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Metformin-associated maternal and neonatal outcomes in women with gestational diabetes — a retrospective cohort study

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ABSTRACT

Objectives: To assess the maternal and neonatal outcomes in women with GDM treated with metformin, medical nutrition therapy (MNT) or insulin.

Material and methods: The current retrospective cohort study includes data from 233 women diagnosed with GDM who gave birth between January 2017 and January 2019 at an obstetrics and gynecology hospital in Sofia, Bulgaria. Patients were assigned to three groups, according to the treatment approach — metformin group (n = 70), insulin group (n = 40), and MNT group (n = 123). Values of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) have been evaluated at diagnosis of GDM and the third trimester of pregnancy. A comparative analysis of pregnancy outcomes and short-term neonatal characteristics in the investigated groups has been performed.

Results: Women indicated for pharmacological treatment (metformin or insulin) had significantly higher BMI ($p < 0.01$), FPG ($p < 0.001$), and HbA1c levels ($p < 0.001$) at baseline. However, during pregnancy, patients treated with metformin showed a significantly lower BMI ($p < 0.01$), FPG ($p < 0.01$), and HbA1c ($p < 0.01$). Neonates born to metformin-treated mothers had lower birth weight compared to those born to women in the MNT and insulin groups (metformin vs MNT, $p < 0.001$; metformin vs insulin, $p = 0.03$). The lowest incidence of newborns with macrosomia and neonatal hypoglycemia has been observed in the metformin cohort. Not a single newborn with an Apgar score under 7 has been identified in the metformin group.

Conclusions: According to the current analysis, women with GDM treated with metformin demonstrated better maternal and neonatal outcomes. No short-term complications in newborns have been associated with metformin use during pregnancy.

Keywords: gestational diabetes; metformin; insulin; maternal outcomes; neonatal outcomes

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INTRODUCTION

Gestational diabetes mellitus (GDM) is the most common cause of hyperglycemia during pregnancy [1]. According to the International Diabetes Federation (IDF), one in six live births (16.7%) in 2021 were to women with hyperglycemia during pregnancy, most often (80.3%) due to GDM [2]. The prevalence of GDM was estimated to vary between 1 and 28% according to different population studies [3]. More than 50% of women with previous GDM are at higher risk of developing type 2 diabetes mellitus (T2DM) in the first five years after birth [4].

Hyperglycemia in pregnancy is a risk factor for maternal and fetal complications. Pregnancies complicated with GDM are linked with an elevated risk of hypertensive disorders and cesarean deliveries [1]. In addition, women with GDM have a 10-fold higher risk of developing T2DM later in life

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compared to normoglycemic pregnancies. [5]. Women with a history of GDM are 30–84% more likely to develop it again in a subsequent pregnancy [6]. The most common perinatal and neonatal complications associated with GDM include macrosomia, shoulder dystocia, respiratory distress syndrome, neonatal hypoglycemia, polycythemia, and hyperbilirubinemia [1]. Exposure to maternal hyperglycemia increases the risk of childhood overweight and obesity associated with the development of T2DM [7].

Treatment of GDM has been proven to reduce the risk of perinatal complications by 75% and fetal macrosomia by 50% [8]. Lifestyle modification (diet and physical activity) is essential to GDM management. According to the American Diabetes Association (ADA) guideline, 70–85% of women with GDM, can maintain adequate glycemic control with lifestyle modification alone [9]. If blood glucose targets have not been achieved by changes in diet and exercise within 1–2 weeks, pharmacotherapy should be further initiated [9, 10]. Up to 30% of patients with GDM may require pharmacological therapy [11].

Since insulin does not cross the placenta, it is recognized by many guidelines as a first-line pharmacological option for GDM treatment [9, 12, 13]. According to the International Federation of Gynecology and Obstetrics (FIGO) Initiative on GDM, insulin is considered the first-line treatment in women with dysglycemia, especially those at high risk of failure of oral antidiabetic therapy. In addition, other factors associated with the need for insulin therapy noted in FIGO guideline include hyperglycemia detected before 20 weeks of gestation; fasting plasma glucose (FPG) > 6.1 mmol/L or post-prandial glucose levels > 7.8 mmol/L; and increased pregnancy weight gain (> 12 kg) [1]. After 30 weeks of gestation, pharmacological therapy has often been needed [1, 9, 14]. Despite the predictive factors mentioned above, there is no universal consensus regarding the timing of the initiation of pharmacotherapy for pregnant women with GDM [15].

