Metformin in gestational diabetes mellitus: predictors of poor response

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Abstract

Objective: Metformin can be regarded as a first-line treatment in gestational diabetes mellitus (GDM) due to its safety and effectiveness. However, a proportion of women do not achieve adequate glycemic control with metformin alone. We aim to identify predictors of this poor response to metformin.

Design and methods: Retrospective multicentre cohort study of women with GDM who started metformin as first-line treatment. The assessed cohort was divided into a metformin group and metformin plus insulin group. Biometric and demographic characteristics, glycemic control data, obstetric, neonatal and postpartum outcomes were compared between groups and analysed in order to identify predictors of poor response to metformin. Data were analysed using STATA, version 13.1.

Results: Of the 388 women enrolled in the study, 135 (34.8%) required additional insulin therapy to achieve the glycemic targets. Higher age (aOR: 1.08 (1.03–1.13), $P=0.003$), higher pre-pregnancy body mass index (BMI) (1.06 (1.02–1.10), $P=0.003$) and earlier introduction of metformin (0.89 (0.85–0.94), $P<0.001$) were independent predictors for insulin supplementation. Regarding all the analysed outcomes, only cesarean delivery rates and postpartum glucose levels were higher in women requiring insulin supplementation.

Conclusions: Although almost 35% of women did not achieve adequate glycemic control with metformin, insulin supplementation was not associated with poor neonatal outcomes. Higher age, higher pre-pregnancy BMI and earlier introduction of metformin could be used as predictors of poor response to metformin.

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Introduction

The incidence of gestational diabetes mellitus (GDM) has risen worldwide over the past few decades, mainly due to an increase in maternal age and in obesity-induced insulin resistance (1, 2, 3).

It is estimated that GDM affects over 10% of pregnancies, depending on the diagnostic methods used and the population studied (1, 3, 4, 5). In Portugal, in 2014, almost 6.7% of pregnancies were complicated by GDM (6).

GDM is an independent risk factor for obstetric complications, such as preterm labour, preeclampsia, large for gestational age (LGA) and macrosomic newborns,

growth restriction, birth trauma, cesarean section and neonatal hypoglycaemia (7).

It is known that adequate glycemic control minimizes the risk of obstetric complications. When lifestyle modifications (dietary and physical activity) are not sufficient to achieve appropriate glucose levels, pharmacological therapy is required (4, 8).

Insulin is historically the first-line treatment because of its safety and effectiveness.

Oral hypoglycaemic agents, especially metformin, are reliable in the management of blood glucose and

Clinical Study	I Gante, L Melo and others	Metformin in gestational diabetes	178:1	130
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are a safe and cheaper alternative (8, 9, 10, 11, 12, 13, 14). Furthermore, metformin is associated with lower gestational weight gain (GWG), had a reduced risk of hypoglycaemia and showed no compromise of the motor, linguistic and social development in recent studies (15).

Despite all these benefits, in up to 46% of women, adequate glycemic control is not achieved with metformin alone, requiring insulin supplementation (14).

The aim of this study was to identify predictors of poor response to metformin alone. Additionally, we want to evaluate glycemic control data and obstetric, neonatal and postpartum outcomes among women with GDM, treated with metformin alone versus metformin plus insulin.

Subjects and methods

Study design

A retrospective multicentre cohort study in Portuguese public hospitals between January 2014 and December 2015 of pregnant women with GDM treated with metformin as first-line pharmacologic therapy. Data were obtained from the analysis of the National Registry of GDM concerning these years ($n=5352$) after consent from the Diabetes and Pregnancy Study Group of the Portuguese Society of Diabetology (*Sociedade Portuguesa de Diabetologia*), which is responsible for this database. Data were collected by the multidisciplinary teams of Obstetrics and Diabetology in 25 Portuguese public sector health institutions (among the total of 44 invited to collaborate), comprising all Portuguese continental districts. Considering the number of Portuguese women with GDM in 2014–2015 ($n=9174$), the total registry participation rate was 58.3%.

Subsequently, 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. Given the retrospective nature of this study and its anonymity, written consent was not required.

Study subjects

The National Registry of GDM includes all women that fulfil GDM criteria and whose follow-up was performed in Portuguese public health care institutions. However, only women without satisfactory glucose levels despite

adequate non-pharmacological therapy and who started the hypoglycaemic therapy with metformin (as first line) were included in this study.

