Role of metformin and glibenclamidein controlling gestational diabetes mellitus

Original Article

Ahmed Mahmoud Abdou MD[1], Arafa M. Elshabrawy MD[2]

[1]Department of Obstetrics and Gynecology, [2]Department of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

ABSTRACT

Aim of the work: The aim of this study is to compare metformin and glibenclamide in treatment of gestational diabetes mellitus regarding the efficacy in glycemic control and safety.

Patients and Methods: Eighty patients aged between 18 and 40 years who were diagnosed to have gestational diabetes mellitus between 16 and 34 weeks that was failed to be controlled by diet and exercise and required medical therapy were recruited. They were allocated to either metformin or glibenclamide therapy. The primary outcome was failure of glycemic control according to fasting and postprandial glucose values. Secondary outcomes were obstetric outcomes, maternal and neonatal complications.

Results: Patients in metformin group had significantly higher failure of glycemic control than patients in glibenclamide group (10 cases in metformin group versus 3 cases in glibenclamide group; p=0.003). Also, mean fasting glucose level was significantly higher in metformin group than glibenclamide group (87.38 ± 7.4 and 82.42 ± 6.4 mg/dl, respectively, *p*= 0.005), while both groups had comparable post-prandial glucose levels (*p*= 0.11).

Both groups had comparable rate of maternal and neonatal complications. There was no significant difference between both groups regarding gestational age and mode of delivery.However, more neonates developed hypoglycemia <40 mg/dl in glibenclamide group than metformin group (11 and 6, respectively, *p*= 0.025).

Conclusion: Metformin and glibenclamide are comparable oral drugs for treatment of gestational diabetes that requires medical treatment regarding maternal and fetal outcomes with preference of glibenclamide in terms of better glycemic control.

Key Words: Gestational diabetes mellitus, glibenclamide, glycemic control, metformin

Received: 23 May 2018, **Accepted**: 16 July 2018

Corresponding Author: Ahmed Mahmoud Abdou, Department of Obstetrics and Gynecology, Zagazig University, Zagazig, Egypt, **Tel:** +201001757917, **Email:** Ahmed_gyna@hotmail.com.

ISSN: 2090-7265, February 2019, Vol.9, No.1

INTRODUCTION

World Health Organization (WHO) defined gestational diabetes mellitus (GDM) as any degree of glucose intolerance thatbegins or first detected during pregnancy[1]. Hyperglycemia may be detected in one in six pregnant women, most of them (about 84%) had GDM, while the rest of them had pre-gestational diabetes (either type 1 or 2)[2].

Women diagnosed with gestational diabetes mellitus (GDM) are more vulnerable to perinatal morbidity and mortality. Perinatal morbidity, birth weight, percentage of babies with macrosomia and caesarean delivery are improved by treatment with glucose lowering drugs[3, 4]. More patients diagnosed with GDM require treatment with glucose lowering drugs due to lowering thresholds of diagnosis and due to increased occurrence of risk factors like obesity[5, 6].

Traditionally, the first line drug therapy in GDM is insulin, as it does not cross the placenta to a measurable extent. However, nowadays, metformin and glibenclamide may be used. Both drugs cross the placenta to the fetus; glibenclamide crosses the placenta to lesser extent than metformin. Long-term safety data about oral drugs are lacking[7]. Insulin therapy requires special handling, storage, frequent monitoring, given in as multiple subcutaneous injections and expensive; thus it is not suitable for low income countries especiallyin ignorant and poor patients[8].

Oral drugs for treatment of GDM-like metformin (a biguanide) and glibenclamide (glyburide, a sulphonylurea) are more attractive than insulin, as they are easy to use, have comparable efficacy to insulin, cheap and more preferred by patients[9, 10]. In UK, metformin is considered the 1st line therapy in treatment of GDM; however national guidelines recommended the use of both

 DOI: 10.21608/EBWHJ.2019.28639

oral drugs[5, 11]. Glibenclamide is more frequently prescribed as a first-line drug in the treatment of GDM in USA[12]. Metformin has a failure rate ranges between 32% and 46% in different randomized trials[9, 13] ; whileglibenclamide has failure rate ranges between 16% and 25%[14].

Regarding the best drug to be used as the first-line therapy in the treatment of GDM, many studies compared metformin and glibenclamide in terms of safety and efficacy and yielded conflicting results[15].

AIM OF STUDY

The aim of this study is to compare metformin and glibenclamide in the treatment of gestational diabetes mellitus regarding efficacy in glycemic control and safety.

PATIENTS AND METHODS

This study was conducted at Zagazig University Hospital, Egypt, in the period between July 2017 and March 2018. It was approved by Ethical Committee of Obstetrics and Gynecology Department. All participants gave written informed consent. Patients aged between 18 and 40 years who were diagnosed to have gestational diabetes mellitus between 16 and 34 weeks that was failed to be controlled by diet and exercise and required medical therapy were recruited.