Although insulin is an effective and safe treatment approach during pregnancy, it is associated with the risk of several adverse outcomes: hypoglycemic episodes, weight gain, and the requirement for multiple daily glucose self-monitoring. In addition, insulin treatment requires special storage conditions and patient education regarding proper injection technique. Patient compliance and adherence are crucial determinants of insulin therapy effectiveness [16].

In comparison to insulin, oral hypoglycemic agents have several advantages like low cost, easier administration, and better patient compliance [16]. The two oral antidiabetic medications reported to be used to treat GDM are metformin and glyburide [17].

Metformin is a biguanide that is the most widely prescribed hypoglycemic medication, currently included in the World Health Organization's Model List of Essential Medicines. It is the first-line monotherapy for the treatment of T2DM [18]. Metformin does not enhance insulin secretion which is associated with a lower risk of hypoglycemia [19]. Several studies have demonstrated the benefits of metformin use for the prevention and treatment of GDM. However, metformin use during pregnancy may rise concerns due may be controversial due to its ability to cross the placenta [20].

According to several practice guidelines, such as FIGO, the UK National Institute for Health and Care Excellence (NICE), the Endocrine Society, and the German Diabetes Association, metformin can be considered as the first-line option for the pharmacological treatment of GDM. [1, 10, 13, 21]. In contrast, other professional organizations like ADA, and the American Congress of Obstetricians and Gynecologists (ACOG), do not recommend metformin as first-line treatment, because of its transplacental transport and lack of data on long-term safety [9, 14]. Although these concerns, ACOG guidelines consider that in some cases, metformin could be a reasonable alternative to insulin [14].

Objective

This study aims to comparatively assess the maternal and neonatal outcomes in women with GDM treated with metformin, medical nutrition therapy (MNT), or insulin.

MATERIAL AND METHODS

Study design and setting

The current retrospective observational cohort study is based on the electronic records of the validated integrated information system of a specialized obstetrics and gynecology hospital with national coverage of patients in Bulgaria (Joystick, ver. 2.1). The study has been considered by the Institutional Review Board of Specialized Obstetrics and Gynecology Hospital "Dr Shterev", Sofia Bulgaria. The research project has been conducted in accordance with ethics and law standards for medical research, as stated in active national legislation and the Declaration of Helsinki. The proposed non-interventional retrospective database does not jeopardize the confidentiality and autonomy of any patients.

Study population

Electronic medical records of 233 pregnant women diagnosed with GDM between January 2017 and January 2019 have been analyzed. GDM was diagnosed with a 2-h 75-g oral glucose tolerance test (OGTT) using the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [22] and American Diabetes Association (ADA) [9] criteria. Early GDM screening (before 20 weeks of gestation) was performed in 109 patients due to a family

history of diabetes mellitus and high body mass index (BMI). The remaining 239 women underwent universal screening at 24–28 weeks of gestation.

Pregnant women aged between 18–40 years old, diagnosed with GDM, and with a singleton pregnancy were included in the analysis. Women with multiple pregnancies and those with pre-existing diabetes (types 1 and 2) have been excluded from the study.

Patients were divided into three groups, depending on the treatment approach – metformin group (n = 70), insulin group (n = 40), and MNT group (n = 123). Only women who did not change the therapeutic strategy until the end of pregnancy were included in the study.

In 33 patients, metformin was started before pregnancy, due to evidence of insulin resistance (IR), most often in the background of polycystic ovary syndrome (PCOS). The metformin treatment was discontinued a week before the OGTT was performed and started again in those patients who met the criteria for GDM diagnosis. In the remaining 37 women included in the metformin group, the oral hypoglycemic therapy was started up to two weeks after GDM diagnosis if the glycemic target was not met with lifestyle modification (diet and exercise changes) alone. The decision to initiate metformin was also based on the pregnant woman's weight gain, medication tolerability and willingness to undergo oral hypoglycemic therapy. Target levels for blood glucose measurements were adopted from ADA guideline and were as follows: FPG < 5.3 mmol/L; 1-h postprandial glucose < 7.8 mmol/L or 2-h postprandial glucose < 6.7 mmol/L [9]. All women receiving metformin were aware by the endocrinologist of the benefits and risks of the off-label treatment and gave their informed oral consent. The initial dose of metformin varied from 500 mg to 1500 mg daily. The dose was subsequently titrated up to a maximum of 1500 mg daily to achieve target blood glucose levels. Insulin treatment was initiated when blood glucose targets were not met with metformin. But as noted above those patients who switched the therapeutic approach were excluded from the study.

