Maternal and Neonatal Outcomes Among Women with Gestational Diabetes Mellitus Treated with Metformin in a Tertiary Hospital: A Retrospective Cohort Study

Francis Xavier Fernandez Mislang, MD,[1] Rebecca Lim Alba, MD,[1]

Abstract

Background: Gestational diabetes mellitus (GDM) is a common disorder associated with both maternal and fetal complications. Treatment for GDM requires lifestyle modification, as well as insulin and oral anti-diabetes medications to prevent unwarranted fetal and maternal outcomes.

Objective: To determine the feto-maternal outcomes of GDM patients treated with either metformin-monotherapy, insulin-monotherapy, and with insulin plus metformin (combination) therapy in a private tertiary hospital in Metro Manila

Methods: This is a retrospective cohort study involving 209 GDM patients admitted from January 2017 to December 2019. Census and chart reviews were done for demographic and clinical data. These were divided into 3 groups: metformin-monotherapy, insulin-monotherapy, and combination treated groups. Analysis of Variance was used to compare the average capillary blood glucose (CBG) levels of patients. Chi-square and Fisher's Exact tests were used for nonparametric data.

Results: Birthweight was significant across all groups: metformin-monotherapy group highest with large-for-gestational-age (LGA) at 25%, small-for-gestational-age (SGA) highest on the insulin-monotherapy group (11.3%) and appropriate-for-gestational-age (AGA) highest in the combination therapy group (84.6%). Age of gestation (AOG) at delivery ($p=0.005$), maternal CBG during labor ($p=0.007$), and chronic hypertension ($p=0.001$) were statistically significant across all groups. Multiple comparisons showed the following statistically significant results as well: chronic hypertension between metformin and combination group ($p<0.01$), AOG during delivery between metformin vs insulin group ($p=0.004$), maternal CBGs during labor between metformin vs insulin group ($p=0.022$), and insulin vs combination treatment group ($p=0.029$). Average maternal CBG levels were also showed statistically significant difference between the metformin vs insulin group ($p=0.029$).

Conclusion: Metformin may be used in controlling CBG levels in GDM patients. Although metformin may be comparable to insulin, more long-term studies need to be done to determine its long-term effects on neonates.

Keywords: gestational diabetes mellitus, neonatal outcomes, maternal outcomes, metformin, insulin

Introduction

Gestational Diabetes Mellitus (GDM) is associated with several adverse effects on the pregnant patient and increases the risk of pregnancy-related complications and adverse fetal outcomes, with an increased prevalence of macrosomia and neonatal hypoglycemia. There are several randomized studies throughout the years demonstrating that effective treatment of hyperglycemia in women with GDM could reduce adverse perinatal outcomes.[1,2]

Insulin is the most effective treatment modality for lowering glucose levels rapidly. It is the treatment of choice for most GDM patients who are severely insulin resistant. However, treatment with insulin comes with several disadvantages, including the need to give injections, the risk of hypoglycemia, the risk of excessive weight gain, and the overall cost for care.

Metformin is a practical option for pregnant women with GDM. Several studies done in Europe and the United States found that Metformin may be a suitable

[1] Endocrinology, Diabetes and Metabolism, Chinese General Hospital and Medical Center
Corresponding Author: Francis Xavier Fernandez Mislang, MD eMail: fxmislang@gmail.com

medication for control of blood sugar in pregnant women with gestational or overt diabetes mellitus.[3,4] Studies done by Saleh et al, Niromanesh et al, and Krstevska all have similar findings with the use of metformin.[1,5,6] They compared patients with metformin and those administered with insulin and noted that mode of delivery, gestational age, Apgar Score, birthweight and occurrence of tachypnea and respiratory distress were comparable between the two groups. They concluded in their study that metformin in general, is a safe choice for treatment of GDM patients. They also noted that neonatal hypoglycemia occurred twice as much in the insulin group compared to the metformin group. The studies also 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.

Simeonova-Krstevska et al also stated that women with GDM treated with metformin had less weight gain and improved neonatal outcomes compared with those treated with diet or insulin.[1] However, a study done by Priya and Kalra reported that approximately half of GDM patients receiving metformin monotherapy eventually needed insulin supplementation, which is mostly influenced by race and body mass index.[7]

Saleh et al also stated that metformin has been found to have a maternal to fetal transfer rate of 10-16% which might be associated with fetal anomalies or potential adverse effects for mother and newborns, but no studies have directly correlated congenital malformations with treatment of metformin.[5] In addition, Given et al did an exploratory case-control study looking at malformed controls via the European surveillance of Congenital Anomalies (EUROCAT).[8] They found that there was no evidence of an overall increased risk of all major congenital anomalies combined after exposure to metformin during the first trimester.

