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Research article

Keywords: Gestational diabetes mellitus, hyperglycemia, prediction risk, diagnosis

Posted Date: June 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-33583/v1

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RISK FACTORS FOR THE PREDICTION OF HYPERGLYCEMIA DURING PREGNANCY – A COHORT STUDY FROM A BRAZILIAN PUBLIC PRIMARY CARE CENTER

Risk factors for the prediction of hyperglycemia during pregnancy

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ABSTRACT

BACKGROUND – In Brazil, the prevalence of maternal hyperglycemia is among the highest, costs are elevated and there is no evidence to recommend universal screening. **OBJECTIVE –** To evaluate the performance of risk factors (RF) for predicting hyperglycemia in pregnancy – Mild Gestational Hyperglycemia (MGH) or gestational Diabetes Mellitus (GDM) in public primary-care centers in Brazil. **METHODS –** A cohort study, including 514 women with a single pregnancy and no hyperglycemia. Study participants were evaluated at GA (gestational age) < or ≥ 20 weeks, and underwent a 75g-OGTT along with glycemic profile (GP) testing between 24 and 28 weeks. Clinical, anthropometric and laboratory data – fasting glucose (FG), glycated hemoglobin (HbA1c), basal insulin and lipid profile were obtained. The most common RF associations (OR and 95% CI and p <0.05) and different cut-off points were tested for the prediction of MGH-GDM. Predictive performance was assessed by Sensitivity/Specificity, negative predictive value NPV (negative predictive value) and false positive rates (FP; 1-Esp). **RESULTS –** At GA <20 weeks, age ≥25 years, WC (Waist circumference) ≥ 88 cm, BMI pre ≥25 kg/m^2 (pre gestational body mass index) and BMI gest ≥25 kg/m^2 (gestational body mass index); at GA (gestational age) ≥20 weeks, age ≥25 years, BMI pre ≥25 kg/m^2 and TG (triglicerides) ≥150 mg/dL showed better performace for predicting MGH-GDM. Irrespective of gestational age, FG (Fasting glucose) ≥ 85 mg/dL, HbA1c ≥5.7% and HOMA-IR ≥2.71 were good predictors to rule out the risk of these complications. **CONCLUSION –** The results of this study should contribute to define the best diagnostic approach to MGH-GDM in our center and in others with similar characteristics.

Key words – Gestational diabetes mellitus, hyperglycemia, prediction risk, diagnosis.

INTRODUCTION

The diagnostic criteria for Gestational Diabetes Mellitus (GDM) have changed over the past decade. According to the American Diabetes Association (ADA), overt Diabetes – diagnosed earlier than 20 weeks of pregnancy, should be differentiated from GDM, which is diagnosed in the second or third trimester of pregnancy. The diagnosis of overt Diabetes is established when fasting glucose (FG) ≥ 126 mg/dL or glycated hemoglobin ≥ 6.5% or random glucose ≥ 200 mg/dL; whereas the GDM diagnosis is made when FG ≥ 92 and < 126 mg/dL or a 75g-Oral Glucose Tolerance Test (75g-OGTT) performed at 24-28 weeks shows that any of the following levels is met: FG ≥92 mg/dL; 1-h ≥180 mg/dL; and 2h ≥153 mg/dL[1,2,3].

At our center, the ADA 2011[2] diagnostic approach has been adopted since August 2011. Furthermore, we combine glucose profile testing (GP) with a 75g-OGTT to identify women with mild gestational hyperglycemia (MGH), who represent 17.3% of our patient population and do not meet GDM diagnostic criteria[4]. Women with MGH show the same maternal and fetal outcomes seen in those with GDM and, therefore, should be identified and treated for glycemic control during pregnancy[5,6].

The ADA 2011 diagnostic guidelines gave rise to an initial trend towards universal screening with fasting glucose (FG) measurement at the first prenatal visit (before 20 weeks of pregnancy) in all pregnant women. If no overt diabetes (FG ≥126 mg/dL) or GDM (FG ≥92 and <126 mg/dL) is detected, a 75g-OGTT is performed at 24-28 weeks[1-3,7,8]. However, as universal screening is associated with an increased number of women diagnosed with GDM, and there is no sufficient evidence that this strategy improves maternal/neonatal outcomes or is cost-effective, screening for GDM is still a subject of debate.

Currently, ADA recommends a two-step testing approach – universal (*one-step*) and selective (*two-step*) – 75g-OGTT offered only to women identified as being at risk by 50g-OGTT [3].

In Brazil, the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO), in consensus with the Brazilian Diabetes Society (SBD), Pan-American Health Organization/World Health Organization (PAHO/WHO Brazil), and Ministry of Health (MS) recommend universal screening with FG and 75-g OGTT[1-3] in settings where technical and financial resources are optimal and, therefore, allow diagnosing 100% of GDM cases. In settings where conditions are lower than optimal, but still good, recommendations are to measure FG at the first prenatal visit; if FG is normal (< 92 mg/dL), measurement should be repeated at 24-28 weeks. In this case, GDM is likely to be diagnosed in 86% of the women investigated[9,10]. Under poorer conditions, risk-factor based selective screening may be an alternative. Risk-factors include, maternal age ≥ 25 years, body mass index (BMI) ≥25 or 30 kg/m^2, history of macrosomia and GDM, family history of Diabetes Mellitus, and non-Caucasian ethnicity[3,11]. These as well other risk factors have already been tested as GDM predictors, but the results were either conflicting or inconclusive[12-17]. The fact that the prevalence of risk factors is low and dependent on the population studied, and the diversity of GDM diagnostic criteria interfere with the predictive performance of these markers[11,13,14].

Considering that evidence to define the optimal approach for GDM diagnosis– universal or selective – is insufficient, and that Brazil is among the eight countries where the prevalence of hyperglycemia during pregnancy is highest[9], it is important to investigate GDM risk factors across the different regions of the country. This might reduce the costs of the universal approach and improve the 86% rate of diagnoses based on FG ≥ 92 mg/dL[9,10].

The objective of this study was to assess the performance of risk factors in the prediction of hyperglycemia during pregnancy in women attending public healthcare centers in the state of São Paulo, Brazil.

METHOD

Study setting, design, and ethical aspects

This cohort study was conducted between March 2014 and December 2016 in primary public healthcare centers of the Botucatu Public Health Network and in the Diabetes and Pregnancy Center of Botucatu Medical School/Unesp, Brazil, a tertiary obstetric referral center. The study protocol was approved by the Human Subject Research Ethics Committee of Botucatu/Unesp (# 3900-2011; Of. No. 244/11). This study complies with national and international regulations for experiments in human beings, including resolution CNS 466/12 of the Brazilian National Health Council and the 1989 Declaration of Helsinki. All participants signed an informed consent form before entering the study.

This study included pregnant women who had undergone a 75g-Oral Glucose Tolerance Test (75g-OGTT) and Glucose Profile (GP) testing between 24 and 28 weeks of pregnancy. Women with a previous diagnosis of type 1 or type 2 DM, overt diabetes or GDM before 20 weeks of pregnancy were excluded[3].

Sample size

Sample size was calculated based on previous studies undertaken by our team and data from the literature that show that the frequency of maternal hyperglycemia is 15-20% [18,19]. Assuming a type 2 error of 20%, and a confidence level of 95%, minimum sample size was

112 estimated as 196 women with gestational age < 20 weeks, and 246 women with gestational
113 age ≥ 20 weeks. Thus, this study included 514 participants – 255 with gestational age< 20
114 weeks and 259 with gestational age ≥ 20 weeks.

115 *Data collection*

116 At enrollment, a specific structured questionnaire was administered to all participants for
117 the collection of epidemiological and clinical data including information on family and
118 personal obstetric risk factors for GDM[3,14,20]. Incomplete or missing information was
119 recovered from the participant's prenatal care chart. Also at enrollment, clinical and
120 anthropometric data were collected including blood pressure (BP), weight, height, waist
121 circumference, and gestational body mass index [21]. Blood samples were drawn for the
122 analysis of FG, glycated hemoglobin (HbA1c), basal insulin and complete lipid profile (LDL
123 and HDL-cholesterol, total cholesterol and TG).