Insulin was selected as first-line therapy in pregnant women who refused metformin therapy and in those who did not meet the glycemic target for pregnancy through lifestyle modification alone. In most cases (n = 32), only basal insulin (detemir) was administered to maintain normal FPG levels. The remaining patients (n = 8) were treated with a basal-bolus regimen receiving insulin aspart at meals and insulin detemir once daily.

Measurements and laboratory data

A comparative analysis of the maternal characteristics, pregnancy outcomes and neonatal characteristics of the three groups, has been performed. The following data, extracted from medical records, were analyzed:

- **maternal characteristics and pregnancy outcomes** — age, BMI, values of FPG, HbA1c, family history of diabetes, previous history of GDM, parity, conception mode, gestation age at delivery, mode of delivery, the incidence of pregnancy-induced hypertension or preeclampsia, the incidence of PCOS;
- **neonatal outcomes** — birth weight, macrosomia, baseline APGAR scores after delivery, neonatal hypoglycemia, shoulder dystocia, small-for-gestational-age (SGA), and respiratory distress.

The maternal characteristics, including BMI, values of fasting plasma glucose and HbA1c, were measured at the time of GDM diagnosis and the end of pregnancy. All observed women were Caucasian.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) v.20.0. Continuous variables are expressed as the mean ± standard deviation, and categorical variables are presented as numbers and percentages. Continuous variables were compared between the groups using Mann–Whitney U-test. Fisher's exact test and Pearson's chi-square test were used for categorical variables. The p values less than 0.05 were considered statistically significant.

RESULTS

The maternal characteristics of the observed women are presented in Table 1. Patients who needed pharmacological therapy showed significantly higher BMI at baseline. The mean FPG levels were significantly lower in the MNT group (5.27 ± 0.67 mmol/L) and metformin group (5.72 ± 0.80) compared to the insulin group (6.69 ± 0.74 mmol/L) (Tab. 1, Fig. 1A). Patients who needed pharmacological therapy showed significantly higher mean FPG levels ($p < 0.01$). Similar findings have been identified when HbA1c levels at baseline were compared (Tab. 1, Fig. 1B).

Spontaneous pregnancies predominated in metformin and MNT groups (51.4% vs 53.7%). Significant differences have been identified regarding GDM incidence in primiparous pregnancies. Regarding the mode of delivery, caesarean sections predominated in all three groups. No statistically significant differences have been found in gestational weeks at birth.

Neonatal birth weight in the metformin-treated group was lower compared to the insulin group (3154.13 ± 463 g vs 3421.79 ± 553 g, $p = 0.03$) and MNT group (3154.13 ± 463 g vs 3323.66 ± 521 g, $p < 0.01$). The biparietal diameter was larger in newborns in both the insulin and MNT groups. How-

Table 1. Maternal characteristics and biochemical measures

Maternal characteristics	Metformin group (n = 70)	Insulin group (n = 40)	MNT group (n = 123)	p value metformin vs insulin	p value metformin vs MNT
Age [years]	36.8 ± 4.9	34 ± 3.8	35.13 ± 4.3	0.01*	0.02
BMI [kg/cm^2] (1st trimester)	27.83 ± 5.351	27.17 ± 5.21	25.70 ± 5.81	NS	< 0.01*
BMI [kg/cm^2] (3rd trimester)	28.96 ± 4.21	30.53 ± 4.202	28.65 ± 3.98	NS	NS
Parity, n (%) Primiparous Multiparous	 38 (54.3%) 32 (45.7%)	 27 (67.5%) 13 (32.5%)	 68 (55.3%) 55 (44.7%)	0.02*	NS
Mode of conception, n (%) Spontaneous ART	 36 (51.4%) 34 (48.6%)	 18 (45.0%) 22 (55.0%)	 66 (53.7%) 57 (46.3%)	NS	NS
Family history of diabetes, n (%) Yes No	 42 (60.0%) 28 (40.0%)	 27 (67.5%) 13 (32.5%)	 55 (44.7%) 68 (55.3%)	NS	0.04*
FPG [mmol/L] (baseline)	5.72 ± 0.801	6.69 ± 0.74	5.27 ± 0.679	< 0.01*	< 0.01*
FPG [mmol/L] (3rd trimester)	5.06 ± 0.784	5.41 ± 0.723	5.3 ± 0.751	< 0.01*	< 0.01*
HbA1c [%] (baseline)	5.61 ± 0.9	6.29 ± 0.35	5.34 ± 0.32	< 0.01*	< 0.01*
HbA1c [%] (3rd trimester)	5.27 ± 0.9	5.58 ± 0.42	5.39 ± 0.31	< 0.01*	< 0.01*

