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ORIGINAL ARTICLE

The risk stratification of adverse neonatal outcomes in women with gestational diabetes (STRONG) study

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Abstract

Aims To assess the risk of adverse neonatal outcomes in women with gestational diabetes (GDM) by identifying subgroups of women at higher risk to recognize the characteristics most associated with an excess of risk.

Methods Observational, retrospective, multicenter study involving consecutive women with GDM. To identify distinct and homogeneous subgroups of women at a higher risk, the RECursive Partitioning and AMalgamation (RECPAM) method was used. Overall, 2736 pregnancies complicated by GDM were analyzed. The main outcome measure was the occurrence of adverse neonatal outcomes in pregnancies complicated by GDM.

Results Among study participants (median age 36.8 years, pre-gestational BMI 24.8 kg/m^2), six miscarriages, one neonatal death, but no maternal death was recorded. The occurrence of the cumulative adverse outcome (OR 2.48, 95% CI 1.59–3.87), large for gestational age (OR 3.99, 95% CI 2.40–6.63), fetal malformation (OR 2.66, 95% CI 1.00–7.18), and respiratory distress (OR 4.33, 95% CI 1.33–14.12) was associated with previous macrosomia. Large for gestational age was also associated with obesity (OR 1.46, 95% CI 1.00–2.15). Small for gestational age was associated with first trimester glucose levels (OR 1.96, 95% CI 1.04–3.69). Neonatal hypoglycemia was associated with overweight (OR 1.52, 95% CI 1.02–2.27) and obesity (OR 1.62, 95% CI 1.04–2.51). The RECPAM analysis identified high-risk subgroups mainly characterized by high pre-pregnancy BMI (OR 1.68, 95% CI 1.21–2.33 for obese; OR 1.38 95% CI 1.03–1.87 for overweight).

Conclusions A deep investigation on the factors associated with adverse neonatal outcomes requires a risk stratification. In particular, great attention must be paid to the prevention and treatment of obesity.

Keywords Gestational diabetes · Neonatal outcomes · Risk stratification · Obesity

Introduction

Gestational diabetes mellitus (GDM) is defined as an alteration in blood glucose that occurs or is first identified in pregnancy [1]. Its development is primarily caused by the effect of pregnancy hormonal status. Recently, also a role of gut

Managed by Antonio Secchi.

The members of the STRONG Study Collaborators are listed in Supplementary Appendix.

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microbiota composition was hypothesized, gut microbiota aberrations preceding the diagnosis of GDM [2]. Despite the divergence at international level about the most appropriate screening and diagnostic procedures, its prevalence until 2010 was between 2–9% [3, 4], being about 7% in Italy [5]. GDM represents a pathological condition for the mother and the fetus during pregnancy, at delivery and in the follow-up period. Women with GDM have an increased risk of adverse obstetric events and adverse neonatal outcomes compared to women with physiological pregnancy [6]. In particular, GDM is associated with a greater risk of fetal macrosomia, shoulder dystocia, neonatal trauma, neonatal jaundice, respiratory distress, and neonatal hypoglycemia [7–10]. In addition, children of mothers with GDM could need more neonatal intensive care [11]. Recent evidence underlines the importance of early identification of GDM and its subsequent treatment to promote maternal–fetal health [12–14]. Two major randomized studies have shown that reducing maternal blood glucose levels was associated with a reduction in the occurrence of adverse outcomes [12, 13]. GDM is also associated with an increased risk of cardiovascular disease [15] and type 2 diabetes development [16, 17] after delivery compared to normal pregnancy. A systematic multidisciplinary management of pregnant women in the diagnosis and treatment of GDM is essential to contain these maternal and fetal complications [18].

Based on the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) study [19], a panel of international experts (IADPSG) has defined new guidelines for screening and diagnosis of GDM [20]. They consisted in the modification of the previous threshold glucose values of the diagnostic oral glucose tolerance test (OGTT) and the reduction in the number of altered OGTT points (from 2 to only 1) required to formulate the diagnosis. This led to an increase in the frequency of GDM. Another important change of the IADPSG guidelines is that now a universal one-step approach is recommended with a 75 g OGTT instead of selective screening based on risk factors or screening in a two-step approach with a glucose challenge test.

The new diagnostic criteria implies significant practical consequences in terms of care. Many of the situations previously classified as minor glucose alterations of the pregnancy, usually addressed by a less aggressive management approach, are now included into a single category labeled as GDM. This has a high impact on the caseload of specialist centers and, overall, on healthcare costs. In Italy, the most recent estimates of GDM prevalence diagnosed according to Italian criteria are around 11% [21].

However, GDM intensity of care pathway may be modulated on the basis of GDM severity defined not only as a degree of glucose impairment, but as an overall risk of adverse neonatal outcomes. Recognizing specific subgroups of women at high of risk adverse neonatal outcomes would help to align therapeutic attitudes toward more or less intensity and timeliness to ensure maternal–fetal–neonatal well-being and to maximize the appropriateness of use of available resources.

Aim of our study was to assess the risk of adverse neonatal outcomes in women with gestational diabetes and to identify subgroups of women at a high risk for adverse neonatal outcome.

