The Journal of Obstetrics and Gynecology of India (November–December 2019) 69(6):490–494
https://doi.org/10.1007/s13224-019-01216-4

ORIGINAL ARTICLE

Maternal and Neonatal Outcomes in Patients of Gestational Diabetes Mellitus on Metformin Therapy

Shubhi Gupta[1] · **Navneet Takkar**[2] · **Poonam Goel**[2]

Received: 13 September 2018 / Accepted: 4 March 2019 / Published online: 23 March 2019

Abstract

Background Present study carried out in a tertiary referral hospital in North India attempts to determine the maternal and neonatal outcomes of metformin therapy in patients of gestational diabetes mellitus.

Objectives To evaluate maternal and neonatal outcomes in patients of GDM on metformin therapy and to study its adverse effects.

Method In this prospective observational study, all women diagnosed with GDM not controlled by medical nutrition therapy were started on metformin therapy and the maternal and neonatal outcomes were studied.

Results A total of 104 patients of GDM, not controlled on MNT and requiring pharmacotherapy, were enrolled for the study. An important clinical data from the study were that in 63.5% of patients there was no family history of diabetes mellitus. Average weight gain during pregnancy ranged from 6 to 10 kg. Glycemic control was achieved in 96.2% of patients with varying doses of metformin therapy, and it reached statistical significance. Duration of metformin therapy ranged from a minimum of 2 months to a maximum of 6 months. No serious side effects were noted except for hypoglycemia in one patient. Patient acceptability toward metformin intake was good. Mean birth weight of newborns was 2972 ± 280 g, and no case of fetal macrosomia was seen. Neonatal hypoglycemia was seen in 3.8% of the babies and 6.7% required NICU admission. No case of congenital malformation was reported.

Conclusions Metformin is a clinically effective, inexpensive and safe drug for treating gestational diabetes mellitus.

Keywords Gestational diabetes mellitus · Metformin · Maternal and neonatal outcomes

Introduction

Gestational diabetes mellitus has become an important high-risk pregnancy in the modern era. It is on the rise especially in South Asian countries like India, where the prevalence is estimated to range from 3.5 to 21% [1]. Conventional therapy in the management of women with gestational diabetes mellitus has typically been achieved with diet, exercise and insulin therapy. Oral hypoglycemic agents such as metformin and glyburide are proving to be attractive alternatives to insulin due to their ease of administration, better patient adherence and lower cost. Metformin is a biguanide which is a FDA-approved class B drug in pregnancy. It achieves euglycemia primarily by suppressing hepatic gluconeogenesis and enhancing peripheral glucose uptake [2].

This study was designed to evaluate the maternal and neonatal outcomes of metformin therapy in women with GDM in terms of glycemic control, weight gain during pregnancy, birth weight of the baby, hyperbilirubinemia, hypoglycemia in the neonate and need for NICU care.

Dr. Shubhi Gupta is a Senior resident at JISNH Sector 20D, Chandigarh 160020. Dr. Navneet Takkar is a Associate Professor at Department of Obstetrics and Gynecology, D Block, Level IV, GMCH, Sector 32, Chandigarh 160030. Dr. Poonam Goel is a Professor at Department of Obstetrics and Gynecology, D Block, Level IV, GMCH, Sector 32, Chandigarh 160030.

✉ Shubhi Gupta
shubhigupta162@gmail.com

[1] JISNH Sector 20D, Chandigarh 160020, India

[2] Department of Obstetrics and Gynecology, D Block, Level IV, GMCH, Sector 32, Chandigarh 160030, India

Methods

This prospective observational study was done over 2 years in a tertiary care hospital. Study was approved by the Institutional Ethics Committee. Study population consisted of 104 pregnant women with GDM not controlled on medical nutrition therapy, who were willing to undergo trial for the study. An informed consent about the patient's participation and consent for prospective data collection on the pregnancy outcome was taken from patients. All pregnant women receiving prenatal care at the obstetrics clinic were screened using a 50-gm glucose challenge test (GCT). Women with a 1-h glucose level of 130 mg/dl or more were given a 3-h 100 g glucose tolerance test. Using Carpenter and Coustan criteria, women with two or more abnormal values were diagnosed as having GDM. All women were given counseling on diet and regular physical exercise. The GDM patients were initially placed on dietary instruction from a nutritionist. Daily caloric allotment was based upon body mass index (BMI) as follows: 15 kcal/kg for obese pregnant women (BMI > 30 kg/m^2), 22 kcal/kg in overweight pregnant women (BMI > 25–30 kg/m^2), 30 kcal/kg in normal body weight (BMI = 20–25 kg/m^2) and 40 kcal/kg for pregnant women who are less in the body weight (BMI < 20 kg/m^2).