124 *Risk factors*

125 Risk factors, were defined as described in the literature and some cutoff points were tested
126 based on previous results obtained by our team [3,11,14,20,22-30]. At enrollment, the maternal
127 characteristics assessed included: age in complete years (categorized as < and ≥ 25 years);
128 self-reported race (white and non-white); number of pregnancies including current (1 =
129 primigravida, >1= multigravida); physical activity; smoking; pressure levels (BP < or ≥ 140/90
130 mmHg); waist circumference (86 and 88 cm); pregestational and gestational BMI estimated
131 on the basis of pregestational and gestational weight, respectively (BMI ≥ 25 and BMI ≥ 30
132 Kg/m^2); fasting glucose (≥ 90 and ≥ 85 mg/dL); HDL-cholesterol (HDL-c < 50 and < 35 mg/dL);
133 triglycerides (TG ≥ 250 and ≥ 150 mg/dL); glycated hemoglobin (HbA1c ≥ 5.7%); and
134 *homeostasis model assessment - Insulin resistance* (HOMA-IR ≥ 2.71). Data on personal

history of (arterial hypertension and polycystic ovary syndrome-POS); family history (of Diabetes mellitus-DM, arterial hypertension, obesity, hypercholesterolemia and cardiovascular disease-CVD); and obstetric history (of GDM, macrosomia, fetal death – FD and malformation – MF) were also collected. Gestational age at enrollment was categorized as < 20 and ≥ 20 weeks.

GDM and MGH diagnosing

From week 24 onwards, GDM was diagnosed if 75-g oral glucose tolerance testing (OGTT) showed one abnormal value (92, 180 and 153 mg/dl for fasting, one-hour and two-hour postglucose load, respectively) [1-3,7,8,31].

For MGH diagnosis, a glucose profile test (GP) and a 75g-OGTT were performed over a one-day hospital stay with the participant on a 2840 Kcal- diet fractionated in five meals. Plasma glucose measurement was taken every two hours, from 8 AM to 6 PM. The cutoff points used were 90 mg/dL for fasting (8h) and 130 mg/dL for any postprandial level. MGH was confirmed when 75g-OGGT was normal and one GP measure was equal or greater than cutoff values [5,6].

Subject follow up

Non-diabetic women received follow up at their original primary care center. Women with MGH or GDM were referred for follow up at the Diabetes and Pregnancy Center of Botucatu Medical School/Unesp, a tertiary center. Maternal hyperglycemia control, in both MGH and GDM cases, was performed according to the protocol established in our center as recommended by ADA[2,3].

Statistical analysis

157 Statistical analyses were performed using *Open Source Epidemiologic Statistics for Public*
158 *Health* (*OpenEpi*), v. 3.0.1[32]. The association between GDM-MGH risk predictors and
159 diagnosis was assessed by calculating relative risk (RR) and 95% confidence intervals (95%
160 CI). The performance of risk predictors was evaluated in terms of sensitivity (Sens),
161 specificity (Sp), positive and negative predictive values (PPV and NPV, respectively),
162 accuracy, and positive and negative likelihood ratios (PLR and NLR, respectively) with their
163 *odds ratio* (OR) and 95% CI. Performance analysis also included the assessment of false-
164 positive results, defined by the formula 1-Sp[16,17,33,34].

165

166 **RESULTS**

167 The study flowchart (Figure 1) shows the number of pregnant women included (N = 514),
168 and excluded (N = 03), as well the number of participants assessed before and after 20
169 weeks of pregnancy (255 and 259, respectively). Irrespective of gestational age (GA) at
170 enrollment, GDM-MGH prevalence was 16.5% in the study population.

171

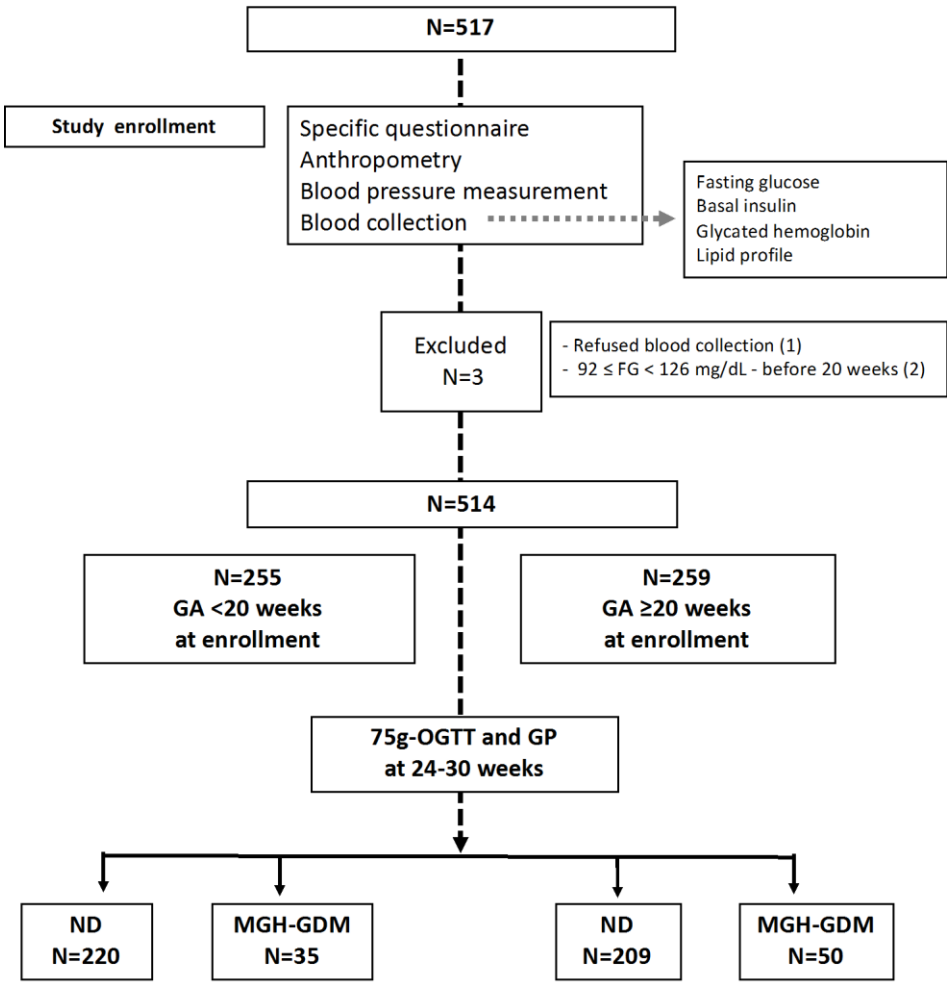

Figure 1. *Study flowchart*

Table 1 shows the frequency [number (N); percentage (%)] of the risk factors investigated according to GA group (< 20 and ≥ 20 weeks).

Table 2 reports the results of association analysis with relative risk (RR) and 95% CI. Before 20 weeks of pregnancy, age ≥ 25 years, WC ≥ 88 cm, pre BMI ≥ 25 Kg/m^2, gest BMI ≥ 25 Kg/m^2, gest BMI ≥ 30 Kg/m^2, FG ≥ 90 mg/dL, FG ≥ 85 mg/dL, HbA1c ≥ 5.7%, HOMA-IR ≥ 2.71 and obstetric history of macrosomia were associated with GDM-MGH risk; personal history of hypertension and obstetric history of GDM showed borderline values (Table 2). After 20 weeks of pregnancy, GDM-MGH risk was associated with age ≥ 25 years, BP ≥ 140/90 mmHg; WC ≥ 88 cm, pre BMI ≥ 25 Kg/m^2, gest BMI ≥ 25 Kg/m^2, gest BMI ≥ 30 Kg/m^2, FG ≥ 90

193 mg/dL, FG ≥ 85 mg/dL, TG ≥ 150 mg/dL, HbA1c ≥ 5.7%, HOMA-IR ≥ 2.71. Obstetric history of
194 GDM, and TG ≥ 250 mg/dL showed borderline values (Table 2).

195 Tables 3 and 4 show the predictive performance of risk factors significantly associated with
196 GDM-MGH. At GA < 20 weeks, optimal Sens/Sp balance was observed with age ≥ 25 years,
197 WC ≥ 88 cm, pre BMI ≥ 25 Kg/m^2, and gestational BMI ≥ 25 Kg/m^2, with Sens/Sp values
198 between 77.1/44.1 and 82.9/46.4% (Table 3). After 20 weeks, the best results were found
199 with age ≥ 25 years, WC ≥ 88 cm, pre BMI ≥ 25 Kg/m^2, gestational BMI ≥ 25 Kg/m^2, and TG ≥
200 150 mg/dL, with Sens/Sp between 78.0/45.9 and 98.0/17.7%. (Table 4).