*Statistically significant difference; ART — Assisted Reproductive Technology; BMI — body mass index; FPG — fasting plasma glucose; GDM — gestational diabetes mellitus; MNT — medical nutrition therapy; NS — not statistically significant difference; Data are presented as number (percentages) or mean ± SD

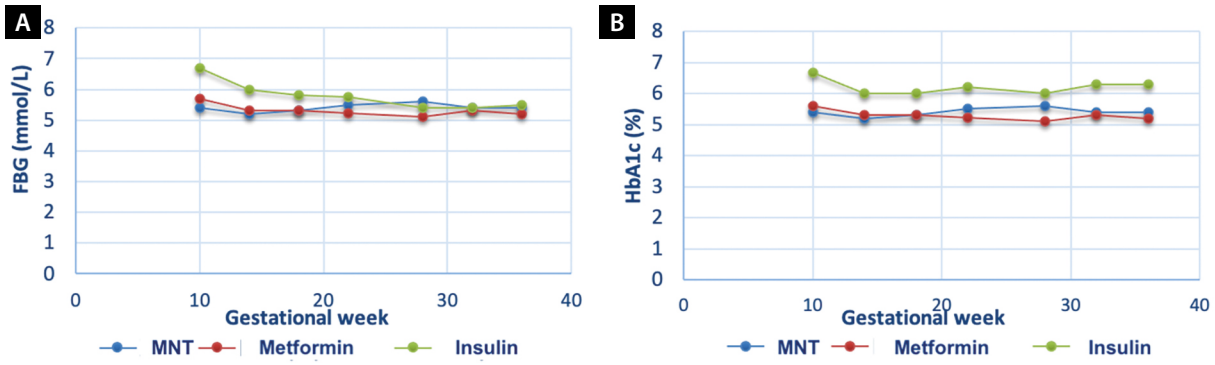

Figure 1. Glycemic control among the three groups of observed women; **A.** Fasting plasma glucose (FPG) [mmol/L] at diagnosis of gestational diabetes mellitus (GDM) and during the course of pregnancy; **B.** HbA1c [%] at diagnosis of GDM and during the course of pregnancy; MNT — medical nutrition therapy

ever, a statistically significant difference was found only in the metformin vs MNT group (p < 0.01). A significant difference in the newborn length has been identified comparing the metformin and insulin groups (p = 0.04) (Tab. 2). The lowest incidence of macrosomia (2.9%) and neonatal hypoglycemia (2.9%) was observed in the metformin group. A statistically significant difference was found regarding macrosomia incidence in the metformin vs insulin group (p = 0.01). The incidence of small-for-gestational-age (SGA) neonates in the three groups was similar. There were no newborns with baseline Apgar score under 7 in the metformin-treated group (Tab. 2).

DISCUSSION

In recent years, the benefits and risks of metformin use in pregnant women have been widely discussed. The main concern associated with metformin therapy in GDM is caused by the transplacental transport. Metformin has

Table 2. Pregnancy and neonatal outcomes

	Metformin group (n = 70)	Insulin group (n = 40)	MNT group (n = 123)	p value metformin vs insulin	p value metformin vs MNT
Pregnancy outcome					
Delivery mode, n (%) Vaginal Cesarian section	 21 (30.0%) 50 (70.0%)	 8 (20.0%) 32 (80.0%)	 36 (29.3%) 87 (70.7%)	NS	NS
Gestational age at delievery [weeks]	38.2 ± 1.2	37.6 ± 0.8	38.5 ± 1.5	NS	NS
Neonatal outcome					
Birthweight [g]	3154.13 ± 463	3421.79 ± 553	3323.66 ± 521	0.03*	< 0.01*
Length [cm]	49.40 ± 3.1	50.18 ± 2.13	49.69 ± 3.9	0.04*	NS
Biparietal Diameter [cm]	92.22 ± 2.1	93.76 ± 3.1	95.11 ± 3.2	NS	< 0.01*
Macrosomia	2 (2.9%)	6 (15.0%)	11 (8.9%)	0.01*	NS
SGA	6 (8.5%)	4 (10%)	4 (4.9%)	NS	NS
Neonatal hypoglycemia	2 (2.9%)	3 (7.5%)	6 (4.9%)	NS	NS
Baseline Apgar score < 7	0 (0%)	2 (5%)	0 (0%)	0.05*	–

*Statistically significant difference; MNT — medical nutrition therapy; NS — not statistically significant difference; SGA — small for gestational age; Data are presented as number (percentages) or mean ± SD

been shown to cross the placenta and its concentration in the umbilical cord at the time of delivery can reach more than 50% of the maternal concentrations [23].