A systematic review by Dodd et al also stated that there was little or no difference in the infant birth weight (mean difference of 6.39 g, 95% CI -81.15 to 93.92), as well as hypoglycemia, hyperbilirubinemia, APGAR < 7 at five minutes, or stillbirth and neonatal death.[9] There was also a slight benefit with metformin on gestational weight gain. With the benefits stated above, metformin is a viable option as the first line for the treatment of GDM.

A retrospective study done by Maslovitz et al included 64 pregnant women who were treated with large doses of insulin (>100 units/day) to achieve euglycemia.[10] The samples were divided into two groups: the first group was treated with increasing doses of insulin solely and the second group, with addition of metformin 850mg bid along with insulin. The groups were compared for parameters of glucose control (number of daily hyperglycemia levels, time needed to achieve optimal control, maternal satisfaction on a scale from 1 to 5 and perinatal outcome (birthweight, macrosomia, shoulder dystocia, neonatal hypoglycemia). Results of the study revealed mean daily insulin requirements that were significantly higher in the insulin monotherapy group (1352.3 vs 1053.6 units, $p<0.05$). Optimal glycemic control was achieved earlier with the combined treatment (8.31.2 days vs 10.11.2 days, $p<0.05$) and was better tolerated by the participants (satisfaction score of 4.3 vs 3.6, $p<0.05$). Obstetrical performance was similar between the two groups with similar birth weights (3485.212 g vs 3387.138 g), neonatal intensive care unit admission rates, neonatal hypoglycemia and macrosomia. This study provided support that combination therapy can be used for GDM patients with minimal risk to the mother and the fetus.

Due to the limited number of researches in this area, the aim of this study is to determine the feto-maternal outcomes of patients with GDM with metformin monotherapy compared to those on insulin monotherapy or those with combination insulin plus metformin therapy

Methods

This is a single center retrospective cohort study. The data was collected between January 2017 to December 2019 via census and/or chart review of patients diagnosed with GDM admitted at the General Wards and Maternal Unit of Chinese General Hospital and Medical Center.

All pregnant patients diagnosed with GDM either on insulin therapy, metformin therapy or combination therapy admitted to the Chinese General Hospital maternal unit, charity division and general wards who are clinically diagnosed to have GDM by using the ADA 2019 Standards of Care were included. However, we did not include those who have (a) diet-controlled gestational or overt diabetes mellitus patients, (b) pregestational diabetes mellitus patients already on insulin therapy or metformin therapy (c) recognized fetal anomaly by ultrasound investigation before metformin use, if any and; (d) patients with pre-existing medical illness affecting glucose metabolism and insulin sensitivity such as prolonged steroid intake (pre-pregnancy due to certain diseases that need maintenance steroid intake), decompensated liver disease or chronic renal failure, or history of any obstetric high-risk condition (eclampsia, frank seizures).

Sample size. The sample size was computed using *G*Power*™ software. The effect size used was based on the study by McGrath.[15] According to this, gestation at metformin initiation (weeks) was statistically higher among patients given metformin only than those given metformin + insulin ($p=0.009$). The computed effect size was 1.794322, which was higher than the effect size convention of *G*Power,* thus, the effect size was set at 0.4 (largest). The computed sample size of 138 (46 per group) was estimated using $p<0.05$ α-level of significance at 99.06% actual power of analysis. This study eventually included 209 GDM patients admitted to the general wards and maternity unit of the Chinese General Hospital from January 2017 to December 2019.

Data collection tools and methods. Medical records from January 2017 up to December 2019 census from the

Table I. Comparison between metformin, insulin and combination groups, as well metformin needing supplemental insulin group on demographic profile