201 The analysis of the percentual of false positive (FP) results (1-Sp) indicated that age ≥ 25
202 years (FP = 55.9%), WC ≥ 88 cm (FP = 54.5%), pre BMI ≥ 25 Kg/m^2 (FP = 49.1%) and gest BMI
203 ≥ 25 Kg/m^2 (FP = 49.1%) were lower at GA < 20 weeks. At GA ≥ 20 weeks, lower values were
204 observed when age ≥ 25 years (FP = 60.3%), pre BMI ≥ 25 Kg/m^2 (FP = 54,1%) and TG ≥ 150
205 mg/dL (FP = 59.8%). In contrast, WC ≥ 88 cm (FP = 82.3%) and gest BMI ≥ 25 Kg/m^2 (FP =
206 69.9%) showed the higher numbers of FP results. Figure 2 illustrates the performance of
207 these risk factors for predicting GDM-MGH evaluated by the Sens/1-Sp ratio.
208

209 Table 1. Frequency of GDM-MGH risk factors in the study population expressed by number

210 (N) and percent (%)

	GS < 20 weeks N = 255		**GA ≥ 20 weeks** N = 259	
	N	%	N	%
Age ≥ 25 years	150	58.82	169	66.80
Non-white	35	13.73	19	7.51
Multigravida	167	65.49	148	58.50
Physical exercise (no)	198	77.65	167	66.01
Smoking (yes)	78	30.59	50	19.76
BP ≥ 140/90 mmHg	3	1.18	3	1.19
WC ≥ 88 cm	147	57.65	221	87.35
Pre BMI ≥ 25 Kg/m^2	134	52.55	152	60.08
Gest BMI ≥ 25 Kg/m^2	147	57.65	191	75.49
FG≥ 90 mg/dL	3	1.18	21	8.30
HDL-c < 50 mg/dL	61	23.92	27	10.67
TG ≥ 250 mg/dL	12	4.71	40	15.81
HbA1c ≥ 5.7%	30	11.76	7	2.77
HOMA-IR ≥ 2.71	37	14.51	31	12.25
PH-hypertension	13	5.10	21	8.30
PH-POS	2	0.78	2	0.79
FH-DM	146	57.25	151	59.68
FH-hypertension	146	57.25	180	71.15
FH-obesity	64	25.10	80	31.62
FH-Hypercholesterolemia	63	24.71	62	24.51
FH-CVD	75	29.41	110	43.48
OH-GDM	2	0.78	1	0.40
OH-Macrosomia	12	4.71	15	5.93
OH-FD	6	2.35	8	3.16
OH-MF	4	1.57	6	2.37

211 BP = blood pressure; WC = waist circumference; BMI = body mass index (pre = based on pregestational weight; gest = based on gestational
212 weight); FG = fasting glucose; HDL = HDL-cholesterol; TG = Triglycerides; HbA1c = glycated hemoglobin; HOMA-IR = homeostasis model
213 assessment - Insulin resistance; PH = personal history; FH = family history; OH = obstetric history; POS = Polycystic ovary syndrome; DM =
214 Diabetes mellitus; CDV = Cardiovascular disease; FD = fetal death; MF = Malformation

215 .

ENTER Table 2. Association analysis – risk factors for MGH-GDM and respective RR and 95%CI values (at the end of the document text file)

Table 3. Performance of the risk factors for MGH-GDM and respective OR and 95%CI values at gestational age <20 weeks

GA < 20 weeks	Sens (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	PLR	NLR	OR
age ≥ 25 years	77.1 (60.98–87.93)	44.1 (37.69–50.71)	18.0 (12.68–24.92)	92.4 (85.68–96.09)	48.6 (42.56–54.74)	1.4 (1.33–1.43)	0.5 (0.30–0.67)	2.7 (1.16–6.12)
WC ≥ 88 cm	77.1 (60.98–87.93)	45.5 (39.01–52.06)	18.4 (12.94–25.41)	92.6 (86.06–96.21)	49.8 (43.72–55.91)	1.4 (1.36–1.47)	0.5 (0.38–0.66)	2.8 (0.02–0.17)
Pre BMI ≥ 25 Kg/m^2	74.3 (57.93–85.84)	50.9 (44.34–57.44)	19.4 (13.6–26.91)	92.6 (86.47–96.04)	54.1 (47.99–60.13)	1.5 (1.45–15.82)	0.5 (0.40–0.64)	2.9 (1.34–6.69)
gest BMI ≥ 25 Kg/m^2	82.9 (67.32–91.91)	46.4 (39.89–52.96)	19.7 (14.1–26.91)	94.4 (88.41–97.43)	51.4 (45.26–57.44)	1.6 (1.50–1.59)	0.4 (0.26–0.52)	4.2 (1.67–10.46)
Gest BMI ≥ 30 Kg/m^2	51.4 (35.57–67.01)	78.2 (82.27–83.13)	27.3 (18–39.04)	91.0 (86.07–94.31)	75.5 (68.82–79.47)	2.4 (2.04–2.72)	0.6 (0.55–0.70)	3.8 (1.82–7.92)
FG≥ 90 mg/dL	8.6 (2.96–22.38)	100.0 (98.28–100)	100.0 (43.85–100)	87.3 (82.62–90.86)	87.5 (82.82–90.97)	— —	0.9 (0.86–0.97)	— —
FG ≥ 85 mg/dL	14.3 (6.26–29.38)	95.5 (91.84–97.51)	33.3 (15.18–58.29)	87.5 (82.72–91.11)	84.3 (79.34–88.26)	3.1 (0.25–40.17)	0.9 (0.84–0.96)	3.5 (1.12–10.94)
HbA1c ≥ 5,7%	25.7 (14.16–42.07)	90.5 (85.85–93.67)	30.0 (16.66–47.88)	88.4 (83.61–91.99)	81.6 (76.35–85.85)	2.7 (1.31–5.55)	0.8 (0.76–0.89)	3.3 (1.36–7.92)
HOMA-IR ≥ 2,71	31.4 (18.55–47.98)	88.2 (83.25–91.81)	29.7 (17.49–45.78)	89.0 (84.14–92.49)	80.4 (75.08–84.81)	2.7 (1.67–4.23)	0.8 (0.71–0.84)	3.4 (1.50–7.79)
PH-hypertension	11.4 (4.54–25.95)	95.9 (92.41–97.83)	30.8 (12.68–57.63)	87.2 (82.39–90.83)	87.3 (79.34–88.26)	2.8 (0.05–154.9)	0.9 (0.87–0.98)	3.0 (0.88–10.42)
OH-GDM	2.9 (0.51–14.53)	99.6 (97.47–99.92)	50.0 (9.453–90.55)	86.6 (81.81–90.22)	86.3 (81.51–89.96)	6.3 (0.40–98.20)	1.0 (0.92–1.03)	6.4 (0.39–105.4)
OH-Macrosomia	11.4 (4.54–25.95)	96.4 (92.99–98.15)	33.3 (13.81–60.94)	87.2 (82.46–90.87)	84.7 (79.78–88.61)	3.1 (0.06–179)	0.9 (0.86–0.98)	3.4 (0.98–12.03)

- Sens = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; PLR= positive likelihood ratio; NLR = negative likelihood ratio; OR = Odds ratio; 95%CI = 95% confidence interval
- WC = waist circumference; BMI = body mass index (pre = based on pregestational weight; gest = based on gestational weight); FG= fasting glucose; HbA1c = glycated hemoglobin; HOMA-IR = homeostasis model assessment - Insulin resistance; PH = personal history; OH = obstetric history; GDM= gestational diabetes mellitus