Diagnosis of GDM was based on criteria of International Association of the Diabetes and Pregnancy Study Groups (IADPSG); fasting plasma glucose level equal or more than 92 mg/dl or plasma glucose level after 2 hours equal or more than 153mg/dl during 75 gm oral glucose tolerance test.

We excluded patients with type 1diabetes diagnosed during pregnancy,patients with allergy to either metformin or glibenclamide and patients with major fetal malformations and if sulphonylurea was contraindicated.

Full medical history and BMI were recorded during the initial visit. All participants were educated about lifestyle and diet recommended for diabetic patients. Also, they were educated about the method of blood glucose measurement by glucometer at home and how to fill in a special chart for daily glucose measurement for one week.

Patients were randomly allocated to either metformin therapy (group 1) or glibenclamide therapy (group 2). Simple randomization with 1:1 allocation ratio was performed. The treatment allocation was recorded on special cards and was put inside opaque sealed and sequentially numbered envelops that were kept in Zagazig University Antenatal Clinic. Closed envelope was chosen by third parties.

Women in group 1 started metformin 500 mg as a single morning dose, if proper control was not achieved, up-titrating the dose was performed as much as 2000 mg divided in two doses. Participants randomized to glibenclamide, started glibenclamide 2.5 mg before breakfast. If proper control was not achieved, up-titrating the dose was performed as much as 15 mg divided in two or three doses during routine visits. The dose was down-titrated if hypoglycemia occurred.

All patients were advised to measure their blood glucose level before breakfast and 2 hours after each meal (breakfast, lunch and dinner) and they were asked to record these levels on daily glucose chart.

Based on Australian Carbohydrate Intolerance Study in Pregnant women (ACHOIS), diagnosis of glycemic control failure was established if fasting glucose level ≥100 mg/dl and/or two hours postprandial blood glucose level ≥126 mg/dl, in more than two readings during a fortnight[11]. If oral medication did not achieve proper glycemic control, insulin was initiated.

Weekly assessment by obstetrician and diabetologistat outpatient clinic was done till achieving proper glycemic control, then every two weeks till delivery. During these visits, weight and blood pressure were measured and sonographic assessment of fetal weight,amniotic fluid index (AFI) and fetal well-being was done. Routine anomaly scan was done between 18 and 26 weeks for all participants. Also,data on patient's daily glucose chart were collected by researcher.

Delivery was decided according to fetal size, presentation, fetal well-being, maternal condition and glycemic control. Maternal outcomes in the form of glycemic control, medical complications, time and mode of delivery were documented. After delivery, neonatal outcomes were recorded(birth weight, blood glucose level during first hour, APGAR score at 1 and 5 minutes, rate and duration of NICU admission and neonatal jaundice). If neonatal blood glucose level was ≤ 40 mg/dl during the first day after delivery, hypoglycemia was diagnosed.

Statistical Analysis

Sample Size:

As failure of glycemic control was 26% with metformin and 2% with glibenclamide use as shown in the study of Pujara *et al.*, 2017[8], so with power 80% and confidence level 95% sample size will be 64 distributed between two groups and with 20% non-responder rate it will be 80 (40 in each group).

Methods of statistical analysis

Microsoft Excel software and Statistical Package for the Social Sciences (SPSS version 20.0) software were used to analyze the collected data. Testing differences for significance was done using Chi-square test (X2) for qualitative data and t test for quantitative values. Significant difference was defined when p value was <0.05 and high significant difference was defined when p was <0.001.

RESULTS

Ninety-five cases were diagnosed to have gestational diabetes that was not controlled by diet and exercise program between 16 and 34 weeks of gestation at antenatal clinic, but only87 patients were eligible for the study. After explanation of study protocol to all of them, 80 patients accepted and were consented for their enrolment in the study. These 80 patients were divided into two groups, 40 in each by simple randomization. During follow up,sixpatients werelost (twopatients from group 1 and four patients from group 2). Thus, final statistical analysis was performed on 74 patients (38 patients in group 1 and 36 patients in group 2).

Table 1 shows that both groups were matched in terms of age (31.1±3.36 years in metformin group and 30.4±4.61 years in glibenclamide group), parity (85% of women in metformin group and 82.5% of women in glibenclamide group were multiparous), BMI (30.6±4.82 kg/m^2 in metformin group and 31.4 ±3.46 kg/m^2 in glibenclamide group), family history of diabetes (30% of women in metformin group and 35% in glibenclamide group had family history of diabetes), past history of gestational diabetes (only 5% of women in metformin group and 7.5% of women in glibenclamide group had past history of gestational diabetes), mean gestational age at enrolment (22.3±5.83 weeks in metformin group and 24.2 ±6.45 weeks in glibenclamide group), mean fasting blood glucose (111.67±10.3 and 113.36±8.7 mg/dl, respectively) and mean post-prandial glucose (152.46±16.4 and 148.57±11.7 mg/dl, respectively).

