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Metformin in overweight and obese women with gestational diabetes: a propensity score-matched study

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Abstract

Purpose Obesity and gestational diabetes mellitus (GDM) have an independent negative impact in pregnancy outcomes. Excessive gestational weight gain (GWG) represents an additional high-risk condition for adverse outcomes. The aims of this study were to evaluate the potential effect of metformin in GWG in overweight or obese women with GDM, to report our experience and to assess metformin's safety in this population.

Methods Retrospective observational cohort study involving pregnant women with GDM and pregestational overweight or obesity. Demographic, anthropometric, glycemic control data, obstetric, fetal and neonatal outcomes were evaluated. The sample was divided into two groups according to metformin treatment. A propensity score-matched analysis was performed using age, initial body mass index (BMI), trimester at GDM diagnosis and previous history of GDM or macrosomia as covariates.

Results Of the 457 enrolled in the study, 177 (38.7%) were treated with metformin. Two groups of 130 well matched patients were balanced regarding baseline characteristics. Women in metformin group had significantly less excessive GWG (29.23% vs. 42.31%, OR 0.56, 95% CI 0.34–0.94, $p = 0.028$) and more adequate GWG (36.92% vs. 23.08%, OR 1.95, 95% CI 1.14–3.35, $p = 0.015$). No significant differences were found between both groups regarding glycemic control, rate of insulinization, and obstetric, fetal, and neonatal outcomes.

Conclusions This study highlights metformin as an important and safe tool to prevent excessive GWG and promote adequate GWG in overweight or obese women with GDM, regardless of age, BMI, timing of GDM diagnosis, previous history of GDM or macrosomia.

Keywords Gestational diabetes · Metformin · Obesity · Overweight · Gestational weight gain

Introduction

Obesity and diabetes mellitus (DM) are two major public health problems worldwide. According to the World Health Organization (WHO), in 2016, the estimate prevalence of obesity and overweight among adult women in Portugal was 21.2% and 52.0%, respectively [1, 2]. The prevalence of gestational diabetes mellitus (GDM) in Portugal was 7.5% in 2016 and has duplicated in the last decade [3].

Both GDM and obesity have an independent and additive negative impact in pregnancy [4]. Maternal obesity is associated with higher risk of preeclampsia, cesarean section, antepartum and post-partum hemorrhage, longer hospital stay, preterm birth, large-for-gestational age (LGA) newborns, macrosomia, birth trauma, low umbilical arterial pH, neonatal hypoglycemia, low Apgar scores, Neonatal Intensive Care Unit (NICU) admission, congenital birth

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defects, stillbirth, neonatal and perinatal mortality [5]. The risk of the majority of these complications is proportional to the degree of obesity. GDM also increases the risk of maternal, fetal and perinatal outcomes, namely pre-eclampsia, preterm delivery, primary cesarean section, LGA newborns, birth injury, neonatal hypoglycemia, hyperbilirubinemia, and NICU admission [6]. In general, there is a continuous association between higher maternal hyperglycemia and increased frequency of the adverse outcomes.

There is a strong relationship between obesity and GDM [5, 7]. Maternal obesity is an independent risk factor for developing GDM. The risk of GDM is up to fivefold higher in morbidly obese women, when compared to women with normal weight. Conversely, the intrauterine exposure to hyperglycemia, regardless of maternal DM type, is an independent risk factor for obesity and type 2 DM in the offspring [8]. Furthermore, a recent systematic review found that 47% of pregnant women had GWG above the recommended range [9]. Obesity is associated with excessive gestational weight gain (GWG), which has been linked to increased risk of LGA neonates, macrosomia, cesarean delivery, gestational hypertension, offspring obesity, and postpartum weight retention with long-term obesity [9–12]. Indeed, GDM, obesity, and excessive GWG represent, individually and additively, high-risk conditions associated with adverse maternal and infant outcomes. Therefore, an effort to reduce excessive GWG in a high-risk population, such as overweight or obese women with GDM, seems imperative.

Metformin is an insulin-sensitizing drug that acts primarily by decreasing hepatic glucose production by inhibiting gluconeogenesis and increasing glucose uptake in peripheral tissues [13]. Metformin can be beneficial in reducing weight and could be an option to prevent excessive weight gain during pregnancy [14]. Its use in pregnancy has been considered in several guidelines [15–20].

