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COMPARATIVE STUDY BETWEEN EFFECTIVENESS OF GLIBENCLAMIDE VERSUS INSULIN IN MANAGEMENT OF GESTATIONAL DIABETES

By

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) offers an important opportunity for diagnosis and implementation of clinical strategies for diabetes prevention.

Objective: To evaluate the effectiveness of glibenclamide versus insulin in the management of GDM in second half of pregnancy.

Patients and methods: This experimental prospective comparative study was carried out. A total of 100 women aged below 35 years were included in the study from those attending the Outpatient Clinic of Obstetrics and Gynecology Department of Al-Ahrar Teaching Hospital in Zagazig, Egypt, through the period from July 2017 to March 2020, and they were randomly allocated and divided into two groups 50 patients in each. The first group (A) received glibenclamide at an oral dose of 2.5-5 mg once or twice a day with a maximum dose of 10 mg/day and the second group (B) received standard insulin mixtard therapy. Dosing was based upon subcutaneous two shot combined dose of intermediate acting and short-acting insulin given prior to breakfast and dinner. The starting dose was 0.7 units per kilogram of the body weight at admission and increased weekly as necessary.

Results: The delivery type was comparable in both groups, 28% of women underwent vaginal delivery in glibenclamide group, and 22% of women underwent vaginal delivery in insulin group. 72% and 78% of women underwent cesarean section in glibenclamide and insulin groups respectively. The gestational age at delivery was comparable in both groups.

Conclusion: Glibenclamide seem to be a simple, safe, inexpensive and attractive alternative to insulin for the treatment of gestational diabetes mellitus.

Keywords: Gestational diabetes mellitus, Glibenclamide, Insulin.

INTRODUCTION

Pregnancy is a potentially glucose intolerant condition. Insulin sensitivity decreases as the pregnancy advances. Of these women, some develop GDM due to inadequate insulin secretion, particularly in obese women with pre-existing insulin resistance *(Colberg et al., 2016)*.

GDM is associated with an increased maternal hazard of preeclampsia, cesarean section, in addition to an increased risk for developing type 2 Diabetes (T2D) after

pregnancy *(Griffith et al., 2019)*. Also, there is increasing risk for neonatal loss, still birth and congenital defects resulting from excessive mother-to-fetus glucose transfer *(Mackin et al., 2018)*.

A further major complication is macrosomia, which is a risk factor for instrumental delivery, cesarean section and shoulder dystocia during delivery and neonatal hypoglycemia directly after birth. Moreover, the effect of the intrauterine hyperglycemia might disappear after birth *(American Diabetes Association, 2017)*.

The standard therapy for gestational diabetes is insulin. On the other hand, Insulin has several disadvantages including daily injections, the risk of hypoglycemia and maternal weight gain *(Simeonova-Krstevska et al., 2018)*.

Based on the patient's body mass index, glucose levels and the way of life dose adjustment are required. However, since the trial by means of Langer et al evaluating glibenclamide with insulin, oral hypoglycemic drugs had been more and more regarded as possible alternatives. Several observational and randomized controlled trials have addressed the use of oral agents in gestational diabetes, mainly glibenclamide and metformin *(American Diabetes Association, 2019)*.

Despite the fact that glibenclamide haven't marketing approval for its use during pregnancy, various guidelines had considered its utilization as an aide treatment in gestational diabetes. For example, glibenclamide has been acknowledged in the Fifth International Workshop-Conference in Gestational Diabetes Mellitus *(American Diabetes Association, 2017)*, and both glibenclamide and metformin are considered in National Institute for Health and Care Excellence (NICE) guidance and American College of Obstetricians and Gynecologists (ACOG) practice bulletin *(Webber et al., 2015)*.

Utilization of oral hypoglycemic drugs is expanding, and in some settings they are the first option when drug treatment is required for women with gestational diabetes *(Horvath et al., 2010)*.

The aim of the present study was to evaluate the effectiveness of glibenclamide versus insulin in the management of GDM in second half of pregnancy.

PATIENTS AND METHODS

This experimental prospective comparative study was carried out. A total of 100 women aged below 35 years were included in the study from those attending the Outpatient Clinic of Obstetrics and Gynecology Department of Al-Azhar Teaching Hospital in Zagazig, Egypt.

Total sample size was 100 patients agreeing to participate in the study, by written consents. The patients were randomly allocated and divided into two equal groups: The first group (A) received glibenclamide at an oral dose of 2.5-5 mg once or twice a day with a maximum dose of 10 mg/day and the second group (B) received standard insulin mixtard therapy. Dosing was based upon subcutaneous two shot combined dose of intermediate acting and short-acting insulin given prior to breakfast and dinner. The starting dose was 0.7 unit per kilogram of the body weight at admission and increased weekly as necessary.

