some adverse outcomes was low in the HAPO Study (3, 13).

In addition to FPG, it is important to underline the role of pre-pregnancy BMI, further differentiating the risk of GDM among women with intermediate levels of FPG. This confirms the recent acquisition of a perhaps overly glucocentric approach that could change in a vision considering more the BMI as an equally important RF (26). Therefore, even in the absence of a clear FPG impairment, pre-pregnancy BMI is *per se* a parameter capable of leading to an increased risk of developing GDM (Fig. 1).

Among the RFs considered, we showed that maternal age was not associated with an increased risk of developing GDM, as indicated by the multivariate analysis, and it did not define a subgroup of women at a higher risk in the RECPAM analysis. Even when using the final logistic regression model, with the RECPAM classes forced in, maternal age was not detected as a globally predictive variable associated with an increased risk of developing GDM. This is certainly an interesting point, because among the scientific societies that use a similar two-step procedure with SS, there is still a discrepancy on the definition of the RFs to be considered, specifically concerning maternal age (5, 27). The Australasian Diabetes in Pregnancy Society (ADIPS) recommends universal screening for GDM. However, it advises that where resources are limited SS based on RFs may be appropriate (27), and among the considered RFs is maternal age > 30 years. NICE (5) has decided not to consider maternal age as a RF. The predictive value of maternal age in the development of GDM has been evaluated in several studies and the risk associated has been shown to be higher with increasing age (20, 21, 28, 29). However, other authors have not reported a much higher risk for older women (22, 30). A recent study examining the individual association of maternal age, BMI, and racial origin with the development of GDM has found different associated risks in relation to the prevalence of GDM for the specific racial group considered. In particular, the most important findings have implied that maternal age is more important in the development of GDM in Black Africans and South Asians than in White Europeans (20). This could explain the possibility of considering older maternal age as a strong RF for GDM in populations other than the White European population.

The limitations of this study are primarily its retrospective design, which also includes the lack of cases of

women with previous GDM who did not develop GDM in the second pregnancy. However, it is widely accepted that previous GDM is one of the best predictors of GDM, as reported in many studies (22). Furthermore, the lack of information on the maternal and fetal outcomes did not allow us to assess the predictive role of individual RFs for GDM in the occurrence of these outcomes.

In conclusion, the current SS based on RFs led to sparing more than 40% of the OGTTs, as compared with universal screening, but at the cost of the lack of identification of about one-fourth of women with GDM without established RFs. In the light of our results, it is clear that some women have distinct characteristics that place them at a greater risk of developing diabetes. In particular, a FPG value > 5.1 mmol/l and pre-pregnancy overweight are the two factors associated with the highest risk of developing GDM, while an increased risk seems to be not associated with maternal age ≥ 35 years. The screening that we suggest consists of a selective RF-based approach. As indicated by the sensitivity analysis that had been carried out, it could lead to a significant reduction in the number of undetected cases of GDM, in the face of a minimum increase in the number of OGTTs required to be carried out.

Even though establishing as to what is an acceptable percentage of missing cases of GDM is difficult, considering our results, a re-evaluation of the RFs used in the screening procedures for the detection of GDM could be useful. This could make the procedures more cost effective and, above all, could reduce the stressful conditions and unnecessary medicalization of healthy women in their pregnancies. However, it is desirable to conduct further studies, with a greater number of participants of different ethnicities, that correlate the RFs with maternal–fetal outcomes.

Declaration of interest

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

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