The main aim of this study was to evaluate the potential effect of metformin in GWG in overweight or obese women with GDM using a propensity score-matched analysis. The second aim was to report the experience of our tertiary center using metformin in GDM and to assess metformin's safety in this population.

Materials and methods

Study design and participants

A retrospective observational cohort study was performed involving pregnant women with GDM followed between January 2014 and December 2017 in the Outpatient Clinic of Obstetrics and Endocrinology of our institution, a tertiary care academic hospital, which is a referral center for obesity and obstetric care in Portugal. Only women with pregestational BMI ≥ 25 kg/m^2 were included. The sample was divided into two groups according to the treatment with metformin during pregnancy.

Data were collected by our team to integrate the National Registry of GDM. All datasets were blinded, ensuring anonymity of the collected data. Analysis of these data was performed after permission from the Diabetes and Pregnancy Study Group of the Portuguese Society of Diabetology, which is responsible for this database. All procedures performed in this study were in accordance with the Declaration of Helsinki on medical protocol and ethics. The study was approved by Diabetes and Pregnancy Study Group of the Portuguese Society of Diabetology. For this type of study using retrospective and anonymized data, participants' written consent was not required.

The GDM diagnosis was established according to the International Association of Diabetes Pregnancy Study Groups' criteria and the WHO: universal fasting plasma glucose (FPG) in the first trimester and a 75-g 2-h oral glucose tolerance test (OGTT) between 24 and 28 gestational weeks (GW) [21, 22]. After diagnosis, women with GDM were followed by a multidisciplinary team consisting of an endocrinologist, an obstetrician and a nutritionist. All women received detailed exercise and nutritional counseling and an individualized nutritional plan according to maternal BMI. Women were evaluated periodically and blood glucose readings and weight were assessed in each visit. Glycemic targets were defined as a fasting or preprandial level ≤ 95 mg/dL and either a 1-h postprandial level ≤ 140 mg/dL or a 2-h postprandial level ≤ 120 mg/dL in the majority of glucose measurements [15, 18–20]. Pharmacological therapy (metformin or insulin) was initiated when satisfactory glycemic control was not achieved despite of two weeks of adequate non-pharmacological therapy.

Clinical data evaluated

Demographic (age, nationality), anthropometric (height, weight and BMI) and previous obstetric data (number of pregnancies, miscarriage, deliveries, history of previous GDM or macrosomia) were obtained. Clinical and laboratorial parameters regarding the diagnosis of GDM (biochemical criteria, GW of diagnosis), treatment (maximum daily dose and GW of initiation of pharmacological treatment, glycated hemoglobin [HbA1c]) and reclassification test (75-g 2-h postpartum OGTT performed 6 to 8 weeks after delivery) were also analyzed. To assess safety, obstetric complications (gestational hypertension, preeclampsia, hydramnios, preterm labor, cesarean section) and neonatal outcomes (gestational age at delivery, stillbirth, birth weight, Apgar score, neonatal hypoglycemia, hyperbilirubinemia,

respiratory distress syndrome, NICU admission, birth trauma, congenital anomalies and neonatal death) were evaluated. Birth weight was classified as small, appropriate and large for gestational age (SGA, AGA, LGA, respectively) using the Fenton curves [23]. Neonates with birth weight higher than 4000 g were considered macrosomic and those with <2500 g were classified as low birth weight.

BMI was defined as weight (kg)/height $(m)^2$ and patients were classified as overweight (BMI 25.00–29.99 kg/m^2), obesity grade 1 (BMI 30.00–34.99 kg/m^2), obesity grade 2 (BMI 35.00–39.99 kg/m^2) and obesity grade 3 (BMI ≥ 40.00 kg/m^2). GWG for the entire pregnancy was calculated according to Institute of Medicine (IOM) recommendations for each category of pregestational BMI [24]. The recommended range for GWG is 7–11.5 kg in overweight women and 5–9 kg in those with obesity. Women who presented GWG below, within or above the IOM range were classified as insufficient, adequate or excessive GWG, respectively. Women with missing GWG values were excluded.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) when normally distributed or as medians (interquartile range [IQR] 25th percentile–75th percentile) when not normally distributed. Normal distribution of continuous variables was evaluated using Kolmogorov–Smirnov test. Continuous variables were compared using independent *t*-test or the Mann–Whitney test, depending on whether they followed a normal or non-normal distribution, respectively. Categorical variables were expressed as frequencies and percentages and compared by chi-squared test, followed by the Bonferroni correction when applied.