Table 1: Demographic data and pretreatment blood glucose levels.

		Metformin N = 40	Glibenclamide N = 40	*P* value
Age (mean ± SD)		31.1 ± 3.36	30.4 ±4.61	0.42
Parity	Nulliparous; n (%)	6 (15%)	7 (17.5%)	0.72
	Multiparous; n (%)	34 (85%)	33 (82.5%)	0.81
BMI (mean ± SD)		30.6 ± 4.82	31.4 ±3.46	0.39
Family history of diabetes; n (%)		12 (30%)	14 (35%)	0.53
Past history of gestational diabetes; n (%)		2 (5%)	3 (7.5%)	0.47
Gestational age at enrollment (mean ± SD)		22.3 ± 5.83	24.2 ±6.45	0.17
Fasting glucose (mean ± SD)		111.67 ± 10.3	113.36 ± 8.7	0.43
Post-prandial glucose (mean ± SD)		152.46 ± 16.4	148.57 ± 11.7	0.21

Table 2 shows that mean fasting glucose level was significantly higher in group 1 than group 2 (87.38±7.4 mg/dl versus 82.42 ± 6.4 mg/dl, respectively, p= 0.005) while, post-prandial glucose levelswere comparablein both groups (112.64±13.5 mg/dl in group 1 and 108.27±12.3 mg/dl in group 2, p= 0.11). Also, failure of glycemic control was significantly higher in group1 than group 2 (10 versus 3 cases, p = 0.003).

Both groups had comparable rate of maternal complications during pregnancy; only two cases (5.2%) in metformin group and 4 cases (11.1%) in glibenclamide group had attacks of hypoglycemia, five cases (13.1%) in metformin group and six cases (16.7%) in glibenclamide group developed preeclampsia, four cases (10.5%) in metformin group and three cases (8.3%) in glibenclamide group had urinary tract infection, four patients (10.5%) in metformin group and six patients (16.7%) in glibenclamide developed polyhydramnios, three patients (7.8%) in metformin group and six patients (16.7%) in glibenclamide group had preterm birth and only one patient in each group suffered from intrauterine fetal death (IUFD) as shown in table 2.

Gestational age at delivery and mode of delivery did not differ significantly in either group (table 2).

Table 2: maternal outcomes

	Metformin N = 38	Glibenclamide N = 36	*P* value
Fasting glucose (mean ± SD)	87.38 ± 7.4	82.42 ± 6.4	0.005*
Post-prandial glucose (mean ± SD)	112.64 ± 13.5	108.27 ± 12.3	0.11
Failure of glycemic control; N (%)	10 (26.3%)	3 (8.3%)	0.003*
Hypoglycemia (<60 mg/dl); N (%)	2 (5.2%)	4 (11.1%)	0.14
PIH; N (%)	5 (13.1%)	6 (16.7%)	0.49
Urinary tract infection; N (%)	4 (10.5%)	3 (8.3%)	0.61
Polyhydamnios ; N (%)	4 (10.5%)	6 (16.7%)	0.23
Preterm delivery; N (%)	3 (7.8%)	6 (16.7%)	0.07
IUFD; N (%)	1 (2.6%)	1 (2.7%)	0.96
Gestational age at delivery (mean ± SD)	38.15 ± 1.67	38.34 ± 1.13	0.64
Mode of delivery — Vaginal delivery; N (%)	9 (23.6%)	11 (30.5%)	0.5
Mode of delivery — Caesarean section; N (%)	29 (76.4%)	25 (69.5%)	

Both groups had comparable birth weight (3612.3±453.6 gm in metformin group and 3587.6 ± 393.7 gm in glibenclamide group), rate of macrosomia > 4000 gm (8 neonates in metformin group and 11 neonates in glibenclamide group) and mean blood glucose at birth (53.49±5.91 mg/dl in metformin group and 52.72±6.43 mg/dl in glibenclamide group). However, more neonates developed hypoglycemia < 40 mg/dl in glibenclamide group than metformin group (11 and 6 respectively; *p*= 0.025) (table 3). Both groups were comparable in terms of APGAR score at 1 and 5 minutes post-delivery, number of neonates admitted to NICU, duration of NICU admission and rate of development of neonatal jaundice (table 3).