Methods

The study had an observational, retrospective, multicentre design. It involved women with pregnancy complicated by GDM cared for by Italian diabetes Centers between January 2012 and May 2015. All the centers with a specialized outpatient clinic dedicated to GDM care have been involved. To have representative data of the centers normally caring for women with GDM only those with more than 30 cases of GDM per year during the study period were involved. Women were universally screened early in pregnancy (in the first trimester) to exclude overt diabetes. The diagnosis of GDM, according to current Italian recommendations, was considered whether it was confirmed at 16–18th or at the 24–28th weeks of gestation [22]. Screening for GDM is recommended for women with physiological pregnancy, using defined risk factors. In particular, it is recommended that women with at least one of the following conditions should be screened at 16–18 weeks of gestation: previous GDM, pre-pregnancy body mass index (BMI) ≥ 30 kg/m^2, plasma glucose values at the beginning of pregnancy (within the first trimester) between 100 and 125 mg/dl (5.6–6.9 mmol/l). An oral glucose tolerance test with 75 g of glucose (OGTT-75 g) should be offered to these women. In case of normal OGTT results the test should be repeated at 24–28 weeks of gestation. The risk factors considered at 24–28 weeks of gestation are: age ≥ 35 years, pre-pregnancy BMI ≥ 25 kg/m^2, fetal macrosomia in a previous pregnancy (≥ 4.5 kg), family history of diabetes (first-degree relative with type 2 diabetes), family origin from areas at high prevalence of diabetes. Women with one or more plasma glucose values above the established thresholds (≥ 92 mg/dl at baseline, ≥ 180 mg/dl after 1 h from the load, ≥ 153 mg/dl after 2 h from the load) are defined as having GDM.

After the diagnosis, women with GDM are invited to perform self-monitoring blood glucose measurement (fasting and 1 h after meal with glycemic targets of < 95 and < 130 mg/dl, respectively), to follow a balanced diet (total kcal calculated according to pre-gestational BMI), and to do regular physical activity. If blood glucose is not in target a pharmacological therapy (in Italy the only possible is insulin) is started.

Women with the following characteristics were eligible for this study: age ≥ 18 years, delivery by May 2015, signature of informed consent. Exclusion criteria were: diagnosis of pre-gestational diabetes, twin pregnancy. The following data of the studied women were collected: socio-demographic characteristics, risk factors for GDM, laboratory parameters, therapy, fetal ultrasound parameters, ketones testing (yes/no), average number of weekly self-monitoring of blood glucose tests, number of diabetes visits from GDM diagnosis to delivery, follow-up visit after delivery.

Information on maternal–fetal outcomes such as adequate, large or small fetal growth for gestational age, macrosomia, minor and major malformations, neonatal intensive care need, neonatal hypoglycemia needing i.v. treatment, neonatal hypocalcemia, neonatal hyperbilirubinemia, shoulder distocia, respiratory distress, type of delivery, stillbirths, maternal mortality, neonatal mortality, child weight, and length at birth was also collected.

Outcomes definition

The variable neonatal adverse outcome was defined as the presence of one or more of the following adverse neonatal outcomes: fetal growth large or small for gestational age, mortality, malformations, shoulder distocia, neonatal intensive care need, hypoglycaemia, hypocalcemia, hyperbilirubinemia, and respiratory distress.

Newborns were considered large for gestational age (LGA) if birth weight was greater than 90th percentile and small for gestational age (SGA) if birth weight was less than 10th percentile, based on national anthropometric standards adapted for sex and parity. Macrosomia was defined as a delivery weight greater than 4000 g. Neonatal hypoglycaemia was defined as blood glucose less than 40 mg/dl during the first 24 h of life. Hyperbilirubinemia was defined as blood bilirubin greater than 12 mg/dl. Respiratory distress was defined as respiratory insufficiency, presenting as changes in respiratory frequency, apnoeic spells, bradycardia and cyanosis. Malformations were classified according to EUROCAT. Shoulder distocia was defined as a damage of the shoulder of a newly delivered child, often as a result of physical pressure or trauma during childbirth.

All information was collected on an electronic data collection platform. To ensure anonymity, all patients have been identified by a unique code. Only the responsible doctor of the center and the authorized subjects were able to link this code to the corresponding patient.

The study was conducted in accordance with the Helsinki Declaration on Medical Research on Humans and with the Good Clinical Practice (GCP). The study was approved by the Ethics Committees of all participating Centers. Participant patients gave informed consent before taking part.

Statistical analysis

Sample size estimation was based on the most prevalent maternal–fetal outcome that was represented by large for gestational age (LGA). From Italian literature a prevalence of LGA of approximately 19.6% [13] for women with GDM was considered. To identify with a statistical power 80% ($\alpha = 0.05$) risk factors with a minimum prevalence of 15% in the study population and associated with an odds ratio (OR) ≥ 1.7, enrollment of at least 1000 women with GDM was required.

Descriptive data were summarized as mean and standard deviation, median and interquartile ranges, or percentages, depending on the type of variables. The characteristics of the study population were categorized based on the presence or absence of unfavorable neonatal outcomes and were compared using Student's test (continuous variables normally distributed), Mann–Whitney test (continuous variables not normally distributed), or the chi-square test (categorical variables). Logistic regression models were used to evaluate the factors most associated with neonatal adverse outcomes. Dependent variables of the single logistic models were the same components of the cumulative neonatal outcome. The same set of covariates was tested in each model: age, pre-pregnancy BMI, previous GDM, family history of diabetes, area of family origin, previous macrosomia, and plasma glucose values at the beginning of pregnancy between 100 and 125 mg/dl (5.6–6.9 mmol/l). Separate multivariate analyses including also OGTT glucose levels at 16–18 gestational weeks or at 24–28 gestational weeks were performed. In addition, to identify distinct and homogeneous subgroups of patients at a higher risk of developing adverse neonatal outcomes, the RECursive Partitioning and AMalgamation (RECPAM) [23–25] method was used. This method chooses the covariate and its best binary split to maximize the risk difference of having adverse neonatal outcomes. In the RECPAM model, both categorical and continuous variables have been tested to allow the algorithm to choose the natural cut-off point. A p value < 0.05 was considered statistically significant. All analyses were performed using the SAS version 9.3 (SAS Institute Inc.) program.