The GDM diagnosis was established according to the Portuguese Directorate-General of Health (*Direção Geral de Saúde*) criteria that were based on the International Association of Diabetes and Pregnancy Study Groups' criteria: universal fasting plasma glucose in the 1st trimester and 75 g two-hour oral glucose tolerance test (OGTT) between 24 and 28 gestational weeks (16).

After diagnosis, during the first specialized appointment, baseline data were collected and all patients were counselled about diet and exercise in order to achieve their glycemic targets.

The goal of therapy was to reduce fasting glucose to <95 mg/dL and the 1-h postprandial level to <120 mg/dL in more than 80% of the glucose measurements.

Metformin as first-line pharmacological therapy was started if the glycemic targets were not achieved in 1–2 weeks of non-pharmacological therapy. It was prescribed in an initial daily dose of 500 mg up to a maximum daily dose of 2500 mg. Insulin supplementation was initiated if the glycemic targets were not achieved in 2 weeks despite the increase in metformin dose. All women stopped the antidiabetic medication at delivery.

The patients included in this study were divided into two groups: those who respond to metformin alone and those who needed insulin supplementation.

Study outcomes

The data analysed included baseline biometric and demographic characteristics; glycemic control data (such as hemoglobin A1c (HbA1c), maximum daily dose of metformin and, for those that needed escalation of therapy, the timing of that decision); obstetric and neonatal outcomes and postpartum OGTT. For the characterization of the neonates weight, we used Cole Curves and considered 90th percentile and 10th percentile for gestational age as upper and lower limits, respectively, for appropriate for gestational age (AGA) newborns (17).

The postpartum OGTT was established 6–8 weeks after delivery with a two-hour 75 g OGTT according to the WHO criteria (18).

Statistical analysis

Categorical data were analysed by the chi-squared test or Fisher exact probability test whenever cell frequencies were <5 . Continuous data were compared using Student's *t*-test.

Based on the data from the univariate analysis, multivariate analysis was performed to identify independent parameters for metformin patients requiring insulin supplementation. This analysis was performed and adjusted odds ratios (aOR) were calculated using stepwise backward logistic regression models, adjusted for the following covariates: age, pre-pregnancy body mass index (BMI), first or second trimester GDM and gestational age at introduction of metformin.

Data are expressed as proportions, means ($\pm$ S.D. of the mean), aOR and 95% confidence intervals (CI).

All calculations were performed with STATA version 13.1 software. The probability of error (P value) was considered significant when <0.05 . Statistical significance was accepted when the 95% CI did not contain one (regression analyses).

Results

Between January 2014 and December 2015, 388 pregnant women with GDM initiated pharmacological therapy with metformin.

Globally, 73.7% ($n=286$) were Portuguese, the mean age was 33.7 ± 5.4 years old, the mean pre-pregnancy BMI was 30.0 ± 6.5 kg/m², 44.6% ($n=173$) had the diagnosis in the 1st trimester and the start of metformin was at 27.3 ± 6.6 gestational weeks. From this cohort, 34.8% ($n=135$) needed insulin supplementation.

Baseline characteristics

As shown in Table 1, both a higher maternal age (35.2 vs 32.9 years old, $P<0.001$) as a higher pre-pregnancy BMI (31.8 vs 29.0 kg/m², $P<0.001$) were strongly associated with the need for insulin supplementation. Thereby, obese women needed insulin supplementation more frequently (42.1% ($n=83$) vs 27.2% ($n=52$), $P=0.002$).

The OGTT showed higher values in metformin + insulin group; however, only the fasting glucose levels had statistically significant differences (85.4 vs 92.7 mg/dL, $P<0.001$) (Table 1).

Earlier GDM diagnosis (17.5 vs 20.3 weeks, $P=0.003$) and earlier metformin introduction (24.3 vs 28.8 weeks, $P<0.001$) were associated with failure of metformin monotherapy, leading to the need for insulin supplementation.

Despite only 5 pregnancies being multiple, 4 of them (80%) needed insulin supplementation ($P=0.05$).

Glycemic control data

Particularly in the 3rd trimester, higher HbA1c values were associated with the need for additional therapy with insulin (5.5 vs 5.2%, $P<0.001$). Also, higher maximum daily dose of metformin was associated with escalation of therapy (1858.8 vs 1384.6 mg/day, $P<0.001$) (Table 2).

Table 1 Baseline characteristics and demographics of women with GDM treated with metformin alone versus metformin and insulin. Proportions were compared by the chi-squared test or Fisher exact probability test and means were analysed with Student's t -test.

