Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2020, 10, 1036-1044
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Predictive Factors of Successful Treatment of Gestational Diabetes with Metformin Monotherapy

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How to cite this paper: Aboelfath, A.M.K. and Sharaf El din, M.T.A. (2020) Predictive Factors of Successful Treatment of Gestational Diabetes with Metformin Monotherapy. *Open Journal of Obstetrics and Gynecology*, **10**, 1036-1044.
https://doi.org/10.4236/ojog.2020.1080097

Received: July 18, 2020
Accepted: August 11, 2020
Published: August 14, 2020

Abstract

Objective: To evaluate the factors affecting the success of metformin in management of GDM. **Methods:** A prospective cohort study was done for 94 patients diagnosed with GDM from April 2019 to March 2020 who needed pharmacological treatments in addition to diet and lifestyle modification. Cases treated with metformin monotherapy were compared with others who needed insulin in addition to metformin for glycemic control. Patient characteristics, glycemic control data and neonatal outcome were evaluated. Univariate and multivariate analysis was done to find the independent factors affecting the success of metformin. **Results:** Of 94 patients with GDM who needed pharmacological treatment, 73 (77.6%) used only metformin for treatment of GDM and 21 (22.4%) needed insulin to be added to metformin. Multivariate analysis revealed that BMI was the only significant factor that affects the success of metformin alone in control of GDM ($p = 0.03$). ROC curve of BMI showed that the cut off value of the highest sensitivity is 32.1 above which metformin monotherapy failed to control GDM. **Conclusion:** Metformin can be considered as a safe and effective drug for treatment of GDM. Obesity was found as a predictive factor for failure of metformin monotherapy.

Keywords

Gestational Diabetes, Metformin, Insulin

1. Introduction

Gestational diabetes mellitus (GDM) is diagnosed when a pregnant lady develops hyperglycemia without previous history of diabetes and it is considered as a serious pregnancy complication [1] [2]. About 3 to 25 percent of pregnancies all over the world are complicated by GDM [3] [4]. The first step in management is

trial to control blood sugar with diet [5] [6]. Diet and physical activity fail to control the condition in about 15% to 60% of cases [7]. Insulin was used as the standard treatment of GDM since 1920s. Recently metformin has been considered as an accepted oral alternative for treatment of hyperglycaemia of GDM [8]. It has the advantage over the use of insulin of being an oral drug with better patient compliance and lower cost [9]. Although metformin is as effective as insulin in blood sugar control, in many cases we need to add insulin to metformin for better maternal and fetal outcome [10].

The aim of our study is to evaluate the factors that affect the success of metformin in management of GDM.

2. Patients and Methods

This prospective cohort study was done for patients attending the antenatal care clinic of Zagazig University hospital in Egypt from April 2019 to March 2020. The study was accepted by the ethical committee of faculty of medicine of Zagazig University. Two hundred patients diagnosed with GDM were enrolled in the study. An informed consent was taken about the patient's participation and acceptance of data collection. Diagnosis of gestational diabetes was based on 100 gm glucose 3 hours GTT (Glucose tolerance test) after fasting for 8 hours. We used Carpenter-Coustan criteria with fasting, 1-hour, 2-hour, and 3-hour plasma glucose levels with lower threshold values of 95 mg/dL, 180 mg/dL, 155 mg/dL, and 140 mg/dL respectively. Diagnosis was established if two values or more were at or above these values [11]. All Patients offered a two weeks trial to control blood sugar with a balanced diet and 30 minutes of daily exercise. Our target was to keep fasting blood glucose below 95 mg/dl and the two hours post prandial below 140 mg /dl. Patients in whom diet and exercise failed to control GDM were included in the study, with the gestational age between 24 and 32 weeks and 18 - 40 years old. Twin pregnancies, fetal growth restriction, congenital anomalies diagnosed by ultrasonography, other medical disorders (cardiac, hepatic or renal troubles) and patients on drugs that alter blood glucose were excluded from the study. Metformin was given to all patients who met our inclusion and exclusion criteria with a starting dose of 500 mg BD, follow up was done on a three times weekly basis by measuring fasting and 2 hours postprandial blood glucose. The dose of metformin was increased weekly up to 2000 mg daily. Insulin was added if the maximum dose of metformin failed to control blood sugar. Analysis of data was done for two groups: those who respond to metformin alone (Group I) and those who needed insulin supplementation (Group II).

Maternal data collected were: GA (gestational age), parity, OGTT and BMI at the start of the study, maternal weight gain throughout pregnancy, results of follow up blood sugar and any pregnancy complications. Neonatal outcome measures were: The age of birth, NICU admissions, birth weight and birth trauma.

