RESEARCH

Predictors of metformin monotherapy failure in gestational diabetes mellitus

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Abstract

Objective: Metformin has emerged as a safe and effective pharmacological alternative to insulin in gestational diabetes mellitus (GDM), being associated with lower maternal weight gain and hypoglycemia risk. Nevertheless, glycemic control is unaccomplished in a considerable proportion of women only treated with metformin. We aim to determine the metformin monotherapy failure rate in GDM and to identify predictors of its occurrence.
Design and methods: This was a retrospective multicenter study including pregnant women with GDM patients who started metformin as a first-line pharmacological treatment (n = 2891). A comparative analysis of clinical and analytical data between the group of women treated with metformin monotherapy and those needing combined therapy with insulin was performed.
Results: In 685 (23.7%) women with GDM, combined therapy to achieve adequate glycemic control was required. Higher pregestational BMI (OR 1.039; CI 95% 1.008–1.071; *P*-value = 0.013), higher fasting plasma glucose (PG) levels in oral glucose tolerance test (OGTT) (OR 1.047; CI 95% 1.028–1.066; *P*-value <0.001) and an earlier gestational age (GA) at metformin introduction (0.839; CI 95% 0.796–0.885, *P*-value < 0.001) were independent predictive factors for metformin monotherapy failure. The best predictive cutoff values were a fasting PG in OGTT ≥87 mg/dL and GA at metformin introduction ≤29 weeks.
Conclusions: In 685 (23.7%) women, combined therapy with insulin to reach glycemic control was required. Higher pre-gestational BMI, fasting PG levels in OGTT ≥87 mg/dL and introduction of metformin ≤29 weeks of GA were independent predictive factors for metformin monotherapy failure. The early recognition of these characteristics can contribute to the establishment of individualized therapeutic strategies and attain better metabolic control during pregnancy.

Key Words
- metformin
- insulin
- monotherapy
- failure
- treatment
- diagnosis
- OGTT
- women

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Introduction

Gestational diabetes mellitus (GDM) is defined as a subtype of hyperglycemia first detected during pregnancy and accounts for 90% of all diabetes diagnoses in pregnant women (1, 2). This represents a worrying gestational complication, with an increasing worldwide prevalence in the last years, which currently affects up to 26% of all pregnancies (3, 4). In Portugal, the 2018 estimated rate of GDM was 8.8% in total pregnancies (5).

The diagnosis of GDM is strongly associated with several maternal, fetal and neonatal complications including birth trauma, preterm birth, large for gestational age (LGA) neonates, neonatal hypoglycemia and increased

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maternal risk for subsequent development of type 2 diabetes mellitus (6, 7, 8). These adverse pregnancy outcomes can be minimized by an optimized glycemic control (7, 8).

The recommended initial treatment is centered in lifestyle modifications, supported by an individualized medical nutrition therapy and a daily physical activity program (9, 10). If glycemic goals were not reached after these measures, pharmacological therapy should be started (9, 10).

For many years, insulin has been used to safely and effectively treat GDM (11). More recently, metformin has emerged as a very attractive oral therapeutic alternative, with several studies proving its positive impact on glycemic control and its easier administration (1, 12). Furthermore, it has been shown that, compared to insulin, metformin is associated with lower maternal weight gain and hypoglycemia risk (13). Nevertheless, the metformin monotherapy failure rate is 22–56% in women with GDM (4, 11, 14, 15). In order to anticipate and overcome this potential problem, it is important to understand if there is any maternal or analytical characteristic that can predict the need for additional insulin, allowing better glycemic control and maternal–fetal outcomes.

Methods

A retrospective multicenter cohort study was conducted with pregnant women with GDM who attended consultation in 25 Portuguese public hospitals from January 2014 and December 2019. Figure 1 describes the types of treatment performed by each pregnant women with GD. Thus, 10,267 women (59.3%) were treated with lifestyle modifications only. Others subsequently started insulin ($n = 3594$ (20.8%)) or metformin ($n = 2891$ (16.7%)). The first-line pharmacological therapy choice did not follow any formal criteria, being mostly dependent on hospital center providers' clinical input. Some characteristics were considered selecting metformin as first treatment option, such as maternal excess weight prior to pregnancy, excessive weight gain during pregnancy and predominance of postprandial hyperglycemia. From a total sample of 17,320 pregnant women, only patients who started treatment with metformin after failure of lifestyle measures were included ($n = 2891$). A comparative analysis of clinical and analytical data between the group of women with metformin only (metformin monotherapy group) and those needing additional insulin (metformin + insulin group) was performed (Fig. 1).