221 Table 4. Performance of the risk factors for MGH-GDM and respective OR and 95%CI values at gestational age ≥20 weeks

IG ≥ 20 semanas	Sens (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	PLR	NLR	OR
age ≥ 25 anos	86.0 (73.81–93.05)	39.7 (33.32–46.47)	25.4 (19.47–32.51)	92.2 (84.81–96.18)	48.7 (42.63–54.71)	1.4 (1.39–1.46)	0.4 (0.26–0.48)	4.0 (1.74–9.43)
BP ≥ 140/90 mmHg	4.0 (1.10–13.46)	99.5 (97.34–99.92)	66.7 (20.77–93.85)	81.3 (76.02–85.56)	81.1 (75.87–85.38)	8.4 (0.77–90.38)	1.0 (0.93–1.0)	8.7 (0.76–97.55)
WC ≥ 88 cm	98.0 (89.5–99.65)	17.7 (13.13–23.45)	22.2 (17.2–28.1)	97.4 (86.5–99.53)	33.2 (27.75–39.15)	1.2 (1.176–1.205)	0.1 (0.01244–1.026)	10.5 (1.41–78.79)
Pre BMI ≥ 25 Kg/m^2	78.0 (64.76–87.25)	45.9 (39.31–52.7)	25.7 (19.37–33.14)	89.7 (82.52–94.16)	52.1 (46.05–58.13)	1.4 (1.30–1.49)	0.5 (0.39–0.59)	0.1 (1.46–6.20)
gest BMI ≥ 25 Kg/m^2	90.0 (78.64–95.65)	30.1 (24.33–36.68)	23.6 (18.1–30.06)	92.7 (83.91–96.82)	41.7 (35.86–47.78	1.3 (1.27–1.31)	0.3 (0.21–0.53)	3.9 (1.47–10.25)
Gest BMI ≥ 30 Kg/m^2	58.0 (44.23–70.63)	61.2 (54.49–67.59)	26.4 (19.03–35.29)	85.9 (79.41–90.59)	60.6 (54.55–66.37)	1.5 (1.39–1.61)	0.7 (0.62–0.76)	2.2 (1.17–4.08)
FG ≥ 90 mg/dL	38.0 (25.86–51.85)	99.0 (96.58–99.74)	90.5 (71.09–97.35)	87.0 (82.1–90.67)	87.3 (82.65–90.78)	39.7 (12.59–125.2)	0.6 (0.59–0.67)	0.5 (0.37–0.58)
FG ≥ 85 mg/dL	56.0 (42.31–68.84)	93.3 (89.07–95.97)	66.7 (51.55–78.99)	89.9 (85.13–93.21)	86.1 (81.36–89.79)	8.4 (6.88–10.16)	0.5 (0.43–0.52)	17.7 (8.14–38.61)
TG ≥ 250 mg/dL	24.0 (14.3–37.41)	86.6 (81.32–90.57)	30.0 (18.07–45.43)	82.7 (77.08–87.09)	84.5 (68.88–79.44)	1.8 (1.00–3.22)	0.9 (0.83–0.93)	2.0 (0.95–4.37)
TG ≥ 150 mg/dL	92.0 (81.16–96.85)	40.2 (33.78–46.96)	26.9 (20.82–34)	95.5 (88.89–98.22)	50.2 (44.15–56.23)	1.5 (1.51–1.57)	0.2 (0.12–0.34)	7.7 (2.68–22.27)
HbA1c ≥ 5,7%	10.0 (4.35–21.36)	99.0 (96.58–99.74)	71.4 (35.89–91.78)	82.1 (76.94–86.38)	81.9 (76.71–86.07)	10.5 (0.12–948.2)	0.9 (0.86–0.95)	11.5 (2.16–61.17)
HOMA-IR ≥ 2,71	38.0 (25.86–51.85)	94.3 (90.23–96.69)	61.3 (43.82–76.27)	86.4 (81.35–90.25)	83.4 (78.38–87.43)	6.6 (4.75–9.22)	0.7 (0.62–0.70)	10.1 (4.45–22.75)
OH-GDM	2.0 (0.35–10.5)	100.0 (98.2–100)	100.0 (20.65–100)	81.0 (75.78–85.33)	81.1 (75.87–85.38)	— —	1.0 (0.94–1.02)	— —

222 - Sens = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; PLR= positive likelihood ratio; NLR = negative likelihood ratio; OR = Odds ratio; 95%CI = 95% confidence interval

223 - BP= blood pressure; WC = waist circumference; BMI = body mass index (pre = based on pregestational weight; gest = based on gestational weight); FG= fasting glucose; TG= triglycerides; HbA1c = glycated
224 hemoglobin; HOMA-IR = homeostasis model assessment - Insulin resistance; PH = personal history; OH = obstetric history; GDM= gestational diabetes mellitus.

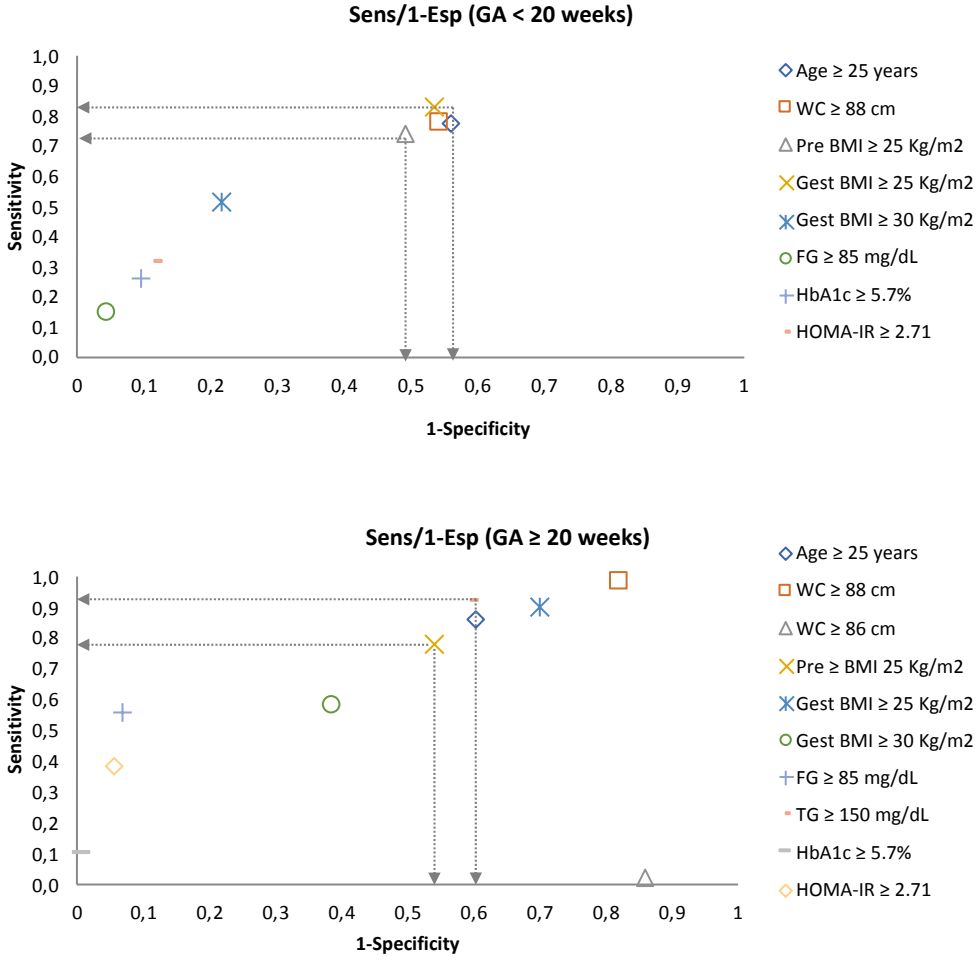

Figure 2. Performance of the risk factors for GDM-MGH expressed by the Sens/1-Esp ratio at gestational age < and ≥20 weeks

DISCUSSION

This study, including 514 pregnant women attending Brazilian public healthcare centers, showed that age ≥ 25 years, WC ≥ 88 cm, pre BMI ≥ 25 Kg/m^2, gest BMI ≥ 25 and 30 Kg/m^2, BP ≥ 140/90 mmHg, FG ≥ 85 and 90 mg/dL, HbA1c ≥ 5.7%, HOMA-IR ≥ 2.71, TG ≥ 150 mg/dL, personal history of hypertension, and obstetric history of GDM and macrosomia are statistically associated with GDM-MGH. GDM-MGH risk factors predictive performance was assessed in terms of sensitivity and NPV at two different

246 gestational ages (< 20 and ≥ 20 weeks of pregnancy). The best GDM-MGH predictors
247 (highest sensitivity and NPV) among study participants were age ≥ 25 years, WC ≥ 88
248 cm, pre BMI ≥ 25 Kg/m^2, and gest BMI ≥ 25 Kg/m^2 at GA < 20 weeks; and age ≥ 25
249 years, pre BMI ≥ 25 Kg/m^2, and TG ≥ 150 mg/dL at GA ≥ 20 weeks. Irrespective of
250 gestational age, FG ≥ 85 mg/dL, HbA1c ≥ 5.7% and HOMA-IR ≥ 2.71 were good
251 predictors of low GDM-MGH risk.

252 By initially assessing Sens/Sp balance, we observed that age ≥ 25 years, WC ≥ 88 cm,
253 pre BMI ≥ 25 Kg/m^2, and gest BMI ≥ 25 Kg/m^2 at GA < 20 weeks; and age ≥ 25 years,
254 WC ≥ 88 cm, pre BMI ≥ 25 Kg/m^2, gest BMI ≥ 25 Kg/m^2 and TG ≥ 150 mg/dL at GA ≥ 20
255 weeks had the best performance. That is, these markers best identified the individuals
256 with the disease that had a positive result with the test (Sens) and those without the
257 disease who were correctly identified by the test (Sp). However, decision making based
258 on these indices alone may be faulty because Sens and Sp are inherent to the test and
259 depend on diagnostic criteria, which are generally defined arbitrarily[35].