Results

Overall, 2736 pregnancies were analyzed. General characteristics of the studied population and information on neonatal outcomes are reported in Table 1.

Six stillbirths, one neonatal death but no maternal death was recorded. Features of participants according to the presence of adverse neonatal outcomes are reported in Table 2. Women with adverse neonatal outcomes (29.8%) had higher pre-gestational BMI, HbA1c levels at diagnosis,

Table 1 General clinical characteristics of the studied population

N	2736
Age (years)	36.6 ± 5.1
Age classes (%)	
≤ 35 years	37.2
> 35 years	62.8
Education (%)	
Low	26.0
Median	48.7
High	25.3
Occupation (%)	
Housewife	35.3
Employed	64.0
Student	0.7
Physical activity before pregnancy (%)	25.2
Physical activity during pregnancy (%)	25.9
Alcohol before pregnancy (%)	7.6
Alcohol during pregnancy (%)	2.6
Smoke (%)	
No	78.5
Yes	9.5
Ex	12.0
Race Caucasian (%)	44.8
Family from areas of high diabetes prevalence (%)	9.4
Family history of diabetes (%)	41.7
First pregnancy (%)	45.3
Number of previous pregnancy (*n*)	1.0 (1.0–2.0)
Previous abortion (%)	26.6
Number of previous abortion (*n*)	0.0 (0.0–1.0)
Previous GDM (%)	14.1
Previous macrosomia (%)	3.5
Weight before pregnancy (kg)	68.6 ± 15.7
Height (cm)	162.4 ± 6.7
Pre-pregnancy BMI (kg/m^2)	24.8 (21.9–28.9)
Pre-pregnancy BMI classes (%)	
< 25 kg/m^2	51.7
25–30 kg/m^2	27.7
> 30 kg/m^2	20.5
Weight at OGTT (kg)	75.4 ± 15.0
Weight at end of pregnancy (kg)	78.8 ± 15.1
Weight gain (kg)	9.9 ± 5.7
Blood glucose at first trimester (mg/dl)	88.8 ± 11.6
First trimester blood glucose between 100 and 125 mg/dl (%)	24.5
HbA1c at diagnosis % (mmol/mol)	5.1 ± 0.8 (32.7 ± 8.4)
16–18 weeks OGTT blood glucose T0′ (mg/dl)	94.7 ± 10.0
16–18 weeks OGTT Blood glucose T60′ (mg/dl)	163.9 ± 35.8
16–18 weeks OGTT blood glucose T120′ (mg/dl)	136.1 ± 33.8
24–28 weeks OGTT blood glucose T0′ (mg/dl)	86.2 ± 21.3
24–28 weeks OGTT blood glucose T60′ (mg/dl)	175.9 ± 31.4
24–28 weeks OGTT blood glucose T120′ (mg/dl)	147.2 ± 31.6
Systolic blood pressure (mmHg)	112.2 ± 13.5
Diastolic blood pressure (mmHg)	70.4 ± 9.7
Total cholesterol (mg/dl)	250.0 (217.0–280.0)

Table 1 (continued)

HDL cholesterol (mg/dl)	68.0 (57.0–79.0)
LDL cholesterol (mg/dl)	139.0 (112.0–165.6)
Triglycerides (mg/dl)	192.0 (146.0–248.0)
Gestational week at first visit (weeks)	28.0 (24.0–30.0)
Number of diabetes visits (*n*)	4.0 (3.0–6.0)
Number of weekly SMBG tests (*n*)	21.0 (14.0–28.0)
Ketones measurement (%)	55.7
Glucose lowering treatment (%)	
Diet	58.7
Insulin	41.3
Insulin treatment started during the first visit (%)	12.5
Anti-ipertensive treatment (%)	5.0
Antiplatelet treatment (%)	6.2
Levotiroxina treatment (%)	13.3
Other treatments (%)	27.7
Women attending the follow-up visit (%)	46.2
Follow-up OGTT T0′ (mg/dl)	91.0 ± 10.7
Follow-up OGTT T120′ (mg/dl)	101.9 ± 28.7
Pregnancy and neonatal outcomes	
Gestational week at delivery (weeks)	39.0 (38.0–40.0)
Gender of the newborn (%)	
Female	47.3
Male	52.7
Weight at birth (g)	3233.2 ± 492.7
Length at birth (cm)	49.7 ± 3.9
Stillbirths (%)	0.3
Mother death (*n*)	0
Neonatal death (*n*)	1
Composite outcome (%)	29.8
Macrosomia (> 4000 g)	4.8
Large for gestational age (%)	9.6
Small for gestational age (%)	5.9
Respiratory distress (%)	3.9
Jaundice (%)	10.4
Neonatal hypocalcemia (%)	0.7
Neonatal hypoglycemia (%)	7.2
Malformation (%)	3.4
Cesarean section (%)	46.4
Neonatal intensive care unit need (%)	4.9
Shoulder distocia (%)	0