Carbohydrate intake was restricted to 45% of calories with the remainder divided between protein (20%) and fat (35%). Total calories were distributed as approximately 10% for breakfast, 30% each for lunch and dinner and approximately 30% as snacks. The diet was divided into three meals and three snacks. An exercise program of 30 min of walking per day was recommended. Women with GDM inadequately controlled by diet and exercise were started on metformin therapy. The objective was to maintain fasting glucose levels of 95 mg/dl or less and postprandial levels of 120 mg/dl or less according to the American Diabetes Association (ADA) guidelines. Women were asked to participate in the study if two or more readings were abnormal on medical nutritional therapy, i.e., diet and exercise. When selected, their fasting and postprandial plasma blood glucose was monitored biweekly. The initial dose of metformin was 500 mg twice daily and was increased up to a maximum daily dose of 2000 mg if glycemic targets were not met. Patients with only fasting hyperglycemia were started on a single night dose of 500 mg metformin. Metformin was continued until the time of delivery. Insulin was added if glycemic control was not achieved despite maximum dose of metformin.

Pregnancy outcomes were recorded by following them till 6 weeks after delivery. Maternal outcome measures were weight gain, duration and dosage of metformin to achieve glycemic control and to study its maternal complications. The neonatal outcome measures were to study birth weight, incidence of preterm birth, shoulder dystocia, perinatal mortality, macrosomia, metabolic complications and NICU care. Patients with overt diabetes mellitus were excluded from the study.

Statistical analysis was carried out using Chi-square test for categorical variables and Student's t test for numerical data. Pearson coefficient of correlation was calculated to find out association between metformin therapy and maternal and neonatal outcomes. Regression analysis using ANOVA was done, and odds ratio was calculated for comparing various outcomes.

Results

This study included a sample population of 104 women with GDM, in the age group ranging from 19 to 44 years, and the mean age was found to be 30 years ± 4.263. An important finding of the study was that most of the GDM patients were in the younger age group, i.e., 26–35 years, and only 3.8% women were in the above 35 years group. As regards socioeconomic status, very few patients (2.9%) belonged to the lower socioeconomic group and about 90% women were in the middle socioeconomic strata. 69.23% of our patients were residing in urban areas as compared to 30.77% of patients who came from rural areas. Also, an important clinical data from the study were that 63.5% of patients did not have a family history of diabetes mellitus. It was also observed that maximum number of patients in the study (48.1%) who had GDM, had a normal pre pregnancy BMI. (Table 1).

Both fasting and postprandial hyperglycemia was seen in 37.5% of the patients, whereas most of the patients had only postprandial hyperglycemia (62.5%). For control of fasting hyperglycemia as a component of abnormal GTT, a bedtime dose of metformin was prescribed, while patients with only postprandial hyperglycemia were well controlled on metformin.

A good glycemic control was achieved using various doses of metformin ranging from 500 mg HS to 1000 mg BD. Most of the patients (47.2%) required metformin in the dose of 500 mg BD, which was given both with breakfast and with dinner. A bedtime dose of 500 mg HS was given at 10 pm in 19.1% of patients to control fasting hyperglycemia. Maximum number of patients (96.2%) achieved a good glycemic control on these dosages, and only four patients required insulin in addition to metformin. The maximum dose of metformin used in our study population was up to 1000 mg BD that is up to 2 g/day. Also, the patient compliance was good as escalating dosages of metformin were prescribed. Most of the patients (41.3%) on metformin had a weight gain between 6 and 10 kg. In our study, it was

Table 1 Baseline characteristics

Baseline characteristics	Study population ($n=104$)	Mean/%
Age	19–44 years	30 ± 4.263 years
Gravida		
Primigravida	43	41.35%
Multigravida	61	58.65%
Socioeconomic status		
Upper	0	0%
Upper middle	45	43.3%
Lower middle	50	48.1%
Upper lower	6	5.7%
Lower	3	2.9%
Educational status		
Illiterate	2	1.9%
Primary education	18	17.3%
Up to tenth	36	34.7%
Graduate	27	25.9%
Postgraduate	21	20.2%
Background		
Urban	72	69.23%
Rural	32	30.77%
Occupation		
Working	77	74%
Housewife	27	26%
Family history		
DM	27	26%
DM and HTN	4	3.8%
HTN	7	6.7%
None	66	63.5%
BMI (kg/m^2)		
18–25	50	48.1%
25.1–30	33	31.7%
30.1–35	21	20.2%

inferred that there was appropriate maternal weight gain in most of the patients and this could be attributed to metformin therapy (Tables 2, 3).