260 The new 75g-OGTT diagnostic criteria (the gold-standard in this study) based on the
261 HAPO study establishes glucose cutoff points that convey an odds ratio of 1.75 for
262 birth weight >90th percentile, cord C-peptide >90th percentile, and offspring percent
263 body fat >90th percentile[36,37]. Our analysis of Sens/Esp balance was complemented
264 with negative predictive values (NPV) so that the risk factor that best indicate the
265 probability of the disease being absent when the test is negative could be identified.
266 NPV depend on the test's sensitivity and specificity as well as the prevalence of the
267 disease and may improve the predictive value of Sens/Sp balance[33,34]. The risk factors
268 showing optimal Sens/Sp also presented the best NPV.

The likelihood ratio has also been used to complement Sens/Sp balance analysis. The positive likelihood ratio (PLR) shows the best test to use for ruling in a disease while the negative likelihood ratio indicates the test to be used to rule it out. However, this strategy should only be used if the consequences from a false-positive test are the same as the consequences from a false-negative test[32,34]. In the case of GDM-MGH, not identifying the women at risk prevents them from being diagnosed and treated, and this might cause serious short- and long-term harm to the mother and her offspring [38-41]. Therefore, neither positive nor negative likelihood ratios would be good indicators of predictive performance in GDM-MGH.

In this study, the analysis of the Sens/1-Sp (false positive) ratio indicated that age ≥25 years, WC ≥88 cm, pre BMI ≥25 Kg/m^2, and gest BMI ≥25 Kg/m^2 at GA <20 weeks would lead about 50% of the women investigated (1-Sp) to diagnostic testing to confirm MGH-GDM in about 70 to 80% of the cases (Sens). At GA ≥20 weeks, patient age ≥25 years, pre BMI ≥25 Kg/m^2 and TG ≥150 mg/dL would lead 50-60% of the women investigated to diagnostic testing to confirm MGH-GDM in 80-90% of the cases. CC ≥88 cm (FP = 82.3%) and gest BMI ≥25 Kg/m^2 (FP = 69.9%) generated a very high rate of FP.

A recent study with data on two large cohorts demonstrated that only age > 25 years and pre BMI ≥ 30 Kg/m^2 reached Sens > 50%. Age > 25 years identified 86% of GDM cases and about 68% of the women investigated underwent diagnostic testing[17]. Given that better Sens indices and FP rates were found in our study, the indication of diagnostic testing may be reduced by 40-50%, with a favorable reflection on universal screening costs.

Several studies have addressed the performance of risk factors as GDM predictors using the 75-g OGTT as gold standard with varying results. Besides focusing on different aspects, such as the application of preventive measures, new diagnostic tests, or different cutoff points, these studies differed in terms of population characteristics and risk factor prevalence as well as gestational age at assessment. In our study, we evaluated the value of risk factor for predicting not only GDM (using 75-g OGTT[3] as gold standard), but also MGH (using glucose profile as gold-standard). Although this approach makes comparison with other studies difficult, it is justified by the fact that the new GDM diagnostic criteria are not met by 17% of our patients, who otherwise would be left untreated to suffer maternal and perinatal consequences[4-6].

Previous studies by our team in the same population have demonstrated that: a) WC ≥ 88 cm and pre BMI ≥25 Kg/m^2 have optimal Sens/Sp for predicting GDM at GA <24 weeks[25]; b) overweight (pre BMI ≥ 25 Kg/m^2) and obesity (pre BMI ≥ 30 Kg/m^2) are risk factors for hyperglycemia in pregnancy (GDM-MGH)[22]; and c) the proportion of metabolic syndrome markers is associated with hyperglycemia level in women with GDM-MGH[26]. The results of other studies in diverse populations do not differ from ours[11,13,14,16,42,43]. Also in agreement with other reports, we observed that the higher Sp shown by FG, HbA1c and HOMA-IR indicate them as the best predictors for ruling out GDM risk and the need for a diagnostic test[10,13,42,44,45].

Finally, the best evidence available show that: (a) the combination of several risk factors may increase sensitivity indices but decrease specificity producing a higher rate of false-positive results; (b) screening by age or BMI is as effective as using multiple risk factors; and, c) the use of risk algorithms (or point scores) does not improve the

performance of screening by one or more risk factors. According to these studies, age >25 years and BMI ≥25 or 30 Kg/m^2 are simpler and more accurate indicators and should be used in GDM screening as long as new and better evidence supporting universal screening are not available[16,17,46]. Therefore, the literature seems to support our results.

Study limitations

Although the size of our sample was adequate, our data might not represent the overall nationwide public healthcare centers or populations with similar characteristics. Moreover, further subdividing the gestational age groups investigated might improve the performance of the risk factors assessed, or even reveal other good predictors of MGH-GDM.

Clinical implications

In the short term, the results of this study can help decision making in favor of the selective MGH-GDM approach in our center. At GA <20 weeks, age ≥25 anos, WC ≥88 cm and pre- or gestational BMI ≥25 Kg/m^2 would identify the women at risk of MGH-GDM, who would then undergo diagnostic testing at 24-28 weeks of pregnancy. In cases of late prenatal presentation (GA ≥20 weeks), age ≥25 years, pre BMI ≥25 Kg/m^2 and TG ≥125 mg/dL could be used to identify MGH-GDM risk or when diagnosis confirmation is necessary. Irrespective of GA at assessment, FG <85 mg/dL, HbA1c <5.7% and HOMA-IR <2.71 would be useful to identify the women at low risk, who would not require diagnostic testing.

Research implications

Based on our results, further studies should be conducted to assess (i) the reproduction of our results or even the use of other predictors in different centers and populations; (ii) the cost-effectiveness of the risk predictors identified in different centers and populations, and thus contribute to determine the optimal approach, universal or selective, to hyperglycemia during pregnancy.

CONCLUSION

In this study, risk factors with good performance for predicting MGH-GDM risk were identified. At GA < 20 weeks, age ≥ 25 years, WC ≥ 88 cm, pre BMI ≥ 25 Kg/m^2 and gest BMI ≥ 25 Kg/m^2 had the best performance; at GA ≥ 20 weeks, idade ≥ 25 years, pre BMI ≥ 25 Kg/m^2 and TG ≥ 150 mg/dL were the risk factors that best predicted GD irrespective of GA; FG ≥ 85 mg/dL, HbA1c ≥ 5.7% and HOMA-IR ≥ 2.71 were the best to rule out MGH-GDM risk. These findings may contribute to determine the optimal diagnostic approach to MGH-GDM in ours as well as in other centers of similar characteristics.

LIST OF ABBREVIATIONS

ADA: American Diabetes Association

FA: Family antecedents

BMI gest: Gestational body mass index

BMI pre: Pre gestational body mass index

BP: Blood pressure

CVD: Cardiovascular disease

FD: Fetal death

FEBRASGO: Brazilian Federation of Gynecology and Obstetrics

FG: Fasting glucose

FP: False positive

GA: Gestational age

GDM: Gestational Diabetes Mellitus

GP: Glycemic profile

HbA1c: Glycated hemoglobin

HDL-c: HDL-cholesterol

HOMA-IR: Homeostasis model assessment - Insulin resistance

MHG: Mild Gestational Hyperglycemia

MS: Ministry of Health

NLR: Negative likelihood ratios

NPV: Negative predictive value

NPV: Negative predictive values

OGTT: Oral Glucose Tolerance Test

OH: Obstetric history

OR: Odds ratio

PAHO: Pan-American Health Organization O Brazil)

PH: Personal history

PLR: Positive likelihood ratios

POS: Polycystic ovary syndrome

PPV: Positive predictive values

RF: Risk factors

RR: Relative risk

SBS: Brazilian Diabetes Society

Sens: Sensitivity

Sp: Specificity

TG: Triglycerides

WC: Waist circumference

WHO: World Health Organization

REFERENCES

1. American Diabetes Association. Standards of Medical Care in Diabetes—2010. Diabetes Care. 2010;33(1 Suppl):S11-61. doi:https://doi.org/10.2337/dc10-S011.
2. American Diabetes Association. Standards of medical care in diabetes - 2011. Diabetes Care. 2011;34(1 Suppl):S11-61. https://doi.org/10.2337/dc11-S011.
3. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2017;40(1 Suppl):S11-24.

