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Maternal and Neonatal Outcomes in Pregnant Women with Gestational Diabetes Mellitus Treated with Diet, Metformin or Insulin

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Abstract

AIM: Aim of the study was to compare outcomes of pregnancy in gestational diabetes mellitus (GDM) treated with metformin, insulin, or diet.

MATERIAL AND METHODS: The study included 48 women with GDM treated with metformin, 101 with insulin, and 200 women on a diet from the Outpatient Department of Endocrinology and University Clinic of Obstetrics and Gynecology in Skopje.

RESULTS: The groups were comparable in age, smoking cigarettes and positive family history of diabetes. Mean glycosylated haemoglobin (HbA1c) at 37 gestation week, mean fasting, postprandial glycaemia, and gestational age at delivery were lower in diet and metformin than insulin group. No differences in mode of delivery were observed between the metformin and insulin group. Women in metformin group had a significantly lower incidence of LGA newborns than diet and insulin groups. The percent of SGA new-borns was higher in insulin group than diet and metformin groups. The incidence of neonatal hypoglycemia was statistically significantly higher in the insulin group than in the metformin and diet group.

CONCLUSION: Metformin in women with GDM can improve maternal and neonatal outcomes compared with those treated with diet or insulin.

Introduction

Pregnancy itself is characterised by insulin resistance [1]. Gestational diabetes mellitus (GDM) develops if there is inadequate insulin secretion to compensate insulin resistance.

GDM increases the risk of pregnancy complications and adverse neonatal outcomes. Excessive mother to fetus glucose transfer increases the risk for large or small for gestational age newborn, neonatal hypoglycaemia and neonatal respiratory distress syndrome, as well as increased risk for preeclampsia, cesarean, preterm delivery and higher risk for development of type 2 diabetes mellitus after pregnancy in women with GDM. Meta-analysis of several randomised trials has shown that appropriate therapy can decrease maternal and fetal morbidity [2] [3]. An effective treatment regimen consists of diet alone for most patients and the administration of insulin if target blood glucose concentrations are not met with diet alone.

Prospective randomised studies demonstrated that effective treatment of hyperglycemia in women with GDM could reduce adverse perinatal outcomes [2]. The treatment is with diet, metformin or insulin. Insulin treatment is safe and effective for pregnant women, but the disadvantages of insulin are: need to give injections, the risk of hypoglycemia, the risk of excessive weight gain, and cost [1]. Therefore, oral metformin is a logical option for pregnant women with GDM. It does not induce

hypoglycemia, and it is not associated with increased weight gain. Also, metformin improves insulin sensitivity probably by activating AMP kinase and reduces hepatic gluconeogenesis, which could be beneficial for preservation of β–cell function [1]. But it has been found that metformin has a maternal to the fetal transfer rate of 10-16% which might be associated with fetal anomalies or potential adverse effects for mother and newborns [4].

The randomised trials and observational studies observed that maternal glucose levels did not differ between pregnant women treated with insulin versus those treated with an oral glucose-lowering agent such as metformin. There is a small number of studies reporting on the use of metformin during GDM pregnancy. They provide conflicting information about the safety of metformin use in GDM pregnancies or type 2 diabetes and pregnancy [1] [10] [17].

The study aimed to compare maternal and neonatal outcomes in patients with gestational diabetes mellitus (GDM) treated with metformin versus those with insulin, or diet alone.

Material and Methods

Three hundred and forty-nine women with GDM that have consulted the Outpatient Department of University Clinic of Endocrinology Diabetes and Metabolic Disorders were enrolled. From them, 48 women were treated with metformin, 101 with insulin, and 200 received no pharmacological treatment, were treated only with the dietary regimen. All were with singleton pregnancies and gave informed consent to participate in the study.

The diagnosis for GDM was made with 75 gr OGTT (normal values: a fasting level < 5.1; 1-hour level < 10.0 and 2-hour level < 8.5 mmol/L), according to The International Association for Diabetes and Pregnancy Study Group (IADPSG). Only one abnormal plasma glucose level was sufficient for the diagnosis of GDM4

The studied outcome measures were: glycemic control, maternal, and neonatal outcomes.