Statistical analysis

Data were collected, tabulated and analyzed. Quantitative continuous data were represented by mean ± SD, while categorical data were represented by number (absolute frequency) and percentage (relative frequency). Differences between the metformin only group and the metformin and insulin group were tested by independent t-test when quantitative and by chi-square test or Fisher exact test when categorical. Multivariate analysis was done by cox proportional hazard test. A p-value of <0.05 was considered statistically significant for all analyses. Data were analyzed using SPSS version 20.

3. Results

Two hundred pregnant women with GDM were followed up during the study period. One hundred & six patients were not included in the study because their blood glucose was controlled with diet and physical exercises. Ninety four patients met our inclusion and exclusion criteria, 73 (77.6%) of them used only metformin for treatment of GDM, and 21 (22.4%) needed insulin to be added to the metformin (Figure 1).

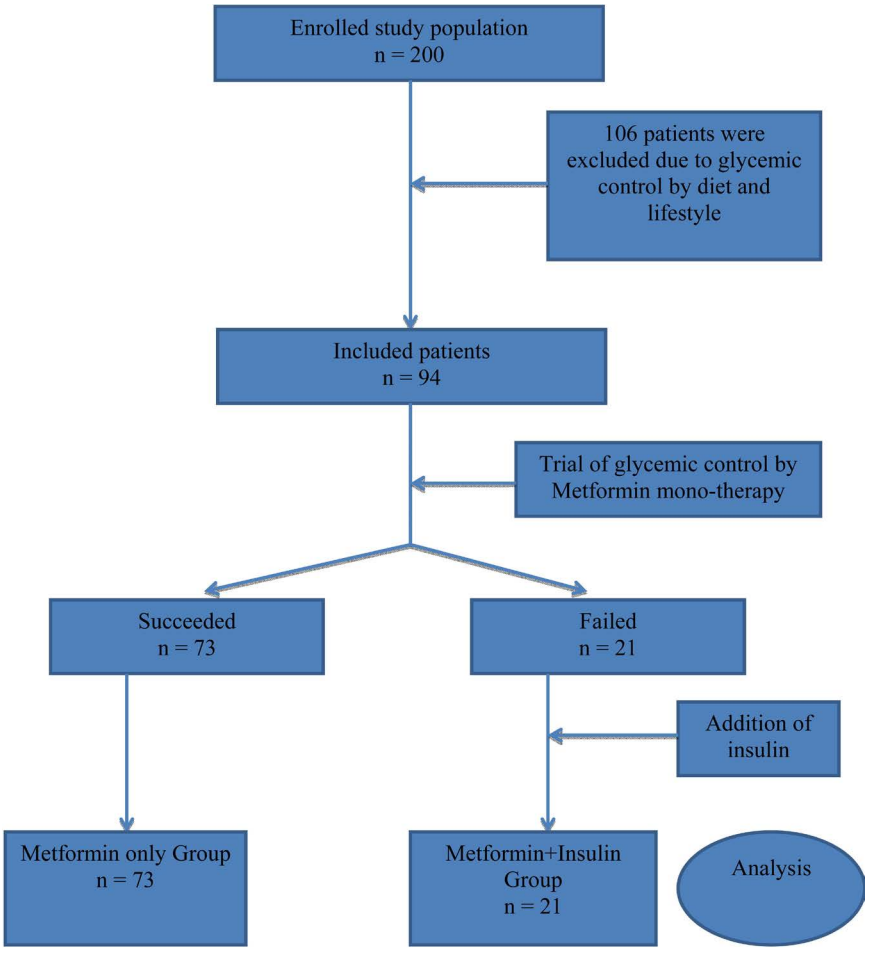

Figure 1. Consolidated standards of reporting trial (CONSORT) flow diagram of the patients through the study.

The mean and standard deviation of BMI of the all patients was (31.5 ± 4.2) and other maternal characteristics were shown in Table 1.

Table 2 shows that there was no significant difference between both groups regarding glycemic control during the whole period of follow up. Also the third trimester HbA1c was not significantly different in both groups.

All obstetric and neonatal criteria were not significantly different in both groups. As shown in Table 3.

In Table 4 univariate analysis shows that primiparity and younger age increase the chance of successful treatment with metformin monotherapy, and, therefore, considered as protective factors. On the other hand, obese patients had a higher chance of need for insulin supplementation. The other factors analyzed did not show any significant difference. Multivariate analysis revealed that BMI was the only significant factor that affects the success of metformin alone in control of GDM with cut off value of highest sensitivity (32.1) as shown in the ROC curve, Figure 2.