398 4. Sirimarco MP, Guerra HM, Lisboa EG, Vernini JM, Cassetari BN, Costa RAA, et al.
399 Diagnostic protocol for gestational diabetes mellitus (GDM) (IADPSG/ADA, 2011):
400 influence on the occurrence of GDM and mild gestational hyperglycemia (MGH)
401 and on the perinatal outcomes. Diabetol Metab Syndr. 2017;9:2. doi:
402 10.1186/s13098-016-0200-2.
403 5. Rudge MV, Peraçoli JC, Berezowski AT,Calderon IM, Brasil MA. The oral glucose
404 tolerance test is a poor predictor of hyperglycemia during pregnancy. Braz J Med
405 Biol Res.1990;23(11):1079-89.
406 6. Rudge MVC, Calderon IMP, Ramos MD, Brasil MAM, Rugolo LMSS, Bossolan G, et
407 al. Hiperglicemia materna diária diagnosticada pelo perfil glicêmico: um problema
408 de saúde pública materno e perinatal. Rev Bras Ginecol Obstet. 2005;27(11):691-7.
409 7. World Health Organization. Diagnostic criteria and classification of hyperglycaemia
410 first detected in pregnancy [Internet]. WHO; 2013 [citado 9 Jan 2017]. Available
411 from:https://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND
412 _13.2_eng.pdf;jsessionid=C68AB95D98D90DD7744FE31AE8D579DF?sequence=1.
413 8. American College of Obstetricians and Gynecologists. Practice Bulletin No. 137:
414 diabetes mellitus gestacional. Obstet Gynecol Clin. 2013;122(2):406-16. doi:
415 10.1097 / 01.AOG.0000433006.09219.f1.
416 9. Organização Pan-Americana da Saúde. Ministério da Saúde. Federação Brasileira
417 das Associações de Ginecologia e Obstetrícia. Sociedade Brasileira de Diabetes.
418 Rastreamento e diagnóstico de diabetes mellitus gestacional no Brasil. Brasília:
419 OPAS;2016.

10. Trujillo J, Vigo A, Reichelt A, Duncan BB, Schmidt MI. Fasting plasma glucose to avoid a full OGTT in the diagnosis of gestational diabetes. Diabetes Res Clin Pract. 2016;105(3):322-6.
11. Van Leeuwen M, Opmeer BC, Zweers EJ, van Ballegooie E, ter Brugge HG, de Valk HW, et al. Estimating the risk of gestational diabetes mellitus: a clinical prediction model based on patient characteristics and medical history. BJOG. 2010;117(1):69-75. doi: 10.1111/j.1471-0528.2009.02425.x.
12. Zhang C, Ning Y. Effect of dietary and lifestyle factors on the risk of gestational diabetes: review of epidemiologic evidence. Am J Clin Nutr. 2011;94(6 Suppl):1975S-9S. doi: 10.3945 / ajcn.110.001032.
13. Cosson E, Benbara A, Pharisien I, Nguyen M, Revaux A, Lormeau B, et al. Diagnostic and prognostic performances over 9 years of a selective screening strategy for gestational diabetes mellitus in a cohort of 18,775 subjects. Diabetes Care. 2012;36(3):598-603. doi: 10.2337 / dc12-1428.
14. Zhang C, Rawal S, Chong Y. Risk factors for gestational diabetes: is prevention possible?. Diabetologia. 2016;59(7):1385-90. doi: 10.1007/s00125-016-3979-3.
15. Bao W, Michels K, Tobias D, Li S, Chavarro J, Gaskins A, et al. Parental smoking during pregnancy and the risk of gestational diabetes in the daughter. Int J Epidemiol. 2016;45(1):160-9. doi: 10.1093 / ije / dyv334.
16. Farrar D. Hyperglycemia in pregnancy: prevalence, impact, and management challenges. Int J Women's Health. 2016;8:519-27.
17. Farrar D, Simmonds M, Bryant M, Lawlor DA, Dunne F, Tuffnell D, et al. Risk factor screening to identify women requiring oral glucose tolerance testing to diagnose gestational diabetes: a systematic review and meta-analysis and analysis of two

444 pregnancy cohorts. PLoS One. 2017;12(4):e0175288. doi:
445 10.1371/journal.pone.0175288.
446 18. Leary J, Pettitt DJ, Jovanovic L. Gestational diabetes guidelines in a HAPO world.
447 Best Pract Res Clin Endocrinol Metabol. 2010;24(4):673-85. doi:
448 10.1016/j.beem.2010.05.009.
449 19. Falavigna M, Prestes I, Schmidt MI, Duncan BB, Colagiuri S, Roglic G. Impact of
450 gestational diabetes mellitus screening strategies on perinatal outcomes: a
451 simulation study. Diabetes Res Clin Pract. 2013;99(3):358-65. doi:
452 10.1016/j.diabres.2012.12.009.
453 20. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes
454 (2015-2016). Diabetes mellitus gestacional: diagnóstico, tratamento e
455 acompanhamento pós-gestação. São Paulo: A.C. Farmacêutica; 2016. p. 69-73.
456 21. Ministério da Saúde (BR). Orientações para coleta e análise de dados
457 antropométricos em serviços de saúde: norma técnica do sistema de Vigilância
458 Alimentar e Nutricional - SISVAN. Brasília: Ministério da Saúde; 2011. (Série G.
459 Estatística e Informação em Saúde).
460 22. Vernini J, Moreli J, Magalhães C, Costa R, Rudge M, Calderon I. Maternal and fetal
461 outcomes in pregnancies complicated by overweight and obesity. Reprod Health.
462 2016;13(1):100. doi: 10.1186/s12978-016-0206-0.
463 23. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The
464 International Federation of Gynecology and Obstetrics(FIGO) Initiative on
465 gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and
466 care. Int J Gynaecol Obstet. 2015;131 (3 Suppl):S173-211. doi: 10.1016/S0020-
467 7292(15)30007-2.

468 24. Ryckman KK, Spracklen CN, Smith CJ, Robinson JG, Saftlas AF. Maternal lipid levels
469 during pregnancy and gestational diabetes: a systematic review and meta-analysis.
470 BJOG. 2015;122(5):643-51. doi: 10.1111/1471-0528.13261.
471 25. Bolognani C, de Sousa Moreira Reis L, de Souza S, Dias A, Rudge M, de Mattos
472 Paranhos Calderon I. Waist circumference in predicting gestational diabetes
473 mellitus. J Matern Fetal Neonatal Med. 2014;27(9):943-8. doi:
474 10.3109/14767058.2013.847081.
475 26. Negrato CA, Jovanovic L, Rafacho A, Tambascia MA, Geloneze B, Dias A, et al.
476 Association between different levels of dysglycemia and metabolic syndrome in
477 pregnancy. Diabetol Metab Syndr. 2009;26;1(1):3. doi: 10.1186/1758-5996-1-3.
478 27. Bartha JL,González-Bugatto F, Fernández-Macías R,González-González NL, Comino-
479 Delgado R,Hervías-Vivancos B. Metabolic syndrome in normal and complicated
480 pregnancies. Eur J Obstet Gynecol Reprod Biol.2008;137(2):178-84.
481 28. Negrato CA, Javanovic L, Tambascia MA, Calderon IMP, Geloneze B, Dias A, et al.
482 Mild Gestacional hyperglycemia as a risk factor for metabolic syndrome in
483 pregnancy and adverse perinatal outcomes. Diabetes Metab Res Rev.
484 2008;24(4):324-30. doi: 10.1002/dmrr.815.
485 29. International Diabetes Federation (IDF). The IDF consensus worldwide definition of
486 the metabolic syndrome [Internet]. Brussels: IDF; 2006 [citado 25 jan 2018].
487 Disponível em:https://www.idf.org/e-library/consensus-statements.html.
488 30. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in
489 Adults. Executive Summary of the third report of the National Cholesterol
490 Education Program (NCEP) Expert Panel on detection, evaluation, and treatment

491 of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;18:126-
492 32.
493 31. International Association of Diabetes and Pregnancy Study Groups.
494 Recommendations on the diagnosis and classification of hyperglycemia in
495 pregnancy. Diabetes Care. 2010;33(3):676-82.
496 32. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for
497 Public Health [Internet]. [atualizado 06 Abr 2013]. [citado 10 01 2018]. Disponível
498 em: www.OpenEpi.com.
499 33. Riegelman RK. Studying a Study and Testing a Test: How to read the medical
500 evidence. 4th ed. Washington: Lippincott Williams & Wilkins; 1999.
501 34. Ayach W, Costa RAA, Calderon IM, Rudge, MV. Comparison between 100-g glucose
502 tolerance test and two other screening tests for gestational diabetes: combined
503 fasting glucose with risk factors and 50-g glucose tolerance test. São Paulo Med J.
504 2006;124(1):4-9.
505 35. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical
506 Diagnostic Test Evaluation. Caspian J Intern Med 2013; 4(2): 627-35.
507 36. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al.
508 Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;
509 8;358(19):1991-2002.
510 37. Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al.
511 International association of diabetes and pregnancy study groups
512 recommendations on the diagnosis and classification of hyperglycemia in
513 pregnancy. Diabetes Care. 2010;33(3):676-82.