All women were asked to perform a daily glucose profile (fasting, pre-prandial and 1-h postprandial measurements) twice a week from the diagnostic moment of GDM until delivery, using a home glucometer (OneTouch Basic 200-200; LifeScan, Milpitas, California, USA). Multiple daily measurements (at least four a day) allowed recognition of women who should begin an anti-hyperglycemic agent. The desirable target glucose levels were: fasting glycaemia between 3.8 to 5.0 mmol/l and one-hour postprandial blood glucose concentration < 7.8 mmol/l (American Diabetes Association). At 37 week of gestation after overnight fasting, HbA1c was taken and was measured by anion-exchange HPLC instrument (DS5; Drew, USA) with a reference range of 4.2–6.5%.

The mode of treatment (diet, metformin or insulin), based on self-monitored plasma glucose values, was determined within a week after starting monitoring. Women with GDM on a diet were educated regarding an individualised diabetic diet based on pre-pregnancy weight (30 kcal/kg/day) with a caloric restriction for overweight and obese women (25 kcal/kg/day). Metformin was given at a dose of 500 mg three times a day to a maximum of 2000 mg/day based on the glycemic profile. Adjustments in the insulin doses were made if two or more glycaemic values were consistently higher than the target blood glucose concentrations, in a two-week interval. Insulin therapy in the regime of multiple injections of short (apart) and long-lasting analogue (detemir) was introduced, starting from 0.3 IU/kg of body weight. According to blood glucose profile, the insulin doses were changed by 2 to 4 units at a time.

At the first visit all patients were asked about their age, weight before pregnancy, gestational week, smoking habits and familial history of diabetes. Body mass index before pregnancy was calculated retrospectively. Weight before delivery was measured again in all patients wearing clothes without shoes in the morning. Height was measured to the nearest 1 cm with a stadiometer.

At every visit, blood pressure was measured twice in a supine position. In a case of hypertension (>145/90 mmHg), the measurement was repeated after five minutes. Preeclampsia was registered if blood pressure was >140/90 mmHg with proteinuria >0.3 g/24 h.

Mode of delivery was noted as spontaneous, assisted or caesarean section. Birth weight and the proportion of LGA (defined as birth weight > 90th percentile for local population after adjusting for gestational age and sex) and SGA (defined as a birth weight < 10th percentile for local population after adjusting for gestational age and sex) were determined. Prematurity was defined as born before 37 gestational weeks. The gestational age of newborns was estimated from the date of the last menstrual period. Neonatal serum glycaemia was measured after delivery and values lower than 2.6 mmol/l were considered as hypoglycemia. Apgar score was measured at 1’ and 5’ after delivery, but we used only values at 5’.

All neonatal outcomes were performed in University Clinic of Gynecology and Obstetrics.

Statistical analyses were performed using SPSS software for Windows, version 14.0. Dates are given as mean ± standard deviation and percent. We used a t-test for independent samples to compare the numeric variables between each of the groups; for

categorical variables, Chi-square test was used. Values of $p < 0.05$ were considered statistically significant.

Results

From 349 GDM pregnancies, 200 were treated with diet alone, 101 with insulin, and 48 with metformin.

Baseline characteristics of the women enrolled in the study are given in Table 1. It can be seen that women treated with diet have lower BMI before pregnancy, but higher weight gain during pregnancy, then the other two groups. The weight gain was lowest in the metformin group. Patients treated with insulin enrolled earlier in the study than patients from other groups. Between the three groups, no significant differences in the incidence of smoking cigarettes and familial history of diabetes were noted.

Table 1: Maternal Characteristics at Baseline

	Diet (N = 200)	Metformin (N = 48)	Insulin (N = 101)	Metfom vs. diet P	Metfom vs.insuli P	Diet vs. insulin P
Age (years)	31.5 ± 5.2	32.2 ± 4.7	32.7 ± 5.7	NS	NS	NS
Pre-pregnancy BMI (kg/m^2)	26.7 ± 5.3	28.8 ± 5.3	27.5 ± 4.9	< 0.05	NS	NS
Weight gain (kg)	10.9 ± 6.1	8.1 ± 4.9	8.7 ± 6.1	< 0.01	NS	< 0.01
Gestational week at enrolment (g.w.)	29.5 ± 5.8	28.6 ± 5.6	24 ± 7.8	NS	< 0.01	< 0.01
Smoking cigarettes (%)	20 (10%)	5 (10.4%)	11 (10.8%)	NS	NS	NS
Familiar history for diabetes (%)	105 (52.5%)	24 (50%)	62 (62%)	NS	NS	NS

Mean glycosylated haemoglobin (HbA1c) at 37 gestation week was statistically significantly lower in diet and metformin groups than in insulin group (Table 2). Mean fasting (FPG) and postprandial glycaemia (PPG) was statistically significantly lower in diet and metformin group than in insulin group (Table 2). The percent of preeclampsia was higher in the metformin group but without statistical significance between metformin and insulin groups; only between diet and other two groups.