Parameter	Frequency (%); Mean + SD				p-value
	Total (n=209)	Metformin Group (n=60, 29%)	Insulin Group (n=97, 46%)	Metformin + Insulin Group (n=52, 25%)	
Age	33.32 ± 5.81	33.4 ± 6.96	33.21 ± 5.56	33.42 ± 4.85	0.968
Parity					
Primiparous	70 (33.49)	24 (40)	28 (28.87)	18 (34.62)	0.350
Multiparous	139 (66.51)	36 (60)	69 (71.13)	34 (65.38)	
Gravidity					
Primigravida	56 (26.79)	18 (30)	21 (21.65)	17 (32.69)	0.280
Multigravida	153 (73.21)	42 (70)	76 (78.35)	35 (67.31)	
Medical history					
Overt/GDM	208 (99.52)	60 (100)	97 (100)	51 (98.08)	0.219
Pregnancy-induced HPN					
Chronic HPN	26 (12.44)	9 (15)	11 (11.34)	6 (11.54)	0.776
Others	24 (11.48)	1 (1.67)	10 (10.31)	13 (25)	**0.001**
	113 (54.07)	29 (48.33)	52 (53.61)	32 (61.54)	0.373

Table II. Comparison between metformin, insulin and combination groups, as well metformin needing supplemental insulin group on maternal complications

Parameter	Frequency (%); Mean ± SD				p-value
	Total (n=209)	Metformin Group (n=60, 29%)	Insulin Group (n=97, 46%)	Metformin ± Insulin Group (n=52, 25%)	
Age of gestation during delivery	37.72 ± 1.5	38.17 ± 0.91	37.38 ± 1.8	37.83 ± 1.28	0.005
Blood sugar during labor	116.5 ± 21.18	112.24 ± 19.9	121.56 ± 22.71	112.19 ± 17.76	0.007
Maternal CBG levels					
Controlled	145 (70.73)	48 (81.36)	61 (64.89)	36 (69.23)	0.091
Elevated	60 (29.27)	11 (18.64)	33 (35.11)	16 (30.77)	
Mode of Delivery					
Cesarean delivery	147 (70.33)	36 (60)	72 (74.23)	39 (75)	0.123
Normal Spontaneous Delivery	62 (29.67)	24 (40)	25 (25.77)	13 (25)	

Department of Obstetrics and Gynecology were used. Demographic profiles of all the participants in the study were documented. Inclusion and exclusion criteria were applied. Parameters included age, family history of diabetes, mean gestational age for diagnosis of GDM. Frequency and proportion were used for nominal variables, median for ordinal variables, and mean and SD for interval/ratio variables. A subgroup analysis was done based on the perioperative capillary glucose levels of all recruited patients. Patients who required insulin therapy after initial metformin therapy were recorded. This was determined and verified with unclear variables via chart review of medical records and/or census from the Section of Endocrinology, Diabetes and Metabolism, if needed.

Maternal outcomes in the form of glycemic control, medical complications, and mode of delivery were documented. Neonatal outcomes, which included glucose level on the 1st hour of life, the birth weight and the Apgar Score were recorded and statistically analyzed. The study was done in accordance to the Philippine National Ethics Guidelines for Health and Health Related Research of 2017 and was approved by the Chinese General Hospital and Medical Center, Department of Medical Education and Research, Research Ethics Review Board last July 22, 2019 with RERB protocol number CGHMC RERB 2019-F-05.

Statistical analysis. Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion were used for categorical variables, median and inter quartile range for non-normally distributed continuous variables, and mean and SD for normally distributed continuous variables. *One-way ANOVA, Kruskal-Wallis test* and *Fisher's exact test* were used to determine the statistically significant differences of mean, median and frequency, respectively, among different groups. *Bonferroni multiple comparison test, Mann-Whitney U test* and *Fisher's exact test* were used for post-hoc pairwise comparison analysis. *Independent Sample T-test, Mann-Whitney U test* and *Fisher's Exact/Chi-square test* were used to determine for statistically significant differences in mean, rank and frequency, respectively, between patients requiring and did not require insulin. All statistical tests were two tailed tests. *Shapiro-Wilk* was used to test the normality of the continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at $p<0.05$ α-level of significance. *STATA 13.1*™ was used for data analysis.

Results

The comparison among groups based on the treatment does not differ significantly based on age, parity, gravidity, and most of the past medical history. Overall mean age of the respondents was 33.32 ± 5.8 years.