514 38. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after
515 gestational diabetes: a systematic review and meta-analysis. Lancet.
516 2009;373)9677):1773-9. https://doi.org/10.1016/S0140- 6736(09)60731-5.
517 39. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A
518 multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J
519 Med. 2009;361(14):1339-48. https://doi.org/ 10.1056/NEJMoa0902430
520 40. Shah BR, Retnakaran R, Booth GL. Increased Risk of Cardiovascular Disease in
521 Young Women Following Gestational Diabetes Mellitus. Diabetes Care.
522 2008;31(8):1668-69. https://doi.org/10.2337/dc08- 0706.
523 41. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of
524 treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med.
525 2005;352(24): 2477-2486. https://doi.org/ 10.1056/NEJMoa042973.
526 42. Kumru P, Arisoy R, Erdogdu E, Demirci O, Kavrut M, Ardic C, et al. Prediction of
527 gestational diabetes mellitus at first trimester in low-risk pregnancies. Taiwan J
528 Obstet Gynecol. 2016;55(6):815-20. doi: 10.1016/j.tjog.2016.04.032.
529 43. Ghodke B, Pusukuru R, Mehta V. Association of lipid profile in pregnancy with
530 preeclampsia, gestational diabetes mellitus, and preterm delivery. Cureus.
531 2017;9(7):e1420. doi: 10.7759 / cureus.1420.
532 44. Odsæter IH, Åsberg A, Vanky E, Mørkved S, Stafne SN, Salvesen KÅ, et al.
533 Hemoglobin A1c as screening for gestational diabetes mellitus in Nordic Caucasian
534 women. Diabetol Metab Syndr. 2016;8:43. doi:10.1186/s13098-016-0168-y.
535 45. Hao M, Lin L. Fasting plasma glucose and body mass index during the first
536 trimester of pregnancy as predictors of gestational diabetes mellitus in a Chinese
537 population. Endocr J. 2017;64(5):561-69. doi:10.1507/endocrj.EJ16-0359.

46. Farrar D, Simmonds M, Griffin S, Duarte A, Lawlor DA, Sculpher M, et al. The identification and treatment of women with hyperglycaemia in pregnancy: an analysis of individual participant data, systematic reviews, meta-analyses and an economic evaluation. Health Technol Assess. 2016;20(86):1-348.
47. Tieu J, McPhee AJ, Crowther CA, Middleton P, Shepherd E. Screening for gestational diabetes mellitus based on different risk profiles and settings for improving maternal and infant health. Cochrane Database Syst Rev. 2017;8:CD007222. doi:10.1002/14651858.CD007222.pub4.
48. Mirghani Dirar A, Doupis J. Gestational diabetes from A to Z. World J Diabetes 2017; 8(12):489-511. doi:10.4239/wjd.v8.i12.489.

DECLARATIONS

Ethics approval and consent to participate

This study complies with national and international regulations for experiments in human beings, including resolution CNS 466/12 of the Brazilian National Health Council and the 1989 Declaration of Helsinki. All participants signed an informed consent form before entering the study.

Consent for publication

All authors approved the final version and agree with the submission of the manuscript for publication.

Availability of data and materials

559 All authors declare that data and any supporting material regarding this manuscript
560 are available and can be requested at any time.

561 ***Competing interests***

562 The authors declare that they have no competing interest.

563 ***Funding***

564 This study was supported by the São Paulo Research Foundation for providing a
565 research grant (FAPESP grant 12/51257-9 CNPq-PPSUS) and National Council for
566 Scientific and Technological Development (CNPq), for the researcher scholarship (PQ-
567 CNPq #304771/2015-5).

568 ***Authors' contributions***

569 IMPC conceived, designed and coordinated the study. JMV, BFN, and MAA collected
570 data; JEC was responsible for the statistical analysis. JMV wrote and discussed the first
571 manuscript version. BFN, RAAC, CGM, SAML, MVCR, and IMPC contributed to the
572 discussion and reviewed/edited the manuscript. All authors read and approved the
573 final manuscript version.

574 ***Acknowledgements***

575 The authors are thankful to the Research Support Center (GAP) of Botucatu Medical
576 School, Unesp, for assisting with statistical analyses.

577

578 Table 2. Association analysis – risk factors of MGH-GDM with respective RR and 95%CI values

	GA < 20 weeks (N = 255)						GA ≥ 20 weeks (N = 259)					
	ND		MGH-GDM				ND		MGH-GDM			
	N	%	N	%	RR	95%CI	N	%	N	%	RR	95%CI
Age ≥ 25 years	123	55.9	27	77.1	2.36	1.12–5.00	126	60.3	43	86	3.27	1.54–6.97
Non-white	32	14.5	3	8.6	0.59	0.19–1.82	13	6.2	6	12	1.72	0.84–3.52
Multigravida	141	64.1	26	74.3	1.52	0.75–3.10	135	64.6	13	26	0.26	0.15–0.47
Physical exercise (no)	171	77.7	27	77.1	0.97	0.47–2.02	134	64.1	33	66	1.07	0.63–1.81
Smoking (yes)	67	30.5	11	31.4	1.04	0.54–2.02	38	18.2	12	24	1.32	0.75–2.34
BP ≥ 140/90 mmHg	2	0.9	1	2.9	2.47	0.48–12.6	1	0.5	2	4	3.56	1.54–8.23
WC ≥ 88 cm	120	54.5	27	77.1	2.48	1.17–5.24	172	82.3	49	98	8.43	1.20–5.92
WC ≥ 86 cm	140	63.6	27	77.1	1.78	0.84–3.75	180	86.1	1	2	0.01	0.00–0.06
Pre BMI ≥ 25 Kg/m^2	108	49.1	26	74.3	2.61	1.27–5.34	113	54.1	39	78	2.4	1.34–4.65
Gest BMI ≥ 25 Kg/m^2	118	53.6	29	82.9	3.55	1.53–8.25	146	69.9	45	90	3.72	1.54–9.03
Gest BMI ≥ 30 Kg/m^2	48	21.8	18	51.4	3.03	1.66–5.53	81	38.8	29	58	1.87	1.13–3.01
FG ≥ 90 mg/dL	0	0	3	8.6	7.88	5.70–10.90	2	1	19	38	6.95	4.86–9.92
FG ≥ 85 mg/dL	10	4.5	5	14.3	2.67	1.21–5.88	14	6.7	28	56	6.58	4.19–10.31
HDL-c < 50 mg/dL	52	23.6	9	25.7	1.1	0.55–2.22	27	12.9	0	0	—	—
HDL < 35 mg/dL	3	1.4	1	2.9	1.85	0.33–10.37	4	1.9	0	0	—	—
TG ≥ 250 mg/dL	10	4.5	2	5.7	1.23	0.33–4.52	28	13.4	12	24	1.73	1.00–3.01
TG ≥ 150 mg/dL	66	30	12	34.3	1.18	0.62–2.26	125	59.8	46	92	5.92	2.20–15.91
HbA1c ≥ 5.7%	21	9.5	9	25.7	2.5	1.35–5.00	2	1	5	10	4.00	2.34–6.85
HOMA-IR ≥ 2.71	26	11.8	11	31.4	2.7	1.45–5.03	12	5.7	19	38	4.51	2.93–6.93

579

580 *Table 2. continued*

	GA < 20 weeks (N = 255)						GA≥ 20 weeks (N = 259)					
	ND		MGH-GDM				ND		MGH-GDM			
	N	%	N	%	RR	95%CI	N	%	N	%	RR	95%CI
PH-hypertension	9	4.1	4	11.4	2.40	1.00–5.79	15	7.2	6	12.0	1.55	0.75–3.11
PH-POS	2	0.9	0	0.0	—	—	2	1.0	0	0.0	—	—
FH-DM	126	57.3	20	57.1	0.90	0.54–1.85	121	57.9	30	60.0	1.07	0.64–1.79
FH-hypertension	125	56.8	21	60.0	1.12	0.60–2.10	147	70.3	33	66.0	0.85	0.51–1.44
FH-obesity	53	24.1	11	31.4	1.37	0.71–2.63	61	29.2	19	38.0	1.37	0.83–2.28
FH-Hypercholesterolemia	52	23.6	11	31.4	1.30	0.73–2.69	56	26.8	6	12.0	0.43	0.19–0.97
FH-CVD	68	30.9	7	20.0	0.60	0.27–1.31	84	40.2	26	52.0	1.47	0.89–2.41
AO-DMG	1	0.5	1	2.9	3.72	1.00–15.40	0	0.0	1	2.0	5.27	4.09–6.77
OH-Macrosomia	8	3.6	4	11.4	2.61	1.10–6.21	12	5.7	3	6.0	1.04	0.37–2.95
OH-OF	4	1.8	2	5.7	2.52	0.78–8.15	6	2.9	2	4.0	1.31	0.38–4.46
OH-MF	3	1.4	1	2.9	1.85	0.33–10.37	6	2.9	0	0.0	—	—