	Metformin group ($n=253$)	Metformin + insulin group ($n=135$)	P value
Portuguese, n (%)	184 (72.7%)	102 (75.6%)	0.547
Brazilian, n (%)	8 (3.2%)	10 (7.4%)	0.058
Other nationality, n (%)	61 (24.1%)	23 (17.0%)	0.107
Age (years)	32.9 ± 5.4	35.2 ± 5.0	<0.001
Family history of diabetes, n (%)	114 (46.5%)	53 (42.7%)	0.490
GDM in previous pregnancy, n (%)	25 (16.9%)	21 (26.6%)	0.084
Pre-pregnancy BMI (kg/m ²)	29.0 ± 6.3	31.8 ± 6.6	<0.001
1st trimester fasting glucose (mg/dL)	95.6 ± 10.8	97.6 ± 10.9	0.203
Diagnosis in the 1st trimester, n (%)	101 (39.9%)	72 (53.3%)	0.011
OGTT (mg/dL)			
Fasting	85.4 ± 11.41	92.7 ± 15.3	<0.001
1 h	171.4 ± 32.2	176.8 ± 33.1	0.297
2 h	144.6 ± 33.8	152.9 ± 40.0	0.141
Diagnosis (GW)	20.3 ± 8.1	17.5 ± 8.0	0.003
Weight gain until diagnosis (kg)	5.2 ± 5.3	3.9 ± 6.1	0.102
1st specialized appointment (GW)	24.1 ± 7.6	22.4 ± 7.7	0.039
HbA1c (1st specialized appointment) (%)	5.3 ± 0.4	5.4 ± 0.5	0.158
Introduction of metformin (GW)	28.8 ± 6.1	24.3 ± 6.6	<0.001

GW, gestational weeks.

Clinical Study	I Gante, L Melo and others	Metformin in gestational diabetes	178:1	132
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Table 2 Glycemic control data and obstetric outcomes of women with GDM treated with metformin alone versus metformin and insulin. Proportions were compared by the chi-squared or Fisher exact test and means were analysed with Student's *t*-test.

	Metformin group (n=253)	Metformin+insulin group (n=135)	P value
3rd trimester HbA1c (%)	5.2±0.5	5.5±0.5	<0.001
Maximum daily dose of metformin (mg)	1384.6±723.6	1858.8±1010.1	<0.001
Time between metformin and insulin therapy (GW)	–	4.0±4.2	–
Gestational weight gain after diagnosis (kg)	3.0±4.5	2.1±4.9	0.130
Gestational hypertension, n (%)	21 (8.7%)	14 (10.8%)	0.510
Preeclampsia, n (%)	7 (3.0%)	8 (6.2%)	0.137
Hydramnios, n (%)	12 (5.0%)	7 (5.4%)	0.880
Induced labour, n (%)	104 (55.9%)	59 (67.8%)	0.065
Eutocic delivery, n (%)	130 (53.5%)	51 (39.5%)	0.010
Instrumental vaginal delivery, n (%)	36 (14.8%)	17 (13.2%)	0.667
Cesarean delivery, n (%)	77 (31.7%)	61 (47.3%)	0.003
Urgent cesarean, n (%)	37 (14.6%)	23 (17.0%)	0.531
Elective cesarean, n (%)	40 (15.8%)	37 (27.4%)	0.006
Delivery (GW)	38.3±1.3	38.4±1.1	0.870
Premature birth, n (%)	18 (7.1%)	8 (5.9%)	0.656

GW, gestational weeks.

Women requiring additional therapy with insulin to achieve desirable glucose levels started taking the insulin supplementation 4.0±4.2 weeks after metformin initiation, at 28.3±5.9 weeks of pregnancy. The mean insulin dose needed was 22.2±20.5 IU.

Independent predictors for insulin supplementation

As shown in Table 3, a higher age (aOR: 1.08 (1.03–1.13)), a higher pre-pregnancy BMI (aOR: 1.06 (1.02–1.10)) and an earlier introduction of metformin (aOR: 0.89 (0.85–0.94)) were independently associated with the need for insulin supplementation.

Specifically, maternal age ≥35 years (aOR: 2.30 (1.47–3.59), *P*<0.001), pre-pregnancy obesity (aOR: 1.90 (1.21–2.98), *P*=0.005) and introduction of metformin before 24 weeks of gestation (aOR: 3.27 (1.77–6.05), *P*<0.001) were independently associated with an increased risk of insulin supplementation.

Obstetric and neonatal outcomes

Obstetric and neonatal outcomes are summarized in Tables 2 and 4.