Table III. Comparison between metformin, insulin and combination groups, as well metformin needing supplemental insulin group on Neonatal Outcomes

Parameters	Frequency (%); Mean ± SD; Median (IQR)				p-value
	Total (n=209)	Metformin Group (n=60, 29%)	Insulin Group (n=97, 46%)	Metformin + Insulin Group (n=52, 25%)	
Birthweight	3050 (2670 to 3400)	3100 (2880 to 3510)	3090 (2590 to 3410)	2925 (2540 to 3235)	0.017
APGAR score					
1-minute	7.80 ± 1.02	7.72 ± 1.38	7.76 ± 1.03	7.96 ± 0.19	0.404
5-minute	8.86 ± 0.91	8.75 ± 1.28	8.85 ± 0.87	9	0.345
10-minute (n=6)	5.5 ± 3.02	4.67 ± 4.04	6.33 ± 2.08	-	0.560
APGAR score (< 7)					
1-minute	13 (6.22)	3 (5)	8 (8.25)	2 (3.85)	0.615
5-minute	5 (2.39)	2 (3.33)	3 (3.09)	0	0.602
10-minute (n=6)	4 (66.67)	2 (66.67)	2 (66.67)	-	1.000
Weight for gestational age					0.003
SGA	16 (7.66)	0	11 (11.34)	5 (9.62)	
AGA	158 (75.6)	45 (75)	69 (71.13)	44 (84.62)	
LGA	35 (16.75)	15 (25)	17 (17.53)	3 (5.77)	
Blood sugar (first hour)	64 (52 to 77)	60 (52 to 72)	65 (53 to 78)	64.5 (52 to 76)	0.706

Table IV. p Values of the Different Pair Comparisons According to Clinical Parameters

Parameter	Pair 1	Pair 2	Pair 3
Chronic HPN	0.052	<0.001	0.018
Age of gestation during delivery	0.004	0.668	0.236
Blood sugar during labor	0.022	1.000	0.029
Maternal CBG levels	0.029	0.137	0.137
Birthweight	0.193	0.013	0.486
Weight for gestational age	0.012	0.001	0.107

Pair 1: Metformin group versus Insulin group
Pair 2: Metformin group versus Metformin ± Insulin Group
Pair 3: Insulin group versus Metformin ± Insulin Group

Table V. Comparison between Required Insulin and Did Not Require Insulin According to Demographic Profile

Parameter	Metformin treatment during pregnancy Frequency (%); Mean ± SD		p value
	Required insulin (n=17, 28%)	Did not require insulin (n=43, 72%)	
Age	31.23 ± 5.67	34.26 ± 7.29	0.131
Parity			
Primiparous	7 (41.18)	17 (39.53)	1.000
Multiparous	10 (58.82)	26 (60.47)	
Gravidity			
Primigravida	5 (29.41)	13 (30.23)	1.000
Multigravida	12 (70.59)	30 (69.77)	
Medical history			
Overt/GDM	17 (100)	43 (100)	-
Pregnancy-induced HPN	5 (29.41)	4 (9.3)	0.101
Chronic HPN	0	1 (2.33)	1.000
Others	8 (47.06)	21 (48.84)	1.000

There was a statistically significant difference in the HPN among the respondents, with the metformin group (1.67%), Insulin group (10.31%), and Metformin + Insulin Group (25%), respectively.

Age of gestation during delivery were noted to be higher (38.17 ± 0.91 years) for the metformin group as compared to the other groupings. The results show that based on age of gestation and groupings based on medication, there is a statistically significant relationship among the variables. Blood sugar levels in the insulin monotherapy group (121.56 ± 22.71 mg/dL) were noted to be higher than the metformin monotherapy group and the combination therapy group with a *p=0.007*. (*Table II*)

Birthweight showed a statistically significant difference (*p=0.017*) with the metformin monotherapy group noted to have given birth to the heaviest infants at 3100 gms (IQR: 2880 - 3510). The weight for gestational age

also had a statistically significant difference (*p=0.003*) as the SGA was noted to be highest in the insulin monotherapy group (11.3%) while AGA was highest in the combination therapy group (84.6%). LGA was noted to be highest in percentage in the metformin monotherapy group at 25%. Blood Sugar at the first hour of neonates showed no difference among groupings.

A multiple comparison of groupings as to clinical parameters was also done. The results show that for the past medical history with Chronic HPN, those given metformin vs metformin + insulin had a statistically significant difference (*p<0.001*). The same was noted in comparing those on insulin alone vs insulin + metformin (*p=0.018*). No statistical difference was observed when comparing metformin alone vs insulin alone.

In terms of AOG during delivery, multiple comparisons show that there is a significant difference in Pair 1 (*p=0.004*) while no significant difference was seen in Pairs 2 and 3. Measuring blood sugar level during labor shows significant differences in Pair 1 (*p=0.022*) and Pair 3 (*p=0.029*). No significant difference was seen in Pair 2. For Maternal CBG levels, the difference was only observed in Pair 1 (*p=0.029*) but not in Pairs 2 and 3.