The Diabetes and Pregnancy Study Group of the Portuguese Society of Diabetology is responsible for the National Registry of GDM. These data are collected by a multidisciplinary Endocrinology and Obstetrics team from each participating health-care institution. All data sets were blinded relatively to the patients and hospital identification, ensuring anonymity of the collected data. This study complies with the Declaration of Helsinki on medical protocol and ethics. Each participating hospital's institutional review board approved data collection. Informed consent was unnecessary, since the study has a retrospective nature and the patient and hospital's anonymity were ensured.

According to the recommendations of the Consensus on Gestational Diabetes from The Diabetes and Pregnancy Study Group of the Portuguese Society of Diabetology (9) which are consensual with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (2), screening for

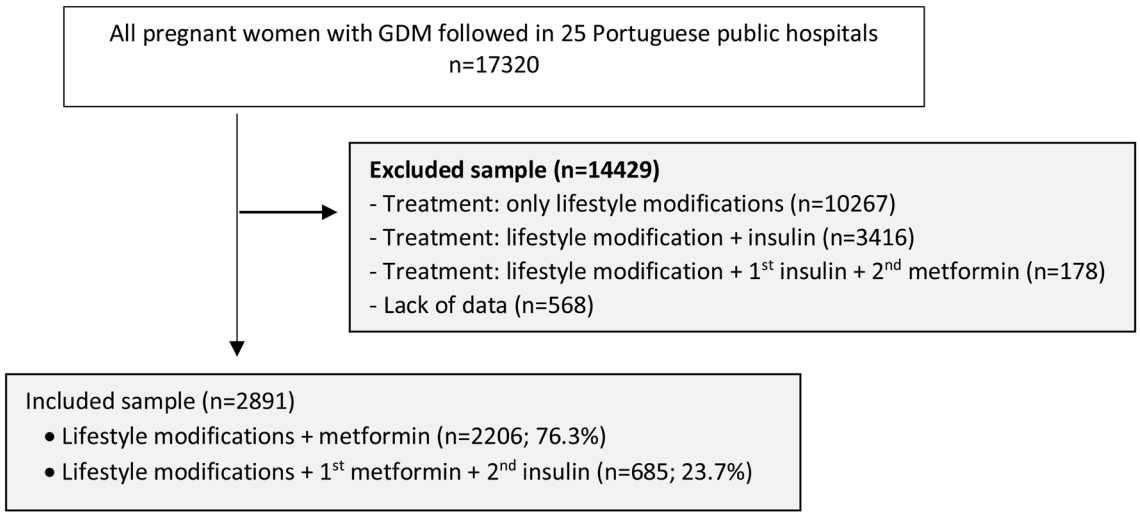

Figure 1
Flowchart of the participants included in the study.

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GDM should be done in two different timings in all pregnant women: in the first trimester through the measurement of fasting plasma glucose (PG) and, if this result was normal, between the 24th and 28th weeks of gestation with the 75-g 2-h oral glucose tolerance test (OGTT).

In this study, the GDM diagnosis was established in the presence of any of the following results: fasting PG ≥92 mg/dL (in the first trimester or at 0 h in OGTT), glycemia ≥ 180 mg/dL or ≥153 mg/dL after 1 h and 2 h in OGTT, respectively – according to the IADPSG criteria (2, 9).

After the diagnosis, all pregnant women were followed-up by a multidisciplinary team with Endocrinology, Nutrition, Obstetrics and Nursing regular evaluations. The standard initial GDM treatment has been universally applied and consists of lifestyle modifications. An individualized meal plan was prescribed by a registered nutritionist according to the pregestational maternal BMI and weight gain before the first appointment. The proportional caloric composition of nutrients was explained in an approximate time of 30 min. In addition, the practice of low-impact physical activity (minimum duration of 30 min per day) was encouraged. Home glycemic self-monitoring by testing capillary blood glucose (CBG) was performed four times a day (before breakfast, and 1 h after breakfast, lunch and dinner). Until 2016, the established glycemic goals were pre-meals CBG values ≤90 mg/dL and 1-h post-meals CBG values ≤120 mg/dL (16, 17). After the publication of the Portuguese consensus update, the intended glycemic targets have been changed to CBG values ≤95 mg/dL and ≤140 mg/dL in pre-meal and 1-h post-meal moments, respectively (9).