OGTT basal glucose levels at 16–18 gestational weeks, previous macrosomia rate, number of previous abortion, and diastolic blood pressure levels, consumed more alcohol before pregnancy, more often were not Caucasian, and delivered at an earlier gestational week when compared with women without adverse outcomes. The occurrence of the adverse outcomes was only associated with previous macrosomia (OR 2.48, 95% CI 1.59–3.87). LGA (OR 3.99, 95% CI 2.40–6.63), fetal malformation (OR 2.66, 95% CI 1.00–7.18), and respiratory distress (OR 4.33, 95% CI 1.33–14.12) were also associated with previous macrosomia. LGA was also associated with obesity (OR 1.46, 95% CI 1.00–2.15). Small for gestational age was associated with first trimester glucose levels (OR 1.96, 95% CI 1.04–3.69). Neonatal hypoglycemia was associated with overweight (OR 1.52, 95% CI 1.02–2.27) and obesity (OR 1.62, 95% CI 1.04–2.51). No significant predictors were found when others multivariate analyses were performed considering neonatal intensive care, hypocalcemia, or hyperbilirubinemia as dependent variable. Separate multivariate analyses including also OGTT glucose levels at 16–18 gestational weeks or at 24–28 gestational weeks did not show any predictive role

Table 2 Characteristics according to the presence of the adverse neonatal outcomes

	Adverse neonatal outcomes—no	Adverse neonatal outcomes—yes	*p*
Age (years)	36.7 ± 5.0	36.5 ± 5.2	0.66
Age classes (%)			0.77
≤ 35 years	36.9	37.7	
> 35 years	63.1	62.3	
Education (%)			0.02
Low	24.3	28.3	
Median	51.3	43.3	
High	24.4	28.3	
Occupation (%)			0.86
Housewife	34.6	35.1	
Employed	64.7	64.0	
Student	0.7	1.0	
Phisycal activity before pregnancy (%)	26.3	24.2	0.38
Phisycal activity during pregnancy (%)	26.2	26.6	0.85
Alcohol before pregnancy (%)	6.4	10.2	0.004
Alcohol during pregnancy (%)	26.2	26.6	0.85
Smoke (%)			0.51
No	79.1	78.5	
Yes	9.8	8.9	
Ex	11.1	12.6	
Race Caucasian (%)	48.7	43.3	0.01
Family from areas of high diabetes prevalence (%)	9.1	10.0	0.52
Family history of diabetes (%)	40.1	43.4	0.12
First pregnancy (%)	44.6	44.5	0.99
Number of previous pregnancy (*n*)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.20
Previous abortion (%)	26.4	26.9	0.80
Number of previous abortion (*n*)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	0.02
Previous GDM (%)	13.8	15.9	0.19
Previous macrosomia (%)	2.3	6.2	< 0.0001
Weight before pregnancy (kg)	67.9 ± 15.2	70.0 ± 16.3	0.003
Height (cm)	162.2 ± 6.5	162.6 ± 6.8	0.29
Pre-pregnancy BMI (kg/m^2)	24.4 (21.7–28.6)	25.3 (22.3–29.4)	0.003
Pre-pregnancy BMI classes (%)			0.04
< 25 kg/m^2	53.5	47.9	
25–30 kg/m^2	27.7	29.9	
> 30 kg/m^2	18.9	22.2	
Weight at OGTT (kg)	74.7 ± 14.4	77.1 ± 16.4	0.01
Weight at end of pregnancy (kg)	78.1 ± 14.5	80.3 ± 16.1	0.008
Weight gain (kg)	9.9 ± 5.5	9.7 ± 5.7	0.56
Blood glucose at first trimester (mg/dl)	88.5 ± 10.9	89.7 ± 12.7	0.14
First trimester blood glucose between 100 and 125 mg/dl (%)	26.1	23.8	0.23
HbA1c at diagnosis % (mmol/mol)	5.2 ± 0.8 (32.2 ± 8.7)	5.1 ± 0.8 (33.8 ± 8.2)	0.001
16–18 weeks OGTT Blood glucose T0′ (mg/dl)	94.3 ± 10.0	97.1 ± 9.2	0.02
16–18 weeks OGTT Blood glucose T60′ (mg/dl)	165.1 ± 35.9	161.5 ± 37.6	0.59
16–18 weeks OGTT Blood glucose T120′ (mg/dl)	135.3 ± 33.3	137.9 ± 34.7	0.43
24–28 weeks OGTT Blood glucose T0′ (mg/dl)	86.0 ± 21.8	86.3 ± 22.2	0.78
24–28 weeks OGTT Blood glucose T60′ (mg/dl)	175.3 ± 32.1	175.9 ± 30.1	0.80
24–28 weeks OGTT Blood glucose T120′ (mg/dl)	146.0 ± 31.9	148.5 ± 31.8	0.10
Systolic blood pressure (mmHg)	111.7 ± 13.4	113.3 ± 13.9	0.008

Table 2 (continued)