Comparing the demographic profile based on the insulin requirement, we can see that there is no significant difference among the respondents in terms of their age, gravidity, and past medical history.

We compared the maternal complications based on their insulin requirements. The results show that there is no difference based on the age of gestation and insulin requirement. We also found no statistical difference based on the mode of delivery and insulin requirement. However, we found a significant difference in the maternal blood sugar level during labor (*p=0.009*), where mothers requiring insulin have higher blood sugar levels during labor (122.71 + 19.63 mmol/L). We also found out that maternal CBG level is statistically different whether it controlled or uncontrolled (*p=0.001*)

We also compared neonatal outcomes based on maternal insulin requirements. The results show that there is no statistically significant difference when it comes with the neonatal outcomes for both requiring insulin and not requiring insulin.

Discussion

Metformin use in the management of GDM has a good number of benefits, such as reducing risk of hypoglycemia peripartum and a reduced risk of neonatal hypoglycemia based on a few studies.[16-18] However, metformin use in pregnancy is thought to be inadequate to control CBG levels. This has been demonstrated in a few patients who eventually needed insulin perioperatively. The trend of sugar levels increased during admission in some patients treated with metformin alone and needed supplemental short-acting insulin to keep sugar levels within control. This was seen in 17 patients in the metformin-treated group, with mean blood sugars perioperatively at 122.71 ± 19.63 mg/dL as compared to those not needing insulin (108 $\pm$ 18.62 mg/dL). We looked at the maternal outcomes based on the insulin needed. The result shows that there is a significant difference in the maternal blood sugar level during labor and maternal CBG. In terms of neonatal outcomes for both groups, no statistically significant differences were found in both.

A review by Priya et al also stated that metformin, although generally deemed safe in pregnant women, freely crosses the placenta, which may lead to significant fetal exposure.[7] However, several randomized, controlled trials showed that metformin may help reduce weight gain in the pregnant state and reduce the risk of neonatal hypoglycemia.[16,18] In our study, neonatal hypoglycemia was observed almost equally across all groups. The metformin group who needed insulin perioperatively was noted to have given birth to the heaviest neonates at 3250 grams (3100 - 3450) which is not statistically significant. This agrees with the study by Priya et al, as they have seen similar birthweights in metformin-treated patients compared to insulin-treated and glyburide-treated patients.[7]

In a study by Bashir et al, metformin was noted to have less neonatal hypoglycemia and macrosomia compared to GDM patients who were diet-controlled.[19] They claimed that the adverse effects of GDM on pregnancy outcomes are multifactorial and include maternal age, maternal obesity, and gestational weight gain, which was mostly addressed by metformin. However, blood sugar lowering effects of insulin far outweigh metformin, and the increased birth weight may be attributable to metformin-treated patients who were inadequately controlled and eventually supplemented with insulin therapy, as reflected in our study, with maternal blood sugar levels being highest in the insulin group perioperatively at 121.56 $\pm$ 22.7 mg/dL.

The gestational age at which GDM is detected is critical. This is because women who are diagnosed with diabetes mellitus for the first time in the first half of their pregnancy are almost always diabetic afterward. They are more likely to suffer obstetric problems, recurrent GDM in subsequent pregnancies, and Type 2 diabetes mellitus later in life.[20] Our study shows that those requiring insulin may lead to higher blood sugar during labor and higher birthweight among neonates.

The limitation of this study was that it did not consider the period or age of gestation each patient had been on treatment. The data is also skewed in favor of the insulin monotherapy group, which had a much higher number of participants than the other groups. Another limitation was the inability to determine when each of the treatments were started and the dose of metformin as well. Furthermore, because this study relied on chart review, the data collected is vulnerable to human error, with no verification.

A randomized, controlled study is suggested to reinforce the findings in our study.

Conclusion

The use of metformin alone as an anti-hyperglycemic agent in GDM may be adequate in controlling blood sugar levels. However, a subset of patients may need supplemental insulin perioperatively to maintain adequate blood sugar control. Furthermore, birthweight in metformin-treated GDM patients is acceptable, compared to those who were treated with metformin plus insulin and insulin alone. Neonatal hypoglycemia frequencies were comparable to that of insulin monotherapy patients, as well as across all the other sub-arms.

Based on our study, metformin alone may be used as treatment for GDM patients. More studies are recommended, particularly randomized controlled trials comparing metformin alone, insulin alone and combination therapy. Fetal and maternal long-term outcomes should also be investigated.

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