A propensity score-matched analysis was performed to balance the distribution of baseline characteristics between groups. Covariates used were as follows: age, initial BMI, trimester at GDM diagnosis, previous diagnosis of GDM, and history of macrosomia. Patients were matched based on the logit of the propensity score using a caliper width of 0.2 of standard deviation of the logit of the propensity score. The matched groups were then compared using student's t-test, chi-square test and logistic regression.

A two-sided *p*-value of <0.05 was considered statistically significant. Stata/IC 14.2 was used as statistical package software.

Results

A total of 457 overweight or obese women with GDM were followed in the Outpatient Clinic of Obstetrics and Endocrinology of our hospital. Of those, 177 (38.7%) were treated with metformin during pregnancy, while 280 (61.3%) didn't received that drug. Women treated with metformin received the drug from 28 ± 7.3 weeks of gestation until delivery, at a mean dose of 2100 ± 560 g per day.

Clinical baseline characteristics of women with GDM according to metformin treatment during pregnancy are presented in Table 1. Women in the metformin group had higher pregestational weight (86.1 ± 16.7 kg vs. 78.5 ± 12.9 kg; $p < 0.001$) and BMI (32.67 ± 5.59 kg/m^2 vs. 30.10 ± 4.34 kg/m^2; $p < 0.001$), more often presenting obesity grades 2 (20.9% vs. 7.5%, $p < 0.001$) and 3 (9.0% vs. 3.9%, $p < 0.001$).

A propensity score-matched analysis was performed using age, pregestational BMI, timing of GDM diagnosis, previous diagnosis of GDM, and history of macrosomia as covariates. As a result, two groups of 130 well matched patients have been generated and were balanced regarding baseline characteristics (Table 2).

Women treated with metformin had lower gestational final weight (89.8 ± 13.5 kg vs. 91.6 ± 14.0 kg; $p = 0.27$), gestational final BMI (34.10 ± 4.24 kg/m^2 vs. 35.00 ± 4.73 kg/m^2; $p = 0.11$) and total GWG (8.2 ± 5.9 kg vs. 9.1 ± 6.9 kg; $p = 0.24$), although not statistically significant (Table 3). There were significant differences regarding GWG classification. Excessive GWG was found in 29% pregnant women in the metformin group and 42% of those in the other group. Furthermore, 37% and 23% of women achieved adequate GWG depending on whether they were treated or not with metformin, respectively. Treatment with metformin reduced the odds of having excessive GWG by 44% (OR 0.56, 95% confidence interval [CI] 0.34 to 0.94, $p = 0.028$) and increased the odds of having adequate GWG by 95% (OR 1.95, 95% CI 1.14 to 3.35, $p = 0.015$). These findings were independent of therapy with insulin or HbA1c level. The proportion of insufficient GWG in both groups was similar.

We did not find statistically significant differences between both groups regarding HbA1c in third trimester, treatment with insulin, GW of insulin initiation, maximum daily dose of insulin and results of reclassification OGTT. Obstetric outcomes (miscarriage, gestational hypertension, preeclampsia, hydramnios, induced labor, vaginal delivery, cesarean section, urgent cesarean section, GW of delivery and preterm birth) did not differ between groups on a statistically significant level (Table 3).

Safety of metformin was also evaluated by fetal and neonatal outcomes. There were no significant differences between groups in gestational age at delivery, stillbirth, birth weight (low birth weight, macrosomia, Fenton curves), Apgar scores, neonatal hypoglycemia, hyperbilirubinemia and respiratory distress syndrome, NICU admission, birth injury, congenital anomalies and neonatal death (Table 4).