One abortion was reported in the metformin group in a woman with antiphospholipid syndrome, and none occurred in the metformin+insulin group (*P*=0.644). There were no cases of foetal death in our cohort.

Although without statistically significant differences, we noted a slight tendency towards less obstetric complications in the metformin group (Table 2). Additionally, cesareans were more common

in metformin+insulin group (47.3% vs 31.7% in the metformin group, *P*=0.003), mainly due to the higher percentage of elective cesarean (27.4% vs 15.8%, *P*=0.006) (Table 2).

The two groups were comparable with respect to weight at birth, Apgar scores and neonatal morbidities (Table 4). Using the Cole Curves, the frequency rate of AGA was 75.8% (*n*=94) in the metformin+insulin group vs 84.3% (*n*=198) in the metformin group (*P*=0.051); 8.1% (*n*=10) vs 4.7% (*n*=11) (*P*=0.194) were small for gestational age (SGA) and 16.1% (*n*=20) vs 11.1% (*n*=26) (*P*=0.172) were large for gestational age (LGA).

Postpartum outcomes

Women in the metformin+insulin group were more likely to have higher postpartum glucose levels ((fasting: 95.7mg/dL vs 88.0mg/dL, *P*<0.001); (OGTT – 2h: 104.1mg/dL vs 94.3mg/dL, *P*=0.019)). Nevertheless, the postpartum OGTT results did not show differences between the two groups (Table 5).

Table 3 Independent predictors for insulin supplementation.

	aOR (95% CI)	P value
Age (years)	1.08 (1.03–1.13)	0.003
Pre-pregnancy BMI (kg/m ²)	1.06 (1.02–1.10)	0.003
Introduction of metformin (GW)	0.89 (0.85–0.94)	<0.001

Multivariate analysis was performed and aORs were calculated using logistic regression models, adjusted for the following covariates: age, pre-pregnancy BMI, first or second trimester GDM and gestational weeks (GW) at the introduction of metformin.

Clinical Study	I Gante, L Melo and others	Metformin in gestational diabetes	178:1	133
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Table 4 Neonatal outcomes of women with GDM treated with metformin alone versus metformin and insulin. Proportions were compared by the chi-squared or Fisher exact test and means were analysed with Student's *t*-test.

	Metformin group (<i>n</i> = 253)	Metformin + insulin group (<i>n</i> = 135)	<i>P</i> value
Neonatal weight at birth (g)	3197.9 ± 457.1	3184.3 ± 555.8	0.802
Low birth weight (<2500 g), <i>n</i> (%)	15 (5.9%)	15 (11.1%)	0.069
Macrosomia (≥4000 g), <i>n</i> (%)	18 (7.1%)	14 (10.4%)	0.267
Apgar score at 5 min	9.8 ± 0.8	9.9 ± 0.4	0.139
Total neonatal morbidity, <i>n</i> (%)	63 (26.5%)	26 (20.7%)	0.218
Hypoglycaemia, <i>n</i> (%)	18 (7.8%)	9 (7.8%)	0.991
Hyperbilirubinemia, <i>n</i> (%)	41 (17.7%)	20 (16.8%)	0.839
Respiratory distress, <i>n</i> (%)	10 (4.3%)	4 (3.5%)	0.711
Neonatal intensive care unit admission, <i>n</i> (%)	19 (8.2%)	6 (5.1%)	0.295

Discussion

As shown in other studies, metformin alone may be insufficient to achieve adequate glycemic control in GDM. In our study, 34.8% required insulin supplementation. This proportion is similar to that reported by Moore and coworkers (34.7%) but lower than that showed by Rowan and coworkers (48.3%) and higher than that by Tertti and coworkers (18%) (14, 19, 20). This reflects the heterogeneity of the populations studied.

Higher age, higher pre-pregnancy BMI and earlier introduction of metformin are the main conditions individualized in our analysis as independent predictors for insulin supplementation.

Similar to our findings, Tertti and coworkers reported that higher age was related to the need for insulin supplementation (20). Specifically, in our study, age above 35 years was associated with more than double the risk of insulin supplementation.

The majority of studies connected obesity and higher BMI with weaker sensitivity to metformin. In particular, lower BMI populations were associated with a better response to metformin alone, as demonstrated by Niromanesh and coworkers, in which the mean BMI was 28.1 kg/m² and only 14% required additional insulin

(21). By contrast, greater BMI populations were associated with a higher proportion of therapy escalation as reported in the MiG trial (14). Our data are in line with previous studies since 42.1% of obese women required additional insulin and obesity was associated with a doubled risk of insulin supplementation.