	Adverse neonatal outcomes—no	Adverse neonatal outcomes—yes	*p*
Diastolic blood pressure (mmHg)	70.1 ± 9.6	70.9 ± 10.0	0.04
Total cholesterol (mg/dl)	250.0 (218.0–280.0)	246.0 (216.0–282.0)	0.67
HDL cholesterol (mg/dl)	68.0 (58.0–79.0)	67.0 (56.0–80.0)	0.55
LDL cholesterol (mg/dl)	144.0 (116.0–170.0)	135.0 (111.0–165.6)	0.16
Triglycerides (mg/dl)	191.0 (142.0–242.0)	182.0 (153.0–249.0)	0.51
Gestational week at first visit (weeks)	28.0 (25.0–30.0)	28.0 (24.0–30.0)	0.96
Number of weekly SMBG tests (*n*)	21.0 (14.0–28.0)	21.0 (14.0–28.0)	0.40
Ketones measurement (%)	54.0	59.8	0.01
Glucose lowering treatment (%)			0.60
Diet	60.1	59.0	
Insulin	39.9	41.0	
Insulin treatment started during the first visit (%)	11.0	14.0	0.14
Follow-up OGTT T0′ (mg/dl)	90.1 ± 9.8	93.3 ± 12.4	0.001
Follow-up OGTT T120′ (mg/dl)	101.1 ± 28.0	103.8 ± 30.2	0.22
Gestational week at delivery (weeks)	39.0 (38.0–40.0)	38.0 (37.0–39.0)	< 0.0001
Weight at birth (g)	3237.5 ± 384.2	3224.6 ± 662.1	0.99
Lenght at birth (cm)	49.9 ± 4.2	49.4 ± 3.1	0.19
Gender of the newborn (%)			0.08
Female	48.7	44.6	
Male	51.3	55.4	

for OGTT glucose levels for none of the single nor for the cumulative neonatal adverse outcome.

RECPAM analysis

The RECPAM analysis led to the identification of four classes at different risks of having an adverse neonatal outcome (Fig. 1). The reference category was represented by the subgroup of women with the lowest prevalence of adverse neonatal outcome. 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 adverse neonatal outcome was represented by pre-pregnancy BMI, with patients with pre-pregnancy BMI levels lower than 25 kg/m^2 having the lowest prevalence. Therefore, this group served as the reference category. On the opposite side of the regression tree, patients with a pre-pregnancy BMI > 30 kg/m^2 represented the subgroup with the highest risk of the adverse neonatal outcome (OR 1.68, 95% CI 1.21–2.33). Women with pre-pregnancy BMI levels between 25 and 30 kg/m^2 (class 2) also had a significant risk of adverse neonatal outcome compared with the reference category (OR 1.38 95% CI 1.03–1.87). Among women with pre-pregnancy BMI lower than 25 kg/m^2 the stratification model built a class on the basis of the presence of family history for type 2 diabetes but this class was not capable of further differentiating the risk for adverse neonatal outcomes (OR 1.17, 95% CI 0.84–1.65). Other factors that were considered in the model did not contribute to the identification of distinct subgroups at an increased risk of adverse neonatal outcomes.

When examining the clinical characteristics of the RECPAM classes (Table 3), women with the highest risk had the highest systolic and diastolic blood pressure levels, first trimester glucose values, first trimester blood glucose between 100 and 125 mg/dl rate, HbA1c levels at GDM diagnosis, fasting OGTT glucose levels both at 16–18 gestational weeks and at 24–28 gestational weeks, insulin treatment rate, and more often were Caucasian. All these differences between RECPAM classes were statistically significant and a between classes trend was clearly detectable.

Discussion

Principal findings

Our study showed that the occurrence of several adverse neonatal outcomes was associated with specific maternal antenatal characteristics. In particular, a strong role of previous macrosomia and pre-pregnancy BMI levels was recognized. Having a macrosomic baby in a previous pregnancy was associated with high risk of babies LGA, fetal malformation, respiratory distress, and a cumulative adverse neonatal outcome. Pre-pregnancy obesity was an independent

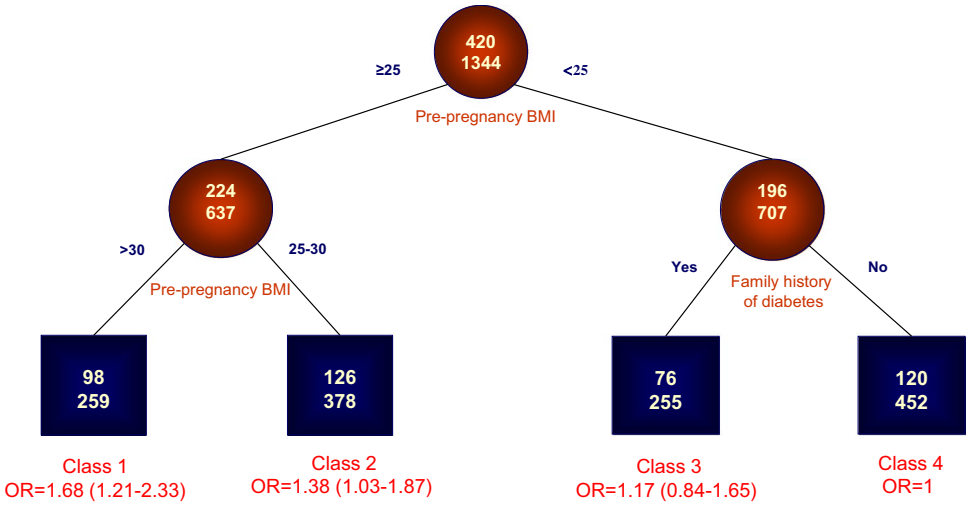

Fig. 1 Identification of subgroups at different risks of developing the cumulative adverse neonatal outcome: results of the RECPAM analysis. The REPCAM analysis identified subgroups of patients at different risks of developing adverse neonatal outcome. The tree-growing algorithm modeled odds ratios (ORs) following a logistic regression with age, pre-pregnancy BMI, previous GDM, family history of diabetes, area of family origin, previous macrosomia, plasma glucose values at the beginning of pregnancy between 100 and 125 mg/dl (5.6–6.9 mmol/l) 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 adverse neonatal outcome was the reference category (OR 1). Circles indicate subgroups of patients; squares indicate the patient subgroup REPCAM 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