Table 1 Clinical baseline characteristics of unmatched women with GDM according to metformin treatment during pregnancy

	Total population ($n = 457$)	With metformin ($n = 177$)	Without metformin ($n = 280$)	p value
Age, years; mean ± SD	34 ± 5	34 ± 5	34 ± 5	0.39
Portuguese; *n* (%)	444 (97.2)	171 (96.6)	273 (97.5)	0.58
Family history of DM, *n* (%)	176 (40.6)	69 (41.8)	107 (39.9)	0.70
Twin pregnancy; *n* (%)	21 (4.6)	7 (4.0)	14 (5.0)	0.60
Pregestational anthropometric data				
Height, cm; mean ± SD	162 ± 7	162 ± 7	161 ± 7	0.25
Weight, kg; mean ± SD	81.5 ± 14.9	86.1 ± 16.7	78.5 ± 12.9	*<0.001*
BMI, kg/m^2; mean ± SD	31.09 ± 5.02	32.67 ± 5.59	30.10 ± 4.34	*<0.001*
BMI classification; *n* (%)				
Overweight	238 (52.1)	72 (40.7)*	166 (59.3)*	
Obesity grade 1	134 (29.3)	52 (29.4)	82 (29.3)	
Obesity grade 2	58 (12.7)	37 (20.9)*	21 (7.5)*	
Obesity grade 3	27 (5.9)	16 (9.0)*	11 (3.9)*	*<0.001*
Obstetric history				
Previous GDM; *n* (%)	54 (11.9)	19 (10.8)	35 (12.5)	0.57
Previous macrosomia; *n* (%)	22 (4.8)	6 (3.4)	16 (5.8)	0.26
Miscarriage; median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0.93
Deliveries; median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	0.20
Pregnancies; median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.57
GDM diagnosis				
FPG first trimester; mg/dL; median (IQR)	95 (93–99)	96 (94–99)	95 (93–98)	*0.038*
OGTT FPG; mg/dL; median (IQR)	84 (77–93)	85 (78–93)	84 (77–93)	0.43
OGTT 60 min; mg/dL; median (IQR)	179 (158–190)	176 (162–188)	180 (152–190)	0.71
OGTT 120 min; mg/dL; median (IQR)	155 (130–166)	155 (132–165)	155 (129–168)	0.81
GW of diagnosis; mean ± SD	17 ± 9	17 ± 8	17 ± 9	0.66
GW of first consultation; mean ± SD	23 ± 8	23 ± 8	24 ± 9	0.50

Significant differences between groups are indicated by italics

BMI body mass index, *DM* diabetes mellitus, *FPG* fasting plasma glucose, *GDM* gestational diabetes mellitus, *GW* gestational week, *IQR* interquartile range, *OGTT* oral glucose tolerance test, *SD* standard deviation

*$p < 0.05$ for comparison between groups using Bonferroni correction

Discussion

To the best of our knowledge, this is the first observational study evaluating the effect of metformin in GWG in overweight or obese women with GDM through a propensity score-matched analysis. This analysis reduces bias in the estimate of the average treatment effect in a nonrandomized study, making the estimate more comparable [25]. Despite all pregnant obese women having received exercise and nutritional individual counseling, we observed that treatment with metformin had an important beneficial effect in preventing excessive GWG and promote adequate GWG. This effect was independent of pregestational BMI, age, timing of GDM diagnosis, previous diagnosis of GDM or macrosomia. It is important for healthcare providers to be aware of current GWG guidelines and make efforts to implement effective strategies to prevent excess GWG, since it is a modifiable risk factor for adverse obstetric and fetal outcomes. Furthermore, it will also help to promote postpartum weight loss and to reduce obesity in a subsequent pregnancy. Tailored and individualized nutritional therapy, increased physical activity and even metformin should contribute to the prevention of excessive GWG. The approach by our multidisciplinary team consisting of an endocrinologist, an obstetrician and a nutritionist, seems helpful in this field.

The IOM GWG guidelines were not specific for GDM pregnancies, but are frequently applied in this population. It was postulated that women with GDM require more stringent GWG targets due to the association and potentially additive effects of excessive GWG and hyperglycemia on adverse pregnancy outcomes. However, a retrospective cohort study didn't support the modification of IOM criteria to improve perinatal outcomes. The authors advised that

Table 2 Clinical baseline characteristics of women with GDM according to metformin treatment after propensity score matching