Table 3: Neonatal outcomes

	Metformin N = 38	Glibenclamide N = 36	*P* value
Birth weight (mean ± SD)	3612.3 ± 453.6	3587.6 ± 393.7	0.81
Macrosomia >4000 gm; N (%)	8 (21.1%)	11 (30.5%)	0.21
Neonatal blood glucose (mean ± SD)	53.49 ± 5.91	52.72 ± 6.43	0.62
Neonatal hypoglycemia; N (%)	6 (15.7%)	11 (30.5%)	0.025*
APGAR score at 1 min. < 7; N (%)	2 (5.2%)	3 (8.3%)	0.39
APGAR score at 5 min. <7; N (%)	1 (2.6%)	1 (2.7%)	0.96
NICU admission; N (%)	10 (26.3%)	13 (36.1%)	0.2
Duration of NICU admission (days); (mean ± SD)	3.12 ± 1.67	3.35 ± 1.87	0.57
INeonatal jaundice; N (%)	17 (44.7%)	20 (55.5%)	0.26

DISCUSSION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that started or diagnosed for the first time in pregnancy. Seven percent of pregnant females are affected by gestational diabetes[16].

Insulin was considered as standard treatment of gestational diabetes that was not controlled by exercise and diet. Recently, oral drugs draw more attention to be incorporated in the treatment of gestational diabetes[17].

Langer *et al.* in 2000 published a randomized trial on glibenclamide use in the treatment of women with GDM. They concluded that glibenclamide in selected population controlled blood glucose like insulin without any rise increase in neonatal complications[18].

Rowan *et al.* in 2008 stated that metformin was more preferable than insulin injections and did not increase perinatal complications[9].

Recently, British Medical Journal in their editorial article in 2015 announced that many studies are required to prove which oral anti-diabetic drug could be alternative to insulin injections in the treatment of gestational diabetes[19].

This study is a randomized prospective study that included 80 patients with gestational diabetes which was failed to be controlled by diet and exercise. They were randomly divided into two groups:Metformin group (40 patients) who received metformin (500-2000 mg) in divided doses and glibenclamide group (40 patients) who received glibenclamide (2.5-15 mg), aiming to compare glycemic control, maternal and neonatal complication between both groups.

Both groups were comparable regarding age, parity, BMI, family history of diabetes, past history of gestational diabetes, mean gestational age at enrolment, mean fasting glucose and mean post-prandial glucose.

Patients in metformin group had significantly higher failure of glycemic control than patients in glibenclamide group (26.3% versus 8.3%, respectively). Also, mean fasting glucose level was significantly higher in metformin group than glibenclamidegroup ; while, both groups had comparable post-prandial glucose levels.

Gestational age at delivery, mode of delivery, maternaland neonatal complications did not differ between groups.However, more neonates developed hypoglycemia <40 mg/dl in glibenclamide group than metformin group (11 and 6 respectively, p= 0.025).

This was in accordance with Moore *et al.* in 2010 who compared glycemic control between metformin and glyburide in patients with gestational diabetes that was not controlled by diet and exercise. They found that proper glycemic control was not achieved in 26 women treated with metformin (34.7%) and 12 women treated with glibenclamide (16.2%) (p= 0.01) ; although the mean value of blood glucose during fasting and 2h postprandial did not differ significantly between groups[17].

Nachum *et al.* in 2017 compared glyburide to metformin in controlling gestational diabetes and concluded that they were equal in controlling GDM and rate of complications. They found that glyburide failed to achieve glycemic control in 23% of patients (12/53) ;while metformin failed in 28% of patients (14/51). However, they did not found any difference between groups regarding the mean daily blood glucose, obstetric and neonatal results[15].

Pujara *et al.* in 2017 compared the efficacy of metformin and glibenclamide in patients with gestational diabetes that required medical treatment. They found that the failure rate of metformin was 9.39 times higher compared to glibenclamide. Glibenclamide was associated with 9.5 times more risk to develop hypoglycemia in mother compared to metformin. While, comparing neonatal variables nursery admission was found to be more and statistically significant in neonates whose mother has received glibenclamidecompared to metformin (p =0.03, RR=2.26). Though statistically insignificant, LGA fetuses and neonatal hypoglycemia were 2.1 times more in glibenclamidegroup compared to metformin[8].

Silva *et al*. in 2012 in their study compared metformin and glyburide and found that there was no difference in glycemic control between the studied groups. Also, there was not any difference in the time of delivery, rate of cesarean section, macrosomia, neonatal hypoglycemia, NICU admission and neonatal deaths. However, neonates in glibenclamide group had higher birth weight (3193 gm) than in metformin group (3387 gm), but they had lower blood glucose level in the first and third hour (54.08 mg/dl and 55.89 mg/dl, respectively) than neonates in metformin group (59.78 mg/dl in first hour and 61.53 mg/dl in third hour)[20].

CONCLUSION

Metformin and glibenclamide are comparable oral drugs for the treatment of gestational diabetes that requires medical treatment regarding maternal and fetal outcomes with preference of glibenclamide in terms of better glycemic control.

CONCLICT OF INTEREST

There are no conflicts of interest.

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