If the glycemic levels did not reach the target with diet and exercise, pharmacological therapy with metformin was started with progressive dose titration up to a maximum of 2500 mg per day (metformin monotherapy group). If the glycemic targets were still not achieved with a maximum well-tolerated dose of metformin for 1–2 weeks, metformin monotherapy failure was considered and insulin treatment was added (metformin + insulin group). In these cases, metformin was continued at its maximum dose.

Immediately after delivery, all pregnant women discontinued GDM therapy (metformin with/without insulin) and 6–8 weeks later, a postpartum OGTT was done to reclassify the diagnosis of diabetes. Impaired fasting glucose (IFG) was defined as fasting plasma glucose levels from 100 to 125 mg/dL and impaired glucose tolerance (IGT) as 2-h PG levels during 75-g OGTT from 140 to 199 mg/dL (18).

For the purpose of this work, demographic and clinical maternal data were collected (age, family history of diabetes in first degree relative, macrosomia and GDM history in previous pregnancies, pregestational BMI, gestational age (GA) at diagnosis, results of second trimester OGTT, third trimester glycosylated hemoglobin (HbA1c), GA at introduction of metformin, maximum used dose of metformin, parity, previous miscarriage, chronic or gestational hypertension, preeclampsia, hydramnios, stillbirth, GA at delivery), delivery and neonatal characteristics (birth weight, prematurity and delivery) and neonatal outcomes (need for intensive care unit (ICU) admission, neonatal jaundice, hypoglycemia or respiratory distress syndrome and congenital anomalies). Preterm birth was defined by any birth before 37 completed weeks of gestation (19). Neonatal hypoglycemia was established according to the consensus of the Portuguese Society of Pediatrics – Neonatology Section (20). Small for gestational age (SGA) and LGA were classified according to Portuguese birthweight charts as a birth weight of less than 10th percentile and greater than 90th percentile for GA, respectively (21).

Statistical analysis was performed using the IBM Statistical Package for Social Sciences for Windows v.27 (IBM Corporation). The normality of data distribution of numeric variables was evaluated through the Shapiro–Wilk test. Nonparametric continuous variables were described with median value (interquartile range (IQR)) and the Mann–Whitney U test was employed to compare them. Categorical variables were presented in number (*n*) and percentage (%), and their univariate analysis were done using the chi-squared test. A multivariate logistic regression was applied to identify independent predictive factors for metformin monotherapy failure, according to the results of univariate analysis. The data were expressed as odd ratio (OR) and 95% CIs. A result was considered statistically significant for a P-value<0.05.

Results

During the study period, metformin was the first-line pharmacological treatment in 2891 pregnant women with GDM, representing the included sample. Of these, 685 (23.7%) presented with metformin monotherapy failure, requiring the introduction of insulin therapy. This percentage was slightly higher in women evaluated before the glycemic targets change in 2016 (25.8% vs 23.2%, $P = 0.197$). Overall, the GDM diagnosis was established in the first trimester in most of these women (n = 1489; 51.5%). The sample presented with a median age of 34 years (IQR: 7), a median GA of 19 weeks (IQR: 16) and a median GA of 29 weeks (IQR: 2) when metformin treatment was initiated. Comparison of demographic and clinical maternal data between the group treated

Table 1 Comparison of demographic and clinical maternal data between women with GDM treated only with metformin vs metformin and insulin.