581 - Pearson chi-square; RR = Relative risk; 95%CI = 95% confidence interval

582 ND = Non diabetic; MGH = mild gestational hyperglycemia; GDM = Gestational diabetes mellitus.

583 -BP = blood pressure; WC = waist circumference; BMI = body mass index (pre = based on pregestational weight; gest = based on gestational weight); FG = fasting glucose; HDL = HDL-cholesterol; TG = Triglicérides;
584 HbA1c = glycated hemoglobin; HOMA-IR = Índice HOMA (*homeostasis model assessment - Insulin resistance*);- Insulin resistance; PH = personal history; FH = family history; OH = obstetric history; POS = Polycystic
585 ovary syndrome; DM = Diabetes mellitus; CDV = Cardiovascular disease; FD = fetal death; MF = Malformation

Figures

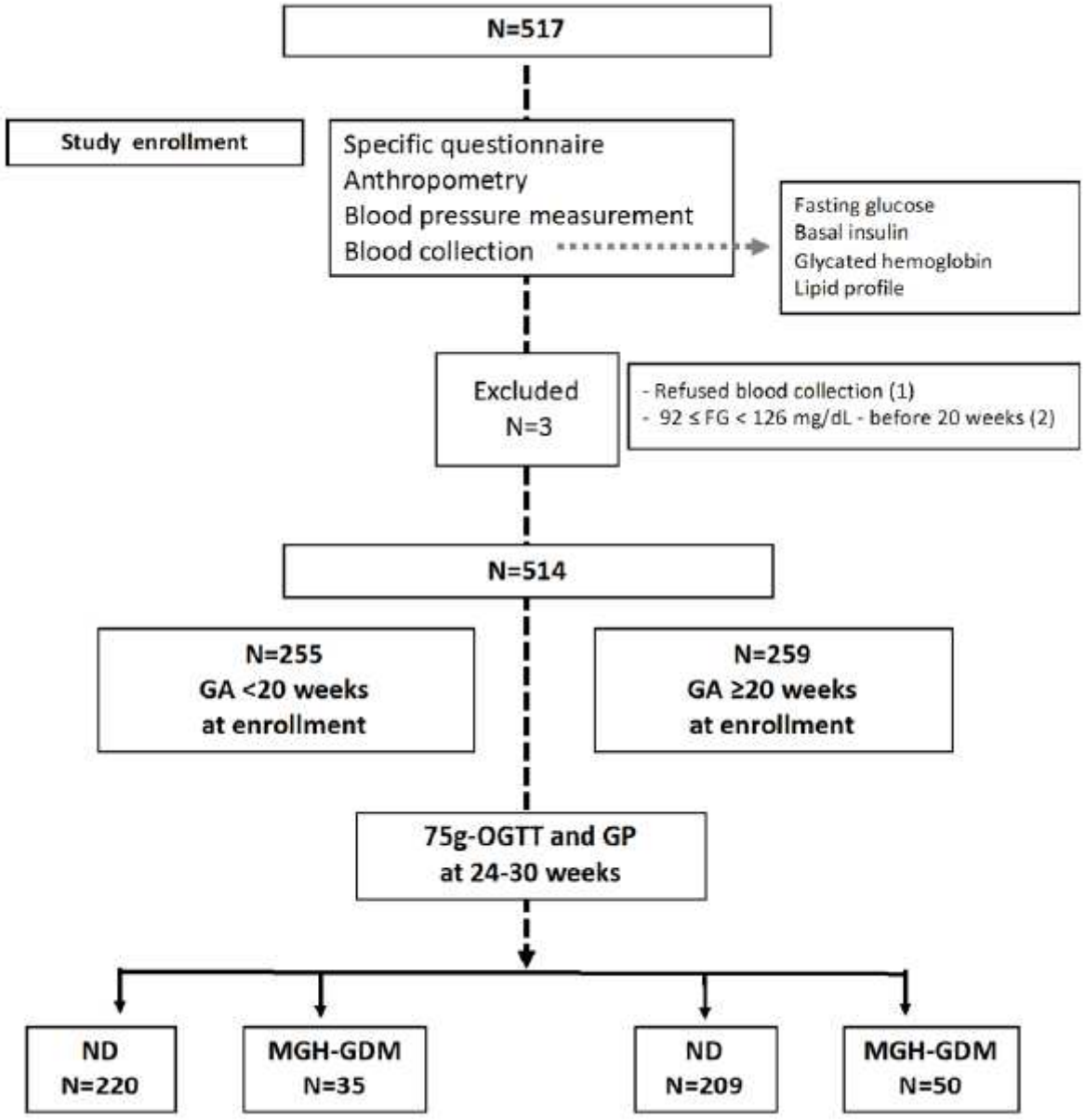

Figure 1

Study flowchart

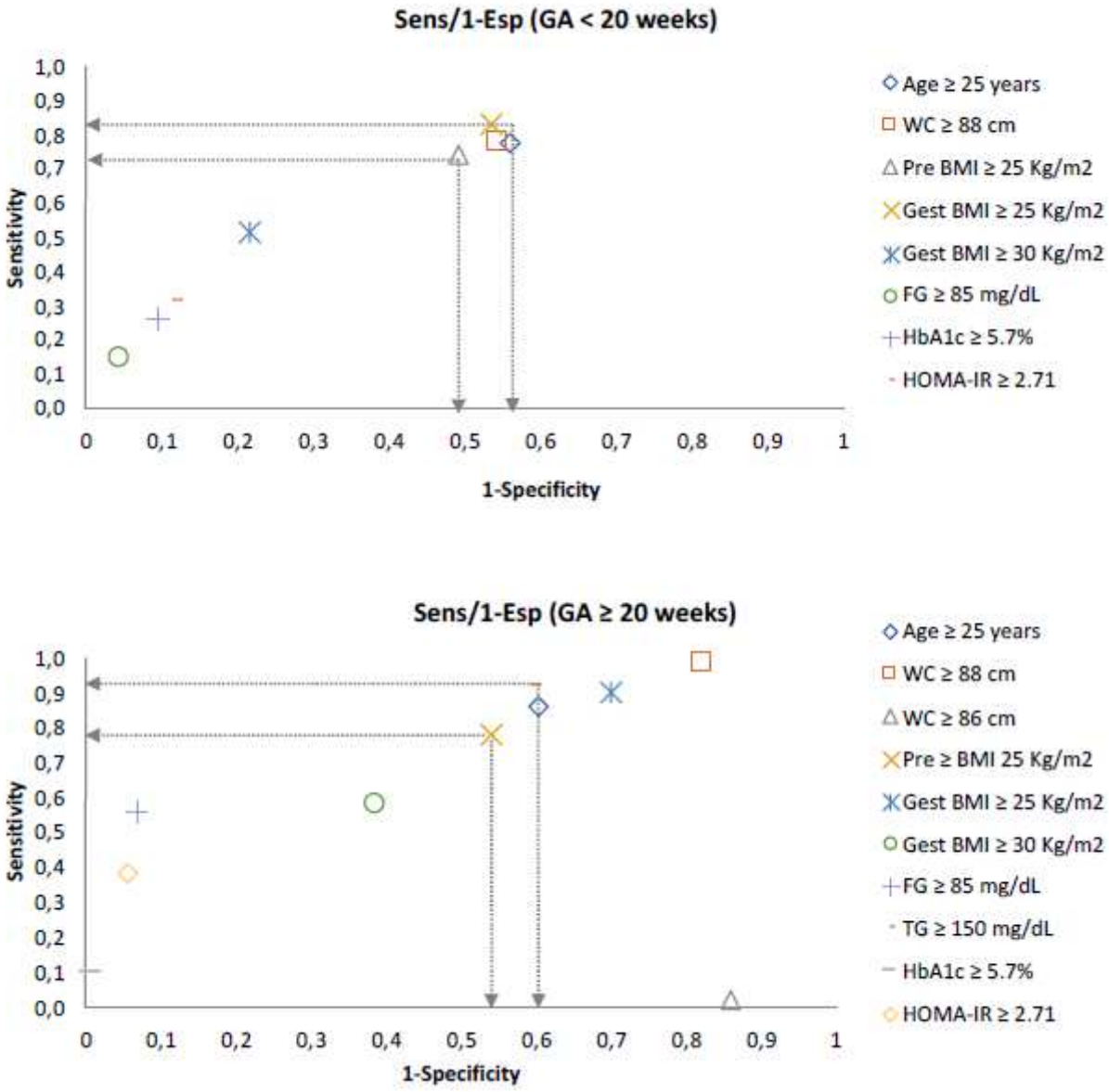

Figure 2

Performance of the risk factors for GDM-MGH expressed by the Sens/1-Esp ratio at gestational age < and ≥20 weeks