risk factor for LGA and neonatal hypoglycemia. The role of pre-pregnancy BMI levels was further highlighted by the regression tree analysis we have performed. It identified obese women as the subgroup with the highest prevalence of adverse neonatal outcome. These high-risk women had also the highest systolic and diastolic blood pressure levels, first trimester glucose values, HbA1c levels at GDM diagnosis, and more often were not Caucasian. Furthermore, they more often required an insulin treatment to keep their glucose levels in target. Overweight women were also at higher risk of adverse neonatal outcome when compared with women with normal BMI. As obesity is known to negatively impact on maternal and neonatal course during pregnancy, it is important to highlight that also in a large Italian cohort this finding is confirmed.

Finally, our study did not show any predictive role of OGTT glucose levels with respect to the occurrence of adverse neonatal outcomes.

Comparison with existing knowledge

The STRONG study is the largest Italian multicenter study on GDM outcomes since new diagnostic criteria for GDM were approved. Other studies focused on this topic were performed. They were national or international clinical data collection or were based on the analysis of administrative data [26–31]. In both cases they showed different risks of adverse neonatal outcomes and different associations with specific antenatal maternal characteristics, this probably depending on the clinical features of the studied population. Obesity during pregnancy represents an important preventable risk factor for adverse pregnancy outcomes. It is associated with negative long-term health outcomes for both mothers and offspring [32]. These effects are often aggravated by the high incidence of abnormal glucose tolerance and excessive gestational weight gain [33]. We found a significant impact of obesity in determining some neonatal outcomes.

Maternal obesity and gestational weight gain are associated with childhood obesity, and this effect extends into adulthood. Childhood obesity in turn increases chances of later life obesity, type 2 diabetes, and cardiovascular disease in the offspring [34]. As compared to normal weight, maternal obesity is associated with increased risks of gestational hypertension, preeclampsia, gestational diabetes, cesarean delivery, delivering large size for gestational age infants, and childhood obesity [35]. A sub-analysis of the HAPO study showed that both maternal GDM and obesity are independently associated with adverse pregnancy outcomes. However, their combination has a greater impact than either one alone [36].

Another interesting study aimed to stratify the risk of neonatal outcomes using a classification and regression tree analysis. The authors found that high pre-pregnancy BMI was a predictor of LGA [37].

Importantly, the STRONG study confirmed that in a large Italian cohort obesity negatively impacts on maternal and

Table 3 Characteristics according to RECPAM classes

	Class 1	Class 2	Class 3	Class 4	*p*
Age (years)	36.1 ± 4.9	36.4 ± 5.3	37.2 ± 5.0	36.7 ± 4.9	0.03
Age classes (%)					0.03
≤ 35 years	43.6	39.4	32.9	34.5	
> 35 years	56.4	60.6	67.1	65.5	
Education (%)					
Low	38.4	31.8	22.2	20.8	
Median	48.0	48.5	48.9	48.3	
High	13.6	19.7	28.9	30.9	
Occupation (%)					0.02
Housewife	38.6	37.9	26.1	28.6	
Employed	59.7	61.4	73.3	70.8	
Student	1.7	0.8	0.6	0.6	
Phisycal activity before pregnancy (%)	15.8	21.5	36.8	27.9	< 0.0001
Phisycal activity during pregnancy (%)	28.6	26.3	33.3	32.9	0.22
Alcohol before pregnancy (%)	4.4	6.2	9.9	7.4	0.12
Alcohol during pregnancy (%)	0.4	1.1	1.3	1.2	0.75
Smoke (%)					0.46
No	74.5	79.4	78.3	78.9	
Yes	12.6	8.5	7.2	9.3	
Ex	13.0	12.1	14.5	11.8	
Race Caucasian (%)	24.8	18.3	17.6	15.0	0.01
Family from areas of high diabetes prevalence (%)	12.0	11.4	8.6	6.4	0.03
Family history of diabetes (%)	44.0	42.9	100	0	< 0.0001
First pregnancy (%)	43.2	45.2	49.4	51.3	0.13
Number of previous pregnancy (*n*)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.04
Previous abortion (%)	23.3	29.4	28.2	24.3	0.21
Number of previous abortion (*n*)	1.0 (0.0–1.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–1.0)	0.05
Previous GDM (%)	18.9	17.5	16.5	13.1	0.15
Previous macrosomia (%)	7.7	5.3	2.4	2.2	0.001
Weight before pregnancy (kg)	92.1 ± 13.1	71.7 ± 6.9	59.1 ± 6.0	58.0 ± 6.7	< 0.0001
Height (cm)	162.9 ± 6.9	162.3 ± 6.7	164.5 ± 5.9	163.1 ± 6.4	0.0002
Pre-pregnancy BMI (kg/m^2)	33.8 (31.2–36.7)	26.0–28.2	22.0 (20.5–23.4)	22.0 (20.3–23.4)	< 0.0001
	34.6 ± 4.1	27.2 ± 1.3	21.8 ± 1.9	21.8 ± 1.9	
Pre-pregnancy BMI classes (%)					< 0.0001
< 25 kg/m^2	0	0	100.0	100.0	
25–30 kg/m^2	0	100	0	0	
> 30 kg/m^2	100	0	0	0	
Weight at OGTT (kg)	97.0 ± 13.5	78.4 ± 8.1	67.3 ± 8.2	66.0 ± 8.3	< 0.0001
Weight at end of pregnancy (kg)	98.9 ± 14.1	81.2 ± 8.5	70.6 ± 7.8	69.3 ± 8.4	< 0.0001
Weight gain (kg)	7.0 ± 6.1	9.5 ± 5.3	11.5 ± 4.9	11.3 ± 4.6	< 0.0001
Blood glucose at first trimester (mg/dl)	91.1 ± 11.0	90.0 ± 10.6	89.2 ± 11.2	85.8 ± 10.4	< 0.0001
First trimester blood glucose between 100 and 125 mg/dl (%)	33.2	27.5	20.4	22.6	0.002
HbA1c at diagnosis % (mmol/mol)	5.5 ± 0.4 (35.4 ± 4.5)	5.4 ± 0.5 (34.9 ± 4.7)	5.4 ± 0.4 (34.3 ± 4.9)	5.2 ± 0.4 (33.3 ± 4.4)	< 0.0001
16–18 weeks OGTT Blood glucose T0′ (mg/dl)	98.7 ± 8.9	97.1 ± 8.7	95.2 ± 8.6	89.3 ± 10.4	< 0.0001
16–18 weeks OGTT Blood glucose T60′ (mg/dl)	171.0 ± 36.0	158.8 ± 31.1	164.3 ± 35.2	165.6 ± 34.3	0.43
16–18 weeks OGTT Blood glucose T120′ (mg/dl)	136.2 ± 34.4	135.0 ± 33.7	129.9 ± 31.9	145.3 ± 38.8	0.36