Only four patients required insulin in addition to metformin to achieve adequate glycemic control. No significant side effects due to metformin therapy were encountered in our study. Only one patient had symptomatic hypoglycemia when treated for fasting hyperglycemia with a bedtime dose of 500 mg HS and hence required discontinuation of metformin therapy and change over to insulin therapy. None of our patients encountered any gastrointestinal side effects despite receiving metformin ranging from 2 to 6 months duration. This could be due to the rational dose titration and prescription of escalating dosages of metformin therapy in the study population. Duration of metformin ranged from minimum of 2 months to a maximum of 6 months.

Table 2 Dose titration used on metformin therapy

Dosages (mg)	No. of patients	Percentage
500 mg BD (with breakfast and with dinner)	49	47.2
500 mg HS (after dinner at 10 pm)	18	17.3
750 mg BD (with breakfast and with dinner)	14	13.4
500 mg WBF (with breakfast)	13	12.7
1000 mg BD (with breakfast and with dinner)	6	5.8
750 mg HS (after dinner at 10 pm)	2	1.8
750/500 (with breakfast and with dinner)	1	0.9
1000 mg WBF (with breakfast)	1	0.9
Total	104	100.0

Maximum number of patients (33.7%) required metformin for a period of 5 months, followed by a period of 4 months in 27.9% of the patients.

The mean birth weight in our study group was 2972 ± 280 g. Most of the babies (74.1%) had a birth weight between 2.5 and 3.5 kg. Fetal macrosomia and shoulder dystocia were not seen in any of the newborns of the study population. Only 1.9% of newborns in the study population had an APGAR of ≤ 7 at 1 min of birth. Similarly, an APGAR score of ≤ 7 at 5 min was found only in one baby. This baby was born at 29 weeks of gestation and ultimately expired after 7 days of NICU stay due to sepsis, thus making this the only case of neonatal mortality of our study. Most of the babies in the study population did not have any neonatal complications, but among the ones who had complications, hyperbilirubinemia was most commonly seen, accounting for 24% of all the neonatal complications. Only 3.8% and 1.9% babies had hypoglycemia and respiratory distress, respectively, while 6.7% required admission and care at the neonatal intensive care unit. Two patients had still births in our study group due to noncompliance with antenatal follow-up. The first patient did not come for routine antenatal follow-up despite the fact that she had decreased fetal movements for two days. The second patient also had Doppler changes (umbilical artery Doppler 4.6) in addition

Table 3 Net weight gain during pregnancy

Weight gain (kg)	No. of patients	Percentage
1–5	29	27.9
6–10	43	41.3
11–15	22	21.2
15–20	8	7.7
> 20	2	1.9
Total	104	100

to noncompliance to antenatal follow-up, adding on to the risk of perinatal mortality. No gross congenital malformation was observed in any newborn of the study population (Table 4).

Discussion

The management of GDM is important because appropriate therapy can decrease adverse pregnancy outcomes, particularly macrosomia. In our study, maternal and fetal outcomes of 104 patients on metformin therapy in gestational diabetes mellitus were assessed. It was a prospective observational study. When given a choice of treatment, injectable (insulin) versus oral medication (metformin therapy), our patients were easily willing to take oral medication. Also, 63.5% of patients did not have a family history of diabetes mellitus which was in comparison with the study by George et al. [3] wherein 50.6% of patients did not have a family history of diabetes mellitus in the metformin arm. Therefore, it reinforces the need for universal screening in the Indian population as more than half of the patients did not have a family history of diabetes mellitus.

Maternal Outcomes

The mean age group of the study population was 30 ± 4.263 years, and this was comparable to the age group in the study by Niromanesh et al. [4] in which the mean age was 30.7 ± 5.5. A good glycemic control was achieved both in terms of postprandial and fasting hyperglycemia such that only four (3.8%) patients in our study group required additional insulin versus 14 to 46% in the meta-analysis by Kitwitee et al. [5]. The low incidence of women requiring insulin therapy (3.8%) in our study could be due to the variation in dosage forms ranging from 500 mg HS to 1000 mg BD (Table 2) and a good patient compliance. The dosage of metformin used was mainly 500 mg BD. But dosages as high as 1000 mg BD have also been used in the study. The MiG trial used a maximum dose of up to 2500 mg, whereas in our study, we used a maximum dose of up to 2000 mg/day [6]. The NICE guidelines also recommend metformin in similar dosage as the first line therapy in the management of GDM [7].

Duration of metformin therapy ranged from a minimum of 2 months (9.6%) to a maximum of 6 months (10.6%). Most of the patients (33.7%) received metformin for a period of 5 months. There are no comparable data on duration of metformin therapy in the literature.

Serious adverse effects from metformin were not encountered in our study. Only one patient had hypoglycemia and no patient reported gastrointestinal side effects. Metformin use was also associated with a lower risk of PIH (4.8%). With respect to preterm birth, only 8 out of 104 patients (7.7%) had preterm vaginal delivery. However, the MiG trial showed a higher preterm delivery rate in the metformin group (12.4%) [6].