Women treated with insulin had delivery earlier than those treated with metformin or diet alone. This difference was statistically significant. Caesarean deliveries were more likely in women treated with insulin and metformin than in the diet group (Table 2). The percent of LGA newborns was statistically significantly lower in metformin-treated group versus diet and insulin groups. The percent of prematurity was statistically significantly higher in the insulin group than in the diet and metformin groups. The percent of SGA was statistically significantly higher in the insulin group than in the diet and metformin groups. Mean birth weight in insulin group was statistically significantly lower than in diet and metformin groups. The incidence of neonatal hypoglycemia was statistically significantly higher in the insulin group compared with those treated with metformin or diet. There were no differences in Apgar scores in 5' between the three groups (Table 3).

Table 2: Maternal primary outcomes

	Diet (N = 200)	Metformin (N = 48)	Insulin (N = 101)	Metfom vs. diet P	Metfom vs.insulin P	Diet vs. insulin P
HbA1c at 37 g.w. (mean)	5.4 ± 0.9	5.3 ± 0.7	6.2 ± 1.8	NS	< 0.01	< 0.01
Fasting glycaemia mmol/l	5.1 ± 0.9	5.3 ± 0.7	5.8 ± 1.4	NS	<0.05	<0.01
Postprandial glycaemia (PPG) mmol/l	6.9 ± 1.6	7.0 ± 1.2	7.9 ± 1.9	NS	<0.05	< 0.05
Preeclampsia	1 (0.5%)	4 (8.3%)	6 (6%)	< 0.01	NS	< 0.01
Gestational age at delivery (g.w.)	38.9 ± 1.9	38.9 ± 1.4	37.5 ± 2.2	NS	< 0.01	< 0.01
Mode of delivery -spontaneous - assisted - caesarean section	86/130 (66.1%) 3/130 (2.3%) 41/130 (31.5%)	22/46(47.8 %) 0 24/46(52.2 %)	34/100 (34%) 0 66/100 (66%)	< 0.05 NS < 0.05	NS NS NS	< 0.05 NS < 0.05

There were no major complications or perinatal deaths in this study. One neonate of a mother treated with insulin had asphyxia. There were no cases of diabetic ketoacidosis or lactic acidosis.

Table 3: Neonatal primary outcomes

	Diet (N = 200)	Metformin (N = 48)	Insulin (N = 101)	Metform vs. diet P	Metform vs.insulin P	Diet vs. insulin P
Birth weight (gr)	3631 ± 650	3496 ± 480	3348 ± 739	NS	NS	< 0.01
Prematurity	13 (6.5%)	2 (4.2%)	20 (19.8%)	NS	< 0.01	< 0.01
LGA (> 2SD/%)	59 (29.5%)	6 (12.5%)	22 (21.7%)	< 0.05	< 0.05	NS
SGA (< 2SD/%)	8 (4%)	3 (6.2%)	14 (13.8%)	NS	NS	< 0.01
Neonatal glycaemia (mean, % with hypoglycae-mia)	3.3 ± 1.2 (24%)	2.8 ± 1.1 (35.4%)	2.6 ± 1.1 (51.5%)	< 0.05 < 0.05	< 0.05 < 0.05	< 0.01 < 0.01
Apgar score at 5	8.9 ± 0.7	8.6 ± 0.7	8.6 ± 0.8	NS	NS	NS

LGA-large for gestational age; SGA-small for gestational age; SD-standard deviation.

Correlation analysis found a statistically significant positive correlation between preeclampsia and pre-pregnancy BMI. Statistically significant positive correlations were found between baby birth weight and weight gain and between baby birth weight and HbA1c at 37 g.w. Also, there was statistically significant positive correlation between HbA1c and incidence of LGA newborns. Fasting plasma glucose values had a statistically significant positive correlation with pre-pregnancy BMI.

Discussion

Our study has shown that women with GDM treated with metformin had similar, even better outcomes than those treated with diet or insulin alone.

Metformin reduces hyperglycemia by

suppressing hepatic glucose output (hepatic gluconeogenesis), increasing insulin sensitivity and enhancing peripheral glucose uptake [6]. The weight gain was lower in metformin and insulin groups compared to the diet group. These effects are potentially useful during pregnancy when glucose control deteriorates with changes in insulin resistance [7].