Table 1. Patient characteristics.

	Of the study population
Continuous data (mean ± SD)	
Age (years)	28 ± 3.5
BMI (Kg/m^2)	31.5 ± 4.2
GA at diagnosis (weeks)	26.7 ± 2.4
GA at start of treatment (weeks)	28.5 ± 1.9
OGTT (mg/dL)	
– Fasting	108.5 ± 8.9
– 1 hour	210.6 ± 15.3
– 2 hours	179.6 ± 10.7
– 3 hours	148 ± 6.7
Categorical data, No (%)	
Parity	
– Primigravida	38 (40.4)
– Multigravida	56 (59.6)
Hypertension	
– Pre-gestational	4 (4.2)
– Gestational	7 (7.4)

SD: Standard deviation, BMI: Body mass index, GA: Gestational age, HbA1c: Glycosylated hemoglobin, OGTT: Oral glucose tolerance test.

Table 2. Glycemic control.

	Metformin alone (Group I) n = 73	Metformin + insulin (Group II) n = 21	P-value
Maternal weight gain till delivery (kg)	4.6 ± 0.9	4.7 ± 0.7	0.26*
Mean fasting glucose level during first week (mg/dL)	93.6 ± 2.6	93.8 ± 2.8	0.498*

Continued

Mean 2 h post-prandial glucose level during first week (mg/dL)	122.5 ± 8.1	123.2 ± 10.3	0.213*
Mean fasting glucose level during first 2 weeks (mg/dL)	101.2 ± 3.5	101.7 ± 5.6	0.414*
Mean 2 h post-prandial glucose level during first 2 weeks (mg/dL)	140.5 ± 14.3	141.9 ± 12.3	0.176*
Mean fasting glucose level during last week (mg/dL)	79.9 ± 7.7	81.2 ± 8.6	0.211*
Mean 2 h post-prandial glucose level during last week (mg/dL)	111.3 ± 14.3	113.9 ± 10.8	0.184*
Mean fasting glucose level during last 2 weeks (mg/dL)	86.8 ± 10.7	88.9 ± 9.5	0.231*
Mean 2 h post-prandial glucose level during last 2 week (mg/dL)	112.2 ± 6.8	114 ± 5.2	0.342*
Maternal hypoglycemia, n (%)	7 (9.5)	3 (14.2)	0.17†
3rd trimester HbA1c (gr/dL)	6.1 ± 0.3	6.0 ± 0.9	0.54*

*: Independent t-test, †: Fisher exact test.

Table 3. Perinatal outcome.

	Metformin alone (Group I) n = 73	Metformin + insulin (Group II) n = 21	P-value
Continuous data, (mean ± SD)			
Apgar score at 1 min	7.9 ± 0.8	7.7 ± 0.9	0.114*
Apgar score at 5 mins	9.5 ± 0.5	9.4 ± 0.6	0.231*
Neonatal weight at birth (g)	3542.3 ± 189.2	3568.5 ± 245.6	0.135*
Categorical data, No (%)			
Cesarean section	42 (57.5)	15 (71.4)	0.15**
Prematurity	2 (2.7)	1 (4.7)	0.18†
Neonatal hypoglycemia	9 (12.3)	4 (19.1)	0.22†
Macrosomia (≥4000 g)	10 (13.7)	8 (38.1)	0.13†
Neonatal congenital anomalies	0 (0.0)	0 (0.0)	-
Neonatal distress	10 (13.7)	4 (19.1)	0.21†
Neonatal ICU admission	19 (26)	6 (28.6)	0.12†
Neonatal jaundice	3 (4.1)	1(4.7)	0.25†
Still birth	1 (1.3)	0 (0.0)	0.07†

SD: Standard deviation, ICU: Intensive care unit, *: Independent t-test, **: Chi-square test, †: Fisher exact test.

Table 4. Analysis of the factors associated success of metformin monotherapy.

	Metformin only (Group I) n = 73	Metformin + insulin (Group II) n = 21	Uni-variate P-value	Multivariate analysis		
				OR	CI 95%	P-value
Continuous data, (Mean ± SD)						