Most of our patients (41.3%) had a weight gain between 6 and 10 kg while on metformin therapy. These data were comparable to the results of Kitwitee et al. [5].

Maternal complications both in the antenatal and postpartum period were minimal in our study. Only one patient in the antenatal period had significant hypoglycemia requiring discontinuation of metformin therapy, while five patients in the postpartum period had maternal complications which were, postpartum hemorrhage in two (1.9%) patients, wound dehiscence in two (1.9%) patients and one (0.9%) patient had puerperal sepsis.

Table 4 Perinatal outcomes

Outcome	Frequency	Percentage
Hypoglycemia	4	3.8
Hyperbilirubinemia	25	24.0
Respiratory distress	2	1.9
NICU care	7	6.7
Birth weight (2.5–3.5 kg)	78	74.1
Still born	2	1.9

Neonatal Outcomes

Though metformin crosses the placenta, it has no teratogenic effects [8]. Data from this study reinforce the conclusions of the MiG trial, as in the study we found no increase in adverse perinatal effects on babies exposed to metformin [6]. The mean birth weight in our study group was 2972 ± 280 g. Birth weight more than the 90th centile was not encountered in any baby in our study group, hence implying that no baby was macrosomic. However, the incidence of respiratory distress was lower in our study as compared to the MiG trial (p value $= 0.5438$) [6]. The incidence of neonatal hypoglycemia and hyperbilirubinemia in our study was similar to that seen in the study by George et al. [3]. NICU care was given to 6.7% of neonates. Two perinatal deaths were reported in our study group, and they were most likely due to poor patient compliance. There was no case of congenital malformations in our study.

The strengths of our study were, it was a prospective study and most patients received metformin for an average duration of 5 months during antenatal period. The limitations of our study were that the number of participants was not large. Also, we have not evaluated the long term outcomes in infants exposed to metformin therapy.

Conclusions

Metformin treatment in gestational diabetes had advantages of appropriate maternal weight gain, minimal risk of maternal hypoglycemia, cost effective oral therapy with good patient compliance and acceptability. Our study showed statistical significance in terms of glycemic control with metformin therapy. Metformin therapy is associated with good maternal and neonatal outcomes and hence can be recommended for treating gestational diabetes mellitus. These findings are important for designing future multicenter studies with bigger sample size.

Funding Information The authors declare that this study was not funded by any organization as facilities were available in Government Medical College free of cost as far as treatment of pregnant women was concerned.

Compliance with Ethical Standards

Conflicts of interest There is no conflict of interest.

Ethical Statements All the procedures followed in study were in accordance with the ethical standards of institution, and ethical committee of institution had critically evaluated the study and its methodology and given the approval before study was started. I am sending scanned document of the approval with this title page, kindly make note of it.

References

1. Ainuddin J, Karim N, Hasan AA, Naqvi SA. Metformin versus insulin treatment in gestational diabetes in pregnancy in a developing country. A randomized control trial. Diabetes Res Clin Pract. 2015;107:290–9.
2. Spaulonci CP, Bernardes LS, Trindade TC, Zugaib M, Francisco RP. Randomized trial of metformin vs insulin in the management of gestational diabetes. Am J Obstet Gynecol. 2013;209:34.
3. George A, Mathews JE, Sam D, Beck M, Benjamin SJ, Abraham A, Antonisamy B, Jana AK, Thomas N. Comparison of neonatal outcomes in women with gestational diabetes with moderate hyperglycemia on metformin or glibenclamide: a randomized controlled trial. Aust N Z J Obstet Gynaecol. 2015;55:47–52.
4. Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial. Diabetes Res Clin Pract. 2012;98:422–9.
5. Kitwitee P, Limwattananon S, Limwattananon C, Waleekachonlert O, Ratanachotpanich T, Phimphilai M, Nguyen TV, Pongchaiyakul C. Metformin for the treatment of gestational diabetes: an updated meta-analysis. Diabetes Res Clin Pract. 2015;109:521–32.
6. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–15.
7. National Institute for Health and Clinical Excellence. NICE clinical guideline CG63. Diabetes in pregnancy. Management of diabetes and its complications from pre-conception to the postnatal period. London: NICE; 2008, 2015, 2017.
8. Ryu RJ, Hays KE, Hebert MF. Gestational diabetes mellitus management with oral hypoglycemic agents. Semin Perinatal. 2014;38:508–15.

About the Author

Dr. Shubhi Gupta has obtained MBBS from Government Medical College and Hospital, Chandigarh, MD in Obstetrics and Gynecology from Government Medical College and Hospital Chandigarh, and currently working as a senior resident at a private hospital in Chandigarh.