Table 3 (continued)

	Class 1	Class 2	Class 3	Class 4	*p*
24–28 weeks OGTT Blood glucose T0′ (mg/dl)	93.8 ± 17.5	90.5 ± 16.4	88.8 ± 14.8	86.2 ± 16.0	< 0.0001
24–28 weeks OGTT Blood glucose T60′ (mg/dl)	175.2 ± 33.2	176.3 ± 29.2	179.2 ± 29.5	173.7 ± 30.0	0.35
24–28 weeks OGTT Blood glucose T120′ (mg/dl)	143.8 ± 32.9	148.7 ± 31.3	149.3 ± 28.0	145.8 ± 31.1	0.34
Systolic blood pressure (mmHg)	118.5 ± 14.7	112.6 ± 13.1	109.7 ± 12.4	109.7 ± 12.7	< 0.0001
Diastolic blood pressure (mmHg)	72.8 ± 10.0	70.9 ± 9.5	69.1 ± 8.7	68.4 ± 8.8	< 0.0001
Total cholesterol (mg/dl)	224.0 (187.0–254.0)	249.0 (210.0–269.0)	244.0 (217.0–268.5)	247.5 (211.0–277.0)	0.01
HDL cholesterol (mg/dl)	58.0 (49.0–74.0)	65.0 (55.0–79.0)	69.5 (62.5–79.5)	71.0 (62.0–83.0)	0.0003
LDL cholesterol (mg/dl)	128.4 (108.0–147.2)	138.5 (114.5–162.5)	141.5 (119.0–161.2)	144.0 (119.0–163.0)	0.07
Triglycerides (mg/dl)	171.0 (128.0–210.0)	186.0 (128.0–249.0)	146.0 (106.0–199.0)	154.0 (103.0–201.0)	0.02
Gestational week at first visit (weeks)	25.0 (19.0–28.0)	27.0 (23.0–30.0)	28.0 (24.0–30.0)	28.0 (26.0–30.0)	< 0.0001
Ketones measurement (%)	52.5	51.9	51.8	51.0	0.98
Glucose lowering treatment (%)					< 0.0001
Diet	46.7	61.9	65.5	70.3	
Insulin	53.3	38.1	34.5	29.7	
Insulin treatment started during the first visit (%)	13.3	18.8	13.0	12.1	0.35
Anti-ipertensive treatment (%)	10.8	4.0	1.6	1.8	< 0.0001
Antiplatelet treatment (%)	7.3	6.1	2.4	2.9	0.006
Levotiroxina treatment (%)	10.9	13.6	8.2	13.7	0.12
Other treatments (%)	22.2	15.5	16.9	17.1	0.19
Women attending the follow-up visit (%)	47.1	46.0	52.5	49.3	0.40
Follow-up OGTT T0′ (mg/dl)	94.4 ± 10.7	92.9 ± 11.5	89.3 ± 9.7	87.9 ± 8.8	< 0.0001
Follow-up OGTT T120′ (mg/dl)	109.4 ± 30.9	104.6 ± 26.7	100.4 ± 27.9	98.6 ± 27.4	0.003
Gestational week at delivery (weeks)	39.0 (38.0–40.0)	39.0 (38.0–40.0)	39.0 (38.0–40.0)	39.0 (38.0–40.0)	0.14
Gender of the newborn (%)					0.91
Female	48.4	46.9	46.3	45.5	
Male	51.6	53.1	53.7	54.5	
Number of glucose tests (*n*)	21.0 (14.0–28.0)	20.0 (14.0–28.0)	16.0 (12.0–28.0)	18.0 (14.0–28.0)	0.004
Weight at birth (g)	3315.9 ± 514.3	3267.3 ± 528.0	3214.8 ± 419.3	3232.8 ± 500.3	0.07
Lenght at birth (cm)	49.6 ± 2.7	50.4 ± 8.2	49.8 ± 2.2	49.8 ± 2.7	0.84
Composite outcome (%)	37.8	33.3	29.8	26.5	0.01

neonatal course during pregnancy. Therefore, great attention should be paid to obesity by clinicians.