	n	**Metformin monotherapy** (*n* = 2206)	***N***	**Metformin+insulin** (*n* = 685)	***P*-value**
Age (years)[a]	2203	34 (7)	684	35 (7)	0.203
Family history of diabetes (n,%)	2140	1038 (48.5)	671	352 (52.5)	0.074
Previous GDM (n, %)	1550	338 (21.8)	504	142 (28.2)	**0.003**
Macrosomia in previous pregnancies (n, %)	1543	140 (9.1)	503	53 (10.5)	0.329
Parity	2194		682		0.196
Multigravida (n, %)		1352 (61.6)		439 (64.4)	
Primigravida (n, %)		842 (38.4)		243 (35.6)	
Twin pregnancy (n, %)	2206	14 (0.6)	685	2 (0.3)	0.421
Pregestational BMI (kg/m^2)	2178	28.11 (24.49–32.74)	682	30.12 (25.89–35.12)	**<0.001**
Classification according BMI (n, %)	2178		682		**<0.001**
Low weight		12 (0.6)		5 (0.7)	0.589
Normal weight		591 (27.1)		132 (19.4)	**<0.001**
Overweight		754 (34.6)		194 (28.4)	**0.003**
Obesity		822 (37.7)		350 (51.3)	**<0.001**
OGTT (mg/dL)[a]					
0 h	1235	85 (15)	228	93 (12)	**<0.001**
1 h	1215	182 (33)	223	183 36)	0.057
2 h	1222	154 (39)	224	157 (38)	0.057
Diagnosis of GDM	2203		683		**<0.001**
In the first trimester (n,%)		1024 (46.5)		465 (68.1)	
In OGTT (n, %)		1179 (53.5)		218 (31.9)	
GA at diagnosis (weeks)[a]	2197	24 (16)	684	11 (16)	**<0.001**
GA in the introduction of metformin (weeks)[a]	2162	31 (8)	682	23 (12)	**<0.001**
Maximum daily dose of metformin (g)[a]	2161	1000 (850)	670	1500 (1000)	**<0.001**
Third trimester HbA1c (%)[a]	1479	5.3 (0.5)	496	5.4 (0.5)	**<0.001**
Chronic hypertension (n,%)	2183	147 (6.7)	681	71 (10.4)	**0.002**
Gestational hypertension (n,%)	2183	103 (4.7)	681	49 (7.2)	**0.012**
Previous miscarriage (n, %)	2195	694 (31.6)	682	246 (36.1)	**0.030**
Pre eclampsia (n, %)	2182	68 (3.1)	680	34 (5.0)	**0.021**
Hydramnios (n, %)	2183	65 (3.0)	680	18 (2.6)	0.654
Stillbirth (n, %)	2183	4 (0.2)	679	2 (0.3)	0.580

[a]Data are presented as median (Interquartile range).
GA, gestational age; GDM:,gestational diabetes mellitus; OGTT, oral glucose tolerance test.
Bold indicates statistical significance.

Table 2 Predictive factors for metformin monotherapy failure during the gestational diabetes mellitus treatment.

	Univariate analysis, *P*-value	**Multivariate analysis**		
		aOR[a]	CI (95%)	*P*-value
Pregestational BMI	<0.001	1.039	1.008–1.071	**0.013**
Previous GDM	0.003	1.088	0.714–1.659	0.695
GA at diagnosis	<0.001	1.010	0.961–1.062	0.697
0 h OGTT	<0.001	1.047	1.028–1.066	**<0.001**
GA in the introduction of metformin	<0.001	0.839	0.796–0.885	**<0.001**
Chronic hypertension	0.002	0.653	0340–1.255	0.201
Gestational hypertension	0.012	0.766	0.320–1.835	0.550

[a]aORs were calculated using multivariate logistic regression, adjusted for GA at diagnosis, pregestational BMI, previous GDM, BG at 0 h in OGTT, GA in the introduction of metformin, chronic and gestational hypertension.
GA, gestational age; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; aOR, adjusted odds ratio.
Bold indicates statistical significance.