	With metformin ($n = 130$)	Without metformin ($n = 130$)	p value
Age, years; mean ± SD	34 ± 5	34 ± 6	0.40
Portuguese; *n* (%)	129 (99.2)	127 (97.7)	0.31
Family history of DM, *n* (%)	54 (43.5)	41 (32.8)	0.08
Twin pregnancy; *n* (%)	7 (5.4)	9 (6.9)	0.61
Pregestational anthropometric data			
Height, cm; mean ± SD	162 ± 7	162 ± 7	0.61
Weight, kg; mean ± SD	81.6 ± 13.2	82.6 ± 14.5	0.58
BMI, kg/m^2; mean ± SD	30.98 ± 4.15	31.52 ± 4.98	0.34
BMI classification; *n* (%)			
Overweight	65 (50.0)	63 (46.5)	
Obesity grade 1	46 (35.4)	41 (31.5)	
Obesity grade 2	14 (10.8)	16 (12.3)	
Obesity grade 3	5 (3.8)	10 (7.7)	0.55
Obstetric history			
Previous GDM; *n* (%)	14 (10.8)	17 (13.1)	0.57
Previous macrosomia; *n* (%)	5 (3.8)	7 (5.4)	0.55
Miscarriage; median (IQR)	0 (0–1)	0 (0–1)	0.69
Deliveries; median (IQR)	1 (0–1)	1 (0–1)	0.24
Pregnancies; median (IQR)	2 (1–3)	2 (1–3)	0.40
GDM diagnosis			
FPG first trimester; mg/dL; median (IQR)	95 (93–98)	95 (93–99)	0.45
OGTT FPG; mg/dL; median (IQR)	85 (78–93)	84 (77–94)	0.98
OGTT 60 min; mg/dL; median (IQR)	176 (162–186)	182 (156–192)	0.31
OGTT 120 min; mg/dL; median (IQR)	157 (138–168)	149 (117–163)	0.051
GW of diagnosis; mean ± SD	17 ± 8	17 ± 9	0.85
GW of first consultation; mean ± SD	23 ± 8	23 ± 9	0.90

BMI body mass index, *DM* diabetes mellitus, *FPG* fasting plasma glucose, *GDM* gestational diabetes mellitus, *GW* gestational week, *IQR* interquartile range, *OGTT* oral glucose tolerance test, *SD* standard deviation

more restrictive targets may still be considered, especially among obese women, to minimize postpartum weight retention and thus long-term maternal morbidity related to obesity and type 2 DM in this high-risk population [26]. Some authors have discussed the role of weight loss instead of weight gain in overweight and obese women during pregnancy, whether with or without DM [27, 28]. In overweight and obese women with GDM, gestational weight loss was associated with improvement of some outcomes (lower macrosomia, NICU admission, and cesarean delivery), but impairment in other outcomes (SGA neonates and preterm delivery < 34 weeks). Kapadia et al. reported that GWG below the guidelines had higher odds of SGA and low birth weight, and lower odds of LGA, macrosomia, cesarean delivery and shoulder dystocia than GWG within the guidelines. There was a lack of adequate investigation on preterm birth. Therefore, gestational weight loss for obese women cannot be routinely recommended, but it should be a possibility in some women based on individual known risk factors. Further focus is needed on lifestyle interventions and weight loss prior to conception.

Several international guidelines, namely the American Diabetes Association (ADA), the Endocrine Society and the American College of Obstetricians and Gynecologists (ACOG) [18–20] recommend insulin as the preferred pharmacotherapy for treating hyperglycemia in GDM as it does not cross the placenta to a measurable extent. Metformin has been considered as a reasonable and safe first-line pharmacologic therapy alternative to insulin in guidelines of the National Institute for Health and Care Excellence (NICE), the International Federation of Gynecology and Obstetrics (FIGO) and the Society of Maternal-Fetal Medicine (SMFM) [15–17]. Nevertheless, metformin is associated with a failure rate of 33.8–46.3% (defined as a requirement for additional insulin) [14, 29], even in a Portuguese study [30]. The rate of insulinization in our study was greater than previously reported, but it is probably related to inclusion of only overweight and obese woman.