There are observed differences in metformin effects during each trimester of pregnancy. During the first trimester, the embryo has much fewer, albeit more active mitochondria. Therefore, many clinicians prefer to use metformin until the end of the first trimester. In the later stages of pregnancy, the use of metformin may be associated with reduced nutrient supply to the fetus. This could be a prerequisite for delivering a newborn with a lower weight, which corresponds with the results listed above. However, meta-analyses show that metformin improves maternal glycemic control and insulin sensitivity, reduces pregnancy weight gain and fetal insulin resistance [24]. According to the available data, metformin is considered a non-teratogenic drug [25]. A meta-analysis conducted by Gilbert et al. [26] shows that there is no evidence of an increased risk for major malformations when metformin is taken during the first trimester of pregnancy.

As noted, in our study, in 33 patients, metformin treatment was a continuation of therapy started before pregnancy due to evidence of IR, most commonly in the background of PCOS. All pregnant women underwent aneuploidy screening by the end of the first trimester and fetal morphology scanning between 19–23 and 30–32 weeks of gestation. No teratogenic effect of metformin use in these pregnant women has been observed. In the remaining women (n = 37), oral therapy was initiated after the diagnosis of GDM. In all of them, metformin was started after the end of the first trimester. No side effects or complications for both the mother and the fetus were found. In our analysis women treated with metformin showed a significant improvement in glycemic control and less weight gain during pregnancy.

Over the past two decades, several studies have discussed the short- and long-term effects of metformin use in GDM. Metformin use during pregnancy was first studied in a cohort study involving 118 pregnant women with type 2 diabetes and GDM [27]. Due to increased perinatal mortality with metformin in the third trimester compared with insulin (11.6% vs 1.3%, $p < 0.02$), many clinicians are suspicious to consider metformin as an alternative to insulin until the results of the first large, randomized trial (Metformin in Gestational Diabetes - MiG) were published in 2008 [28]. The study was conducted in Australia and compared pregnancy outcomes in 751 women with GDM treated with metformin and insulin and divided into two groups. The results regarding neonatal hypoglycemia, respiratory distress syndrome, birth trauma, and premature birth were similar in both groups. In the metformin-treated

group was established less weight gain during pregnancy. No serious adverse outcomes associated with metformin have been observed [28].

The current study confirms the acceptable efficacy and safety profile of metformin for both the mother and the newborn. No short-term complications in the group treated with metformin were observed. During pregnancy, patients treated with metformin showed lower BMI, lower FPG, and lower levels of HbA1c ($p < 0.01$) compared to the insulin group. Our findings support observations from a previous study, conducted by McGrath et al. [29]. The results from this retrospective, case-control study show that women managed with metformin had a higher early pregnancy BMI compared to those receiving insulin or diet and lifestyle modification ($p < 0.001$). Pregnant women, successfully managed by diet and lifestyle modification had significantly lower FPG levels ($p < 0.001$) and HbA1c ($p < 0.01$) at diagnosis of GDM. Similar findings are generated by our analysis. Furthermore, the authors have observed that there were no differences regarding mode of delivery, birth weight or incidence of large/small-for-gestational-age neonates between the three groups [29].

A similar research design comparing three groups of women with GDM divided regarding the used treatment approach was adopted by several other authors [30, 31]. Tertti et al. [30] suggested that metformin is an effective treatment option for women with GDM and does not seem to be associated with higher risks for maternal or neonatal complications compared with insulin. In an observational study from New Zealand, Goh et al. [31] concluded that the use of metformin in the treatment of GDM was associated with fewer adverse pregnancy outcomes compared with insulin.

CONCLUSIONS

Current observations confirm that metformin improves maternal and neonatal outcomes in women with GDM and mild hyperglycemia. Nevertheless, metformin cannot replace insulin treatment in every GDM patient. The results from this retrospective study revealed that women with higher baseline BMI needed further pharmacological therapy to maintain euglycemia. Women with GDM, treated with metformin had a more favorable profile for all the investigated criteria. Exposure to metformin is not associated with short-term adverse maternal and neonatal outcomes.

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Conflict of interest

The authors declare no conflict of interest.

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