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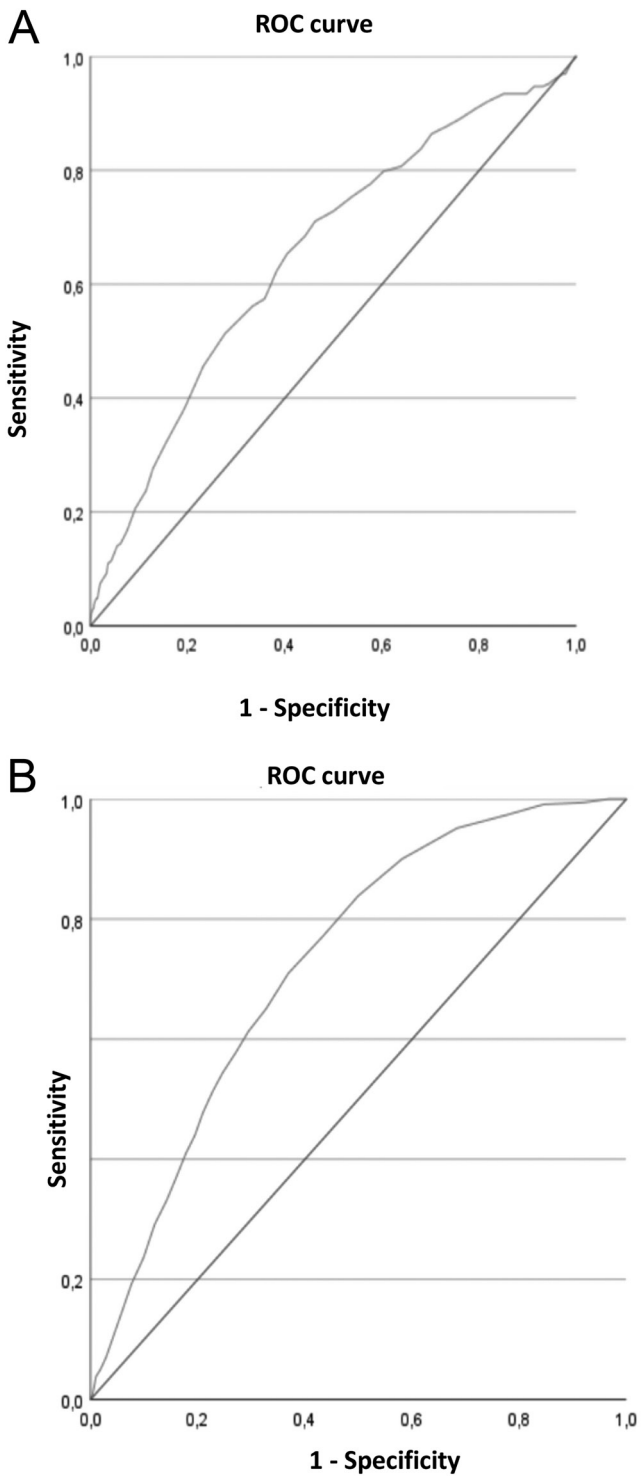

Figure 2
Receiver operator curve (ROC) of predictive factors of metformin failure: (A) fasting blood glucose in oral glucose tolerance test; (B) gestational age in the introduction of metformin.

only with metformin and those who need to start insulin is described in Table 1. Metformin monotherapy failure was significantly more frequent in women with higher pregestational BMI (30.1 kg/m^2 vs <28.1 kg/m^2, *P*-value <0.001), particularly with obesity (51.3% vs 37.7%, *P*-value = 0.001), earlier GDM diagnosis (median GA of 11 vs 24 weeks, *P*-value<0.001) and in the first trimester (68.1% vs 46.5%, *P*-value<0.001), and higher fasting PG levels in OGTT (93 mg/dL vs 85 mg/dL, *P*-value<0.001).

The group that needed to start insulin had earlier introduction of metformin (median GA of 23 weeks vs 31 weeks, *P*-value<0.001) and higher HbA1c percentage in the third trimester (5.4% vs 5.3%, *P*-value<0.001).

Furthermore, history of previous GDM (*P*-value = 0.003), previous miscarriage (*P*-value = 0.030), chronic (*P*-value < 0.002) or gestational hypertensio n (*P*-value =0.012) and development of pre-eclampsia (*P*-value = 0.021) were also associated with a greater need for insulin. Significant differences in maternal age, parity and in the occurrence of hydramnios or stillbirth were not found between groups (Table 1).

Univariate and multivariate analysis results are shown in Table 2. Higher pregestational BMI, history of previous GDM, lower GA at diagnosis and metformin introduction, higher PG levels at 0 h of OGTT and the diagnosis of chronic or gestational hypertension increased the risk of need for insulin supplementation. However, only pregestational BMI (OR 1.039; CI 95% 1.008–1.071; *P*-value = 0.013), fasting glycemia in OGTT (OR 1.047; CI 95% 1.028–1.066; *P*-value < 0.001) and GA at metformin introduction (0.839; CI 95% 0.796–0.885, *P*-value < 0.001) were independent predictive factors of metformin monotherapy failure. The best predictive cutoff values were fasting PG in OGTT ≥87 mg/dL (sensitivity of 71%; specificity of 54%) and GA at metformin introduction ≤29 weeks (sensitivity of 71%; specificity of 63%) (Fig. 2).