Early diagnosis and early introduction of metformin predicted insulin supplementation. Similar to results from McGrath and coworkers and Spaulonci and coworkers, more than a half of the women in our study that required additional therapy with insulin were diagnosed with GDM in the first trimester of pregnancy (22, 23). Also, the introduction of metformin before 24 weeks of gestation tripled the risk of insulin supplementation. When additional therapy with insulin was required, the gap between introduction of metformin and insulin supplementation was very variable (4 ± 4.2 weeks), which is similar to the gap reported by McGrath and coworkers (30 ± 22 days) (22). Third trimester HbA1c and maximum daily dose of metformin were both significantly higher in the group that required additional therapy with insulin. These correlations could be due to the increased insulin resistance during late gestation, since placental growing induces progressive insulin resistance which, associated

Table 5 Postpartum OGTT of women with GDM treated with metformin alone versus metformin and insulin. Proportions were compared by the chi-squared or Fisher exact test and means were analysed with Student's *t*-test.

	Metformin group (<i>n</i> = 167)	Metformin + insulin group (<i>n</i> = 87)	<i>P</i> value
Postpartum OGTT (mg/dL)			
Fasting	88.0 ± 9.1	95.7 ± 15.7	<0.001
2h	94.3 ± 28.2	104.1 ± 32.0	0.019
Postpartum OGTT result, <i>n</i> (%)			
Normal	151 (90.4%)	75 (86.2%)	0.309
Impaired fasting glucose	3 (1.8%)	3 (3.5%)	0.415
Impaired glucose tolerance	11 (6.6%)	7 (8.1%)	0.668
Type 2 diabetes mellitus	2 (1.2%)	6 (2.4%)	0.608

OGTT, oral glucose tolerance test.

to impaired beta cell function, led to increasingly glucose levels.

Hughes and coworkers found that an increased early pregnancy HbA1c measurement ($\geq 5.9\%$) was associated with an increased risk of adverse pregnancy outcomes, including major congenital anomaly, preeclampsia, shoulder dystocia and perinatal death (24). The impact of early detection and active intervention on hyperglycaemia in pregnancy could be responsible for smothering differences on both maternal and foetal outcomes between GDM diagnosed early and later, as we have shown in our study.

Several studies suggest a correlation between higher fasting blood glucose at diagnosis and the need for insulin supplementation (10, 14, 22). In our study, we only found this correlation with the values of fasting blood glucose in 2nd trimester OGTT.

Regarding the obstetric and neonatal outcomes analysed, the cesarean rate was statistically different between the two groups, due to the higher rate of elective cesareans in the metformin+insulin group (27.4%). The majority of studies had similar rates of cesarean deliveries between metformin and insulin groups (14, 25, 26). This suggests that insulin per se might not be a risk factor for cesarean delivery; moreover, in our study, the need for additional therapy with insulin was associated with other known risk factors for cesarean delivery, such as higher BMI and poor glycemic control.

Despite the slightly higher rates of AGA newborns in the metformin group, there were no statistically significant differences in SGA and LGA between the two groups. This corroborates the finding that even in women with inadequate glycemic control with metformin, the gap until escalation of therapy might not determine worse neonatal outcomes.

Although a recent study indicated that short-term metformin therapy does not affect postpartum OGTT results, compared with insulin or diet-only treatments, in our study, the need for additional therapy with insulin was associated with higher glucose levels in the postpartum OGTT (27).

A limitation of this study is the fact that women were followed in 25 different Portuguese hospitals and clinical judgement facing the same situations may have been different despite the well-established standards. Furthermore, the diagnostic criteria for GDM vary between countries and across the time which may induce variations in need for insulin supplementation.

The major strengths of this study are the large sample size and the identification of risk factors for poor response

to metformin. Finally, the conclusions of this study are important for clinical practice as they may disclose some questions about metformin use in GDM.

Conclusion

Metformin can be regarded as an alternative treatment in GDM. Despite being a safe and effective therapy, almost 35% of the women treated with metformin did not achieve adequate glycemic control with monotherapy.

Higher maternal age, higher pre-pregnancy BMI and earlier need for metformin introduction (due to poor glycemic control with non-pharmacological therapy) were the major independent predictors of insulin supplementation. Also, poor glycemic control indicators (such as higher HbA1c or need for higher daily dose of metformin) were associated with failure of the monotherapy with metformin.

Furthermore, in women requiring insulin supplementation there were higher cesarean rates and higher postpartum glucose levels.

Declaration of interest

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

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