All women were provided with standard nutritional instructions for three daily meals. Adherence to the dietary regimen was evaluated and reinforced at weekly visits to the clinic. The diets were designed to provide 25 kcal per kilogram of body weight for the obese women, and 35 kcal per kilogram for the non-obese ones, with 40 to 45 percent of the calories from carbohydrates.

Inclusion criteria:

Age below 35 years old and pregnant females discovered as having gestational diabetes attended to antenatal clinics. The patients selected having gestational diabetes diagnosed according to the Carpenter and Coustan criteria (fasting > 95 mg / dl, 1 h > 180 mg/ dl, 2 h > 155 mg / dl, and 3 h > 146 mg / dl) (Feldman et al, 2016).

Exclusion criteria:

Patients with contraindication to glibenclamide, fetal anomaly, gestational hypertension, preeclampsia, fetal growth restriction, ruptured membranes, and patients in labor.

The goals of treatment was the achievement of a mean blood glucose concentration of 90 to 105 mg per deciliter (5 to 5.9 mmol per liter), a fasting blood glucose concentration of 60 to 100 mg per deciliter (3.4 to 5 mmol per liter), and a postprandial blood glucose concentration of less than 140 mg per deciliter. All patients were exposed to full history taking, clinical examination, laboratory investigations and fetal and neonatal assessment.

Primary outcome: Efficacy of glibenclamide in control of blood glucose level by comparing fasting and postprandial blood glucose level in both groups and the degree of glycemic control.

Secondary outcome: The development of complications in both groups as preeclampsia and antepartum haemorrhage. The incidence of foetal complications as IUFD. The gestational age at delivery and the mode of delivery in both groups. The neonatal outcome in both groups (birth weight, intrapartum complications, blood glucose level, admission to NICU, perinatal mortality and neonatal hypoglycemia).

Statistical analysis:

Results of the present study were statistically analyzed using SPSS 25 (IBM, USA). Data were represented as mean± standard deviation (SD) or number and percentage. Numerical data were compared using Mann Whitney U test, while categorical data were compared using Fisher exact test or Chi-square test as appropriate. The level of significance was taken at P value < 0.05 was significant.

RESULTS

Fasting and postprandial blood sugar did not differ significantly on both groups. However, the number of patients controlled on glibenclamide was lower than insulin group. The percentage of control was 84% and 90% respectively. 16% of patietns on glibenclamide group shifted to insulin and 10% of insulin group shifted from the standard regimen of insulin (mixtard) into regular insulin before meals and long-acting insulin on the bed time **(Table 1)**.

Table (1): Comparison of post-treatment plasma glucose level for both groups

Groups / Parameters	Glibenclamide (A) (n = 50)	Insulin (B) (n = 50)	P
Fasting blood sugar	94.0(65-135)	95.0(60-140)	**>0.05**
Postprandial blood sugar	127.5 (75-169)	132.0(82-178)	**>0.05**
Dose of the drug	4.5(1.5-7.8)	50.0(25-75)	**>0.05**
Mean tests per day	2.0 (1-4)	3.0 (2-5)	**>0.05**
Mean days tested	62.0(15-88)	66.0(12-95)	**>0.05**
Control	**42 (84%)**	**45 (90%)**	**>0.05**

Values were described in mean ± SD.Calculated from the date of the initiation of medican to date of delivery.Within goal defined as FBS < 96 mg/dl and PBS < 140 mg/dl.Dose of glibenclamide by mg and dose of insulin by units/ml.

There was no statistically difference on both groups as regard rate of obstetric complications, but the rate of preeclampsia was higher on glibenclamide group than insulin group (6% and 0% onboth groups respectively), and there was one case of IUFD on insulin group at the 38th week of gestation **(Table 2)**.

Table (2): Comparison between obstetric complications in both groups

Groups / Parameters	Glibenclamide (group A) (n = 50)		Insulin group (group B) (n = 50)		P
	No	**%**	**No**	**%**	
Non-complicated	39	78	44	88	**<0.05)**
IUFD	0	0	1	2	**<0.05**
PET	**3**	**6**	**0**	**0**	**<0.05**

There was no statistically significant differeance on both groups as regard the foetal and pregnancy progress. However, the percentage of development of polyhydramnios was higher on glibenclamide group (four cases on glibenclamide group developed polyhydramnios compared to two cases on insulin group). Also, the rate of IUGR was higher in glibenclamide group (three cases developed IUGR and no cases on insulin group developed IUGR), but the rate of macrosomia was equal on both groups 6% on glibenclamide and insulin groups **(Table 3)**.

Table (3): Comparison of foetal and pregnancy progress in both groups

Groups / Parameters	Glibenclamide (group A) (n = 50)		Insulin group (group B