Table 3 Gestational anthropometric data, GDM treatment and obstetric outcomes of women with GDM according to metformin treatment after propensity score matching

	With metformin ($n = 130$)	Without metformin ($n = 130$)	p value
Gestational anthropometric data			
Gestational final weight; kg; mean ± SD	89.8 ± 13.5	91.6 ± 14.0	0.27
Gestational final BMI; kg/m^2; mean ± SD	34.10 ± 4.24	35.00 ± 4.73	0.11
Total GWG; kg; mean ± SD	8.2 ± 5.9	9.1 ± 6.9	0.24
Excessive GWG; *n* (%)	38 (29.23)	55 (42.31)	*0.028*
Adequate GWG; *n* (%)	48 (36.92)	30 (23.08)	*0.015*
Insufficient GWG; *n* (%)	44 (33.85)	45 (34.62)	0.896
GDM treatment and evolution			
HbA1c third trimester; mean ± SD	5.4 ± 0.3	5.3 ± 0.3	0.38
Treatment with insulin; *n* (%)	74 (56.9)	77 (59.2)	0.71
GW of insulin initiation; mean ± SD	26 ± 7	25 ± 8	0.33
Maximum daily dose of insulin; mean ± SD	32 ± 43	34 ± 26	0.71
Normal reclassification OGTT; *n* (%)	87/95 (91.6)	83/87 (95.4)	0.43
Obstetric outcomes			
Miscarriage; *n* (%)	0 (0)	1 (0.8)	0.32
Gestational hypertension; *n* (%)	7 (5.6)	3 (2.3)	0.18
Preeclampsia; *n* (%)	6 (4.8)	3 (2.3)	0.29
Hydramnios; *n* (%)	6 (4.8)	6 (4.7)	0.97
Induced labor; *n* (%)	59 (46.5)	48 (37.8)	0.16
Vaginal delivery; *n* (%)	74 (58.6)	74 (57.8)	0.88
Cesarean section; *n* (%)	52 (41.3)	54 (42.2)	0.88
Urgent cesarean section; *n* (%)	27 (53)	33 (61)	0.40
GW of delivery; mean ± SD	38 ± 1	38 ± 2	0.71
Preterm birth; *n* (%)	13 (10.2)	11 (8.6)	0.67

Significant differences between groups are indicated by italics

BMI body mass index, *DM* diabetes mellitus, *FPG* fasting plasma glucose, *GW* gestational week, *GWG* gestational weight gain, *HbA1c* glycated hemoglobin, *IQR* interquartile range, *OGTT* oral glucose tolerance test, *SD* standard deviation

Several metformin effects in GDM have been reported [14, 29, 31, 32]. When compared with insulin, metformin was associated with less maternal weight gain in two meta-analyzes (pooled mean difference −1.14 kg, 95% CI −2.22 to −0.06, $p = 0.04$ [14]; 0.4 ± 2.9 kg vs. 2 ± 3.3 kg; $p < 0.001$ [29]). In the meta-analysis performed by Balsells et al. in 2015, women receiving metformin had a lower gestational age at delivery (mean difference −0.16 weeks, 95% CI −0.30 to −0.02; $p = 0.03$), more preterm birth (pooled risk ratio 1.50, 95% CI 1.04 to 2.16; $p = 0.03$), and a trend towards less neonatal hypoglycemia (pooled risk ratio 0.78, 95% CI 0.60–1.01; $p = 0.06$). Among secondary outcomes, patients in the metformin group had significant lower postprandial blood glucose, less maternal weight gain since study entry, less pregnancy-induced hypertension and less severe neonatal hypoglycemia [14]. Additionally, Li et al. found that metformin may significantly reduce several adverse maternal and neonatal outcomes, including pregnancy induced hypertension, neonatal hypoglycemia and the need for NICU admission [29]. Furthermore, lower birth weight, less LGA newborns and less macrosomia were observed in newborns of women treated with metformin in a more recent meta-analysis [33]. The rate of congenital anomalies and neonatal mortality was not increased in the offspring exposed to metformin; it is currently classified as pregnancy category B by Food and Drug Administration (FDA). The majority of women prefer metformin treatment instead of insulin [14]. Similarly to the literature, we didn't observe adverse obstetric, fetal or neonatal outcomes in women treated with metformin in our study.

Metformin has also been studied to reduce GWG, maternal and neonatal outcomes in overweight and obese women without DM [34–36]. However, there is currently insufficient evidence to support the use of this drug in obese women without DM for improving maternal and infant outcomes.