Table 3 shows neonates' characteristics as well as obstetric and neonatal outcomes. Birth weight was significantly higher in neonates from pregnant women with metformin monotherapy failure (*P*-value = 0.018). The rate of LGA neonates in that group was of 17.8% vs 13.5% in women only treated with metformin (*P*-value = 0.047). There were no significant differences in the remaining features and outcomes.

Postpartum OGTT results were evaluated and prediabetes was significantly more frequent in women with metformin monotherapy failure during pregnancy (IFG: 3.8% vs 1.6%, *P*-value = 0.002; IGT: 11.3% vs 4.7%, *P*-value < 0.001) (Table 4).

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Table 3 Comparison of neonates' characteristics and obstetric/neonatal outcomes between women with GDM treated only with metformin vs metformin and insulin.

	n	**Metformin monotherapy** (*n* =2206)	*n*	**Metformin+Insulin** (*n* =685)	***P*-value**
Birth weight (g)[a]	2152	3220 (574)	670	3270 (856)	**0.018**
Low birth weight (<2500 g) (n, %)	2152	130 (6.0)	670	41 (6.1)	**0.015**
Normal birth weight (n ,%)		1943 (90.3)		587 (87.6)	
Macrosomia (≥4000 g) (n, %)		79 (3.7)		42 (6.3)	
Small for GA (n, %)	2148	160 (7.4)	669	52 (7.8)	**0.047**
Large for GA (n, %)	2148	291 (13.5)	669	119 (17.8)	
GA at delivery (weeks)[a]	2158	39 (1)	674	39(1)	**0.019**
Prematurity (n, %)	2158	148 (6.9)	674	54 (8.0)	0.310
Delivery					
Eutocic (n, %)	2148	1015 (47.3)	673	297 (44.1)	0.156
Cesarean (n, %)	2148	802 (37.3)	673	278 (41.3)	0.064
Urgent cesarean (n, %)	761	393 (51.6)	269	143 (53.2)	0.669
Elective cesarean (n, %)	761	368 (48.4)	269	126 (46.8)	
Neonatal ICU admission (n, %)	2129	182 (8.5)	663	61 (9.2)	0.603
Neonatal jaundice (n, %)	2134	279 (13.1)	661	101 (15.3)	0.148
Neonatal hypoglycemia (n, %)	2132	117 (5.5)	661	46 (7.0)	0.159
Neonatal respiratory distress syndrome (n, %)	2133	88 (4.1)	661	27 (4.1)	0.963
Neonatal congenital anomalies (n,%)	2124	90 (4.3)	661	33 (4.9)	0.399

GA, gestational age; ICU, intensive care unit.[a]Data are presented as median (Interquartile range).
Bold indicates statistical significance.

Discussion

In the present study, 23.7% pregnant women with GDM required the addition of insulin to lifestyle intervention and metformin to achieve adequate glycemic control. Higher pregestational BMI and fasting PG levels in OGTT, earlier GDM diagnosis and metformin treatment initiation, and hypertension increased the risk of metformin monotherapy failure, although only the BMI value, fasting PG levels in OGTT and earlier GA at metformin introduction were independent predictive factors.

The metformin monotherapy failure rate we found was similar to other published studies, with values ranged from 18 to 23% (11, 22, 23, 24). However, some groups described even higher rates, such as Moore *et al*. (34.7%), Rowan *et al*. (48.3%) and Khin *et al*. (55.8%) (14, 25, 26). This difference may be attributed to methodological heterogeneity in the study design and differences in the applied PG levels for GDM diagnostic criteria. Likewise, a previous Portuguese study that used part of this database for investigation showed a higher rate of metformin monotherapy failure (34.8%) (15). This discrepancy may be justified partly by the 2016 change in the glycemic targets to achieve and in the criteria for starting pharmacological therapy (9).

It is hypothesized in the literature that the notorious association between maternal pregestational overweight or obesity and the worse efficacy of metformin monotherapy in GDM treatment may be due to greater insulin resistance and/or impaired beta cell function (22, 27). Also, we verified that a higher pregestational BMI was significantly more frequent in the group that needed insulin, 51.3% of these women being obese. This factor represents an independent predictor for the development of metformin failure, which is in concordance with the results obtained in other publications (11, 15, 22, 28). Aboelfath *et al.* stated, for the first time, a cutoff point of BMI of 32.1 kg/m^2 above which the risk of metformin failure increased considerably (11). Despite our similar result, after performing a ROC curve we could not reliably determine a cutoff point, with statistic power.

In our study, higher fasting PG in the OGTT was an independent predictor for metformin monotherapy failure. When glycemia ≥87 mg/dL was considered, there was a significantly increased risk of insulin supplementation requirement (sensitivity of 71% and specificity of 54%). Souza *et al.* complementarily demonstrated that fasting PG in the OGTT <90 mg/dL was a protective factor for the development of poor response to treatment with metformin alone and Khin *et al.* defined that, for fasting PG > 86 mg/dL, metformin failure was predict with a sensitivity of 87%, specificity of 64% and a positive predictive value of 74% (14, 22). This consistent association between fasting PG in OGTT and the prediction of the need for insulin was suggested in several other publications (15, 23, 29, 30).

Table 4 Comparison of postpartum OGTT results between women with GDM treated only with metformin and metformin plus insulin.

	Metformin monotherapy (*n* =1520)	Metformin + Insulin (*n* =496)	*P*-value
Normal	1408 (92.6%)	411 (82.9%)	**<0.001**
Impaired fasting glucose	24 (1.6%)	19 (3.8%)	**0.002**
Impaired glucose tolerance	72 (4.7%)	56 (11.3%)	**<0.001**
DM	16 (1.1%)	10 (2.0%)	**0.099**

DM, diabetes mellitus.
Bold indicates statistical significance.

We additionally observed that an earlier GDM diagnosis strongly increased the risk for insulin supplementation and that earlier introduction of metformin treatment with a gestational age ≤ 29 weeks was an independent predictor of this pharmacotherapy failure. These results are in keeping with other studies (15, 22, 23, 31), and can be explained due to earlier and greater development of insulin resistance or beta-cell disfunction, and consequently hyperglycemia, which aggravates throughout the pregnancy, resulting in metformin monotherapy insufficiency (31).

Curiously, history of GDM in previous pregnancies was associated with greater need of insulin too. No other study reported this result before.

In a prospective study performed by a New Zealand group, the rates of gestational and chronic hypertension were higher in the group of pregnant women with GDM treated with metformin and insulin (30). A similar result was achieved in our study. A recent meta-analysis including numerous epidemiological studies reported a strong correlation between insulin resistance and hypertension development, which probably justify our findings (32).

A higher maternal age has been associated with increased risk of metformin monotherapy failure in various studies (11, 14, 15, 23) and Gante *et al.* presented this variable as a predictive factor for requiring the use of insulin at ages above 35 years (15). Intriguingly, we did not find any difference in maternal age between women treated only with metformin and those who started insulin, and the same result was described by McGrath *et al* and Ali *et al* studies (28, 31). Also, Souza et al observed that, despite maternal age was higher in metformin monotherapy failure group, women with > 30 years did not present with a significant risk of needing insulin (22).

Similarly, we did not observe any relationship between women's parity and metformin monotherapy failure which is in line with several previous studies (23, 28, 29). Nevertheless, there were two publications that showed primiparity as a protective predictor for requiring insulin supplementation (11, 22).

Finally, in women with metformin monotherapy failure during pregnancy, the development of prediabetes in postpartum was significantly more frequent. Data regarding this association are still lacking, but in a multicentric Portuguese study, the group that needed insulin presented higher glucose levels in the postpartum OGTT (15).

This study has limitations. Its retrospective nature and the fact that data were collected through the informatic clinical records by 25 different Portuguese hospital centers imposes some heterogeneity and lower scientific quality. Although, in general, the same recommendations are applied at national level, each professional team had its own clinical approach toward the same clinical situations.

Yet, to our knowledge this is the retrospective study regarding predictors of metformin failure with the largest sample size ever published. Moreover, inclusion of women with different ethnicities and cultures, and from different regions of the country, allowed the results described to be widely applied. In the future, it will require a large prospective study to validate these established results and respective cutoffs.

In conclusion, in spite of the easy and frequent use of metformin as a therapeutic option in GDM, 23.7% of the cases required to add insulin to achieve glycemic control. Higher pre-gestational BMI, levels of fasting PG in OGTT ≥ 87 mg/dL and introduction of metformin ≤ 29 weeks of GA were independent predictive factors for metformin monotherapy failure. The recognition of these characteristics can contribute to the establishment of individualized therapeutic strategies to anticipated which women will most likely need to start insulin and guarantee the best metabolic control during pregnancy.

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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