As for malformations authors recently reported no evidence for consistent association of GDM with birth defects, with the exception of a weak association between GDM and congenital heart defects. When stratified by maternal pre-pregnancy BMI an association between GDM and congenital heart defects and between GDM and neural tube defects was evidenced only in women with both GDM and pre-pregnancy obesity [38].

When we looked at the characteristics of the subcategories determined by the stratification model we noticed some interesting points. Women belonging to the highest risk group had the highest first trimester glucose values. This is in line with the results of the HAPO study [19, 20] and was also documented by another study in which a regression tree analysis was performed [25]. In our study, we did not find a predictive role of first trimester blood glucose levels for none of the outcomes we have considered probably because all the studied women received a careful process of care, this reducing the risk of adverse outcomes. Women of the highest risk RECPAM class had also the highest blood pressure levels. This is a finding that should be investigated in the light of the well-known relationship between blood pressure disorders and adverse pregnancy outcomes. Women of the highest risk RECPAM class were more often Caucasian. Significant differences in perinatal outcomes exist across ethnicity in women with GDM. This finding emphasizes the need to better understand ethnic-specific factors in GDM management and

the importance of developing strategies to address these disparities.

The other predictive factor of adverse neonatal outcomes we have found was previous macrosomia. In our study, it was associated with a high risk for several adverse outcomes as other studies have highlighted [39].

One of the main factor that could be linked to the development of adverse outcomes is the glucose level of each OGTT points. A large retrospective study showed that OGTT measures were significantly associated with most adverse outcomes [40]. However, the magnitude and significance of risk for these outcomes differed by various combinations of abnormal glucose values [40].

When we tested the predictive role of the glucose levels of the OGTT points, we found no associations with neonatal outcomes. This finding was confirmed both in multivariate analyses and in RECPAM models.

We found six stillbirths, one neonatal death but no maternal death in our study. These prevalence rates are in line with national rates reported by official regulatory Agencies.

Implications for clinical practice

The STRONG study allowed to recognize the need for a better approach to care women with GDM. The risk stratification based on the occurrence of adverse neonatal outcomes is a strategy focused on hard clinical parameters. The finding of a significant contribution of obesity and overweight in determining adverse outcomes requires particular attention to those conditions. Obesity is a status at increasing diffusion and it is associated with several cardiovascular and metabolic diseases. Our study showed that it is one of the most important predictors of adverse neonatal outcomes. All women should be advised by health care professionals about the risks linked to obesity. A deep evaluation on risk factors leading to obesity or overweight is needed to prevent these conditions. Our study clearly demonstrates that some categories of women could need a more intensive care during their pregnancy. On the other hand, some women could be considered low risk and they could need a less intensive clinical management and follow-up. This could change the management and follow-up of patients because low-risk women could have longer time between visits, lower number of obstetric visits, and ultrasounds compared to high-risk women. The lack of OGTT prediction for none of the neonatal adverse outcomes has potential implications in the national setting. The two-step risk factor-based screening procedure for GDM now used in Italy could be not exactly well-performing in detecting high-risk pregnancies. The STRONG study could lead to a redefinition of national procedures for screening and diagnosis of GDM, based on the real risk of neonatal complications. Our study also has research implications. We used a regression tree analysis that is not common used. This could mean that a more detailed and sophisticated methodological approach is needed to catch more fine clinical aspects capable of determining high risk for the development of adverse outcomes.

Strengths and limitations

This is a large national multicenter study giving a national picture of the care and the outcome of pregnancies complicated by GDM. Information on a great number of clinical parameters related to the pregnancy complicated by GDM and its follow-up was collected. Information on heath care resources needed for the care of GDM was also collected. This could allow to estimate the costs related to GDM care. Further sub-analyses could be performed on the basis of the collected data. One study limitation is not having planned a longer mother and children follow-up. We collected data until the women performed the first OGTT after pregnancy according to health care professionals advices.

Another important limitation of the study is the selection of women screened for GDM and therefore included in the study. The group of GDM included women who were detected earlier in pregnancy and women with GDM diagnosed at 24–28 weeks of pregnancy, so already providing a heterogeneous group with GDM, with some women receiving treatment earlier in pregnancy which might have affected outcome. However, we have performed a further analysis with the aim to test the effect of early diagnosis (i.e., at 16–18 weeks of pregnancy) in determining adverse neonatal outcomes. We have performed a multivariate analysis with the same set of variables already tested in the multivariate analysis plus a new variable that was “diagnosis of GDM at 16–18 weeks of pregnancy (yes or not)”. We have found that there was no statistically significant association between this variable and the occurrence of adverse neonatal outcomes (OR 1.44, 95% CI 0.54–3.86).

Moreover, being the screening based on risk factors this means that this is a selected group of women. Published data have showed that the application of the selective screening criteria would result in the execution of an oral glucose tolerance test in 58.3% of women and 23.0% cases of GDM would not be detected due to the absence of any risk factor [25].

Data could be, therefore, not applicable to a general GDM population detected by universal screening, but they are representative of populations managed according to a selective screening strategy.

A deep investigation on the factors associated with adverse neonatal outcomes requires a risk stratification to identify subgroups of women at higher risk. This could lead to an improvement in the level of care with a cost reduction and a better resource allocation.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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