Metformin crosses the placenta, resulting in fetal concentrations similar or higher to those in the maternal

Table 4 Neonatal outcomes of women with GDM according to metformin treatment after propensity score matching

	With metformin ($n = 130$)	Without metformin ($n = 130$)	p value
Newborn anthropometric data			
Birth weight; mean ± SD	3166 ± 462	3214 ± 567	0.46
Low birth weight (<2500 g); *n* (%)	12 (9.4)	13 (10.2)	0.85
Macrosomia (≥4000 g); *n* (%)	3 (2.4)	9 (7.0)	0.078
Birth weight (Fenton curves); *n* (%)			
SGA	14 (11.1)	17 (13.3)	
AGA	109 (86.5)	104 (81.2)	
LGA	3 (2.4)	7 (5.5)	0.44
Neonatal outcomes and complications			
Apgar score at first minute; mean ± SD	9 ± 1	9 ± 1	0.63
Apgar score at fifth minute; mean ± SD	10 ± 1	10 ± 1	0.57
Neonatal hypoglycemia; *n* (%)	2 (1.6)	2 (1.6)	0.99
Neonatal hyperbilirubinemia; *n* (%)	38 (30.2)	40 (31.7)	0.79
Respiratory distress syndrome; *n* (%)	3 (2.4)	5 (4.0)	0.47
NICU admission; *n* (%)	6 (4.8)	9 (7.1)	0.42
Birth injury; *n* (%)	3 (2.4)	2 (1.6)	0.65
Congenital anomalies; *n* (%)	8 (6.3)	10 (7.9)	0.62
Stillbirth; *n* (%)	0	0	–
Neonatal death; *n* (%)	0	0	–

AGA appropriate for gestational age, *IQR* interquartile range, *LGA* large for gestational age, *NICU* Neonatal Intensive Care Unit, *SD* standard deviation, *SGA* small for gestational age

circulation and raising concerns for interaction of metformin with fetal environmental factors that could lead to negative offspring outcomes [18, 37, 38]. Higher BMI Z score, central adiposity and obesity in childhood are some of the potential effects on cardiometabolic health of the offspring exposed to metformin described in the literature. We believe that future studies on long-term safety data and a larger number of patients are important in this field.

This study has some limitations. Although all analyzed variables were balanced after propensity score, we cannot exclude that other unmeasured variables may have also influenced the decision to treat with metformin. Our findings may not be may not be generalizable to groups screened with different diagnostic criteria for GDM. Due to the low number of events of some obstetrical (miscarriage, gestational hypertension, preeclampsia and hydramnios) and neonatal adverse events (neonatal hypoglycemia, respiratory distress syndrome, NICU admission and birth injury), our analysis were underpowered to assess differences in these outcomes. All patients have been counseled about eating behavior, nutritional changes, and physical activity during the follow-up, however the adherence to counseling, nutritional and exercise status could influence weight loss and were not evaluated in our study. Currently, we have no long-term data on the offspring, but our group is already working in evaluating the anthropometric outcomes and long-term effects in the offspring exposed to metformin.

Notwithstanding these limitations, our study has several strengths. We evaluated the effect of metformin in GWG in overweight and obese women in GDM using real-world data from a referral center for obesity and obstetric care in Portugal. Besides the limitation of being a retrospective observational study, confounding factors that may have influenced clinical decisions such as the choice of pharmacological treatment was minimized by using a propensity score. There were no self-reported data, which can be inaccurate. Furthermore, we used broad inclusion criteria and a detailed assessment of several obstetric and neonatal outcomes.

Conclusion

We evaluated the effect of metformin in gestational weight variation in overweight or obese women with GDM through a propensity score-matched analysis. No significant differences regarding adverse obstetric, fetal and neonatal outcomes were found between the two groups, confirming metformin's safety in this population. Treatment with metformin was found to prevent the excessive GWG in 44% and to increase adequate GWG in 95%, regardless of age, BMI, timing of GDM diagnosis and previous history of GDM or macrosomia. The present study highlights metformin as an important tool to prevent excessive GWG in overweight or obese women with GDM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the Declaration of Helsinki on medical protocol and ethics. The study was approved by Diabetes and Pregnancy Study Group of the Portuguese Society of Diabetology.

Informed consent For this type of study using retrospective and anonymized data, participants' written consent was not required.

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