Mean HbA1c at 37 gestation week, mean FPG and PPG were statistically significantly lower in diet and metformin groups than in the insulin group. Better glycemic profiles in the metformin group in comparison to the insulin group can be explained by reducing insulin resistance in GDM pregnancies which is the main pathophysiologic way for developing gestational diabetes in pregnancy. Similar results have been noted in other studies [8]. In this study, HbA1c was shown as an important factor for increased incidence of delivery LGA newborns. The better glycemic control means lower risk for LGA, which can be achieved with metformin.

We noted a high incidence of preeclampsia in the metformin group, identically as Hellmuth et al9. But contrary studies found that metformin may reduce preeclampsia in GDM women by reducing the endothelial activation and maternal inflammatory response to insulin resistance [8][10]. However, the percent of preeclampsia in the metformin group was not statistically significantly greater than the percent of preeclampsia in the insulin group. Fluctuating glucose levels have a stronger effect on endothelial function, which is more important in the pathogenesis of preeclampsia, than sustained hyperglycaemia [11] [12]. This can be the explanation for our findings. Unrelated to metformin use, other increased risk factors for pre-eclampsia, such as older age or overweight may exist. In our study, the groups were matched for age, but the percentage of obese woman in the metformin group was higher than in the insulin and diet groups. Also, their antihyperglycemic medication was started four weeks later than the initiation of insulin.-

Average gestational age at delivery was significantly lower in the insulin group, and consequently, the percent of prematurity and SGA newborns was higher in the insulin group. Contrary there is a number of studies with opposite findings10, [13] [14] [15] [16] [17]. Only Balani et al., [14] and Goh et al., [18] presented identical results as ours. In their studies, the percent of prematurity was lower in women treated with metformin compared with insulin group. Also, they found the higher percent of caesarean delivery in insulin group than metformin. Probably, a higher percent of LGA newborns in insulin group was responsible for higher incidence of caesarean section in those patients.

Surprisingly, although mean glycemic values were higher in the insulin group, the percent of SGA newborns was higher. It can be explained by a high incidence of prematurity in the insulin group. Similar results were presented by Lavanya et al., [19].

We found significantly fewer macrosomic neonates in the metformin group than in the diet and insulin groups. Unlike our experience, in the MiG9 trial, there was no significant difference in the proportion of LGA newborns in metformin versus insulin group. The addition of supplementary insulin in metformin group in the above study may be responsible. Similar results as ours were presented in the study of Gandhi et al., [20].

In correlation with the previous studies [9] [17] [18] [21], the incidence of neonatal hypoglycemia was reduced in the metformin group in comparison to the insulin group.

Mean Apgar scores at 5’ were almost identical in the metformin and insulin groups, higher than in the diet group, but without statistical differences. This is consistent with other studies [9] [21].

The study has several limitations. It was not randomised, and small number women were included. Baseline differences between the groups might have influenced the outcomes.

The percentage of GDM patients needing pharmacological treatment varies from 20% to 60% in various studies [22]. That’s not a small number. Insulin has several disadvantages including multiple daily injections, the risk of hypoglycemia and maternal weight gain [23]. On the other hand, metformin is more acceptable to women with GDM, it’s safe, with no significant maternal or neonatal outcomes, and has low cost. If metformin had any unanticipated adverse effect on fetal growth or well-being, there would be more iatrogenic preterm births [1]. But, the frequency of preterm births in our study was higher in the insulin group than in the metformin group. Metformin use in our study was not associated with increased perinatal complications. Even more, metformin treatment resulted in better glycemic control and improved neonatal outcomes compared with insulin. Because metformin crosses the placenta, Glueck et al., [24] assessed long-term effects of metformin on the children. They presented that growth, motor and social development in the offspring of mothers who conceived and continued on metformin did not differ from that of control babies over the first 18 months of life. So, metformin may have its place as first line GDM therapy, especially in a subgroup of patients that are overweight but not obese, but between one third and one half of women will need insulin to achieve glycemic targets. However, further clinical long-term follow-up studies are needed to determine the role of metformin as an alternative treatment to insulin in GDM patients.

In conclusion, according to the current knowledge, metformin is effective and safe in the treatment of GDM, because women with GDM treated with metformin had less weight gain and improved

neonatal outcomes compared with those treated with diet or insulin. But it is not known whether fetal exposure to an insulin-sensitizing agent, such as metformin is beneficial or harmful, and thus caution is warranted in its use in pregnancy.

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