Continued

Age (years)	29.35 ± 2.3	33.73 ± 4.2	0.04*	0.782	0.58 - 1.51	0.61
BMI at diagnosis (Kg/m^2)	30.7 ± 3.6	34.4 ± 4.4	0.02*	1.671	0.12 - 0.96	0.03
GA at diagnosis (weeks)	27.1 ± 2.2	25.9 ± 2.8	0.12*	1.351	0.54 - 2.78	0.42
GA at start of treatment (weeks)	28.9 ± 1.7	28.2 ± 1.8	0.67*	1.298	0.08 - 1.36	0.56
Fasting glucose level at diagnosis (mg/dL)	106.6 ± 8.2	108.2 ± 8.5	0.34*	0.438	1.12 - 4.39	0.67
Categorical data, No (%)						
Parity: (Primigravida/Multigravida) (%)	31/42 (73.8)	7/14 (50)	0.01**	0.267	0.23 - 0.81	0.07
Hypertension						
– Pre-gestational	3 (4.1)	1 (4.7)	0.76†	1.785	0.35 - 0.91	0.97
– Gestational	6 (8.2)	1 (4.7)				

SD: Standard deviation, BMI: Body mass index, GA: Gestational age, HbA1c: Glycosylated hemoglobin, OR: Odds ratio, CI: Confidence interval, *: Independent t-test, **: Chi-square test, †: Fisher exact test.

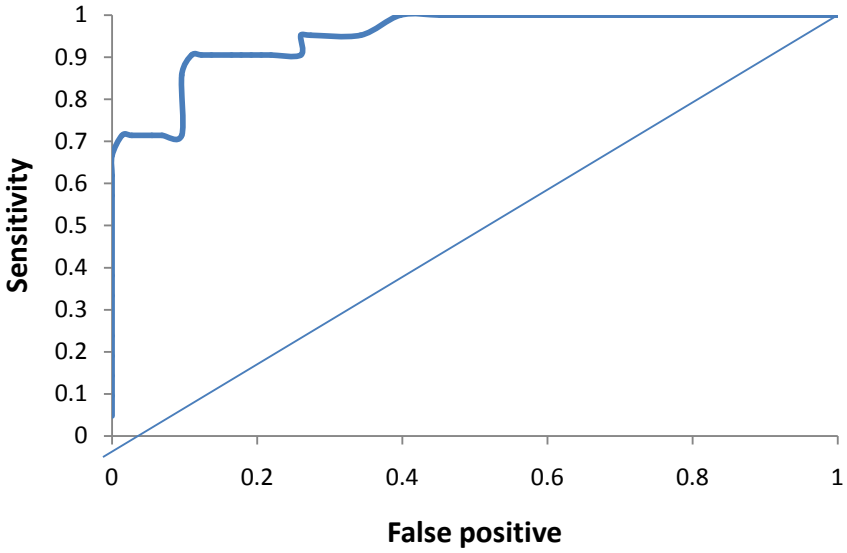

Figure 2. Receiver operating characteristic (ROC) curve of body mass index (BMI) with 32.1 is the cutoff point of highest sensitivity.

4. Discussion

Many recent guidelines recommend the use of metformin for treatment of GDM [12] [13]. Our primary objective is to detect factors that affect the success of metformin alone in treatment of GDM. In our study Adequate glycemic control was not achieved with metformin in 22.4% of cases. This proportion is nearly similar to Tertti *et al.* (18%) and Silva *et al.* (21.2%). However it was lower than showed by Rowan *et al.* (48.3%) and Moore *et al.* (34.7%) [14] [15] [16] [17] that may be attributed to different patient's criteria.

Our results revealed that higher BMI is strongly associated with metformin failure according to multivariate analysis (OR = 1.671 and 95% CI = 0.12 - 0.96) (P value = 0.03) and that reconfirm the results of most of researchers as Gante, Ali, Meshel *et al.* [18] [19] [20]. To our knowledge, it is the first time to state a

cutoff point of BMI above which response to metformin decreased significantly.

Significant difference in response to metformin alone was observed in patients with younger age (P value = 0.04). Similar to our findings, Gante *et al.* in his study on 388 patients found that higher age was related to the need for insulin supplementation [19]. Also we found that primigravid women had a higher chance for successful metformin monotherapy. Similarly Souza *et al.* found primiparity as a protective factor [21].

Although McGrath and coworker in his study on 98 women reported that early diagnosis of GDM and early introduction of metformin were significant factors for insulin supplementation and that was not observed in our study [22].

Regarding the obstetric and neonatal outcomes there was no significant difference between both groups and that was reported by most authors [22] [23]. Although we had more cases in the metformin + insulin group delivered by cesarean section (71.4%) but still with no significant value. On the other hand Gante *et al.* reported that cesarean was significantly more in the combination group [19].

Small sample size was one of the limitations of the study. Also, most of our data collected regarding glycemic control was dependent on sheets that were filled by patients.

5. Conclusion

Metformin can be regarded as a safe and effective drug for treatment of GDM, and about 23% of the patients treated with metformin did not achieve adequate glycemic control. Obesity was found as an independent factor for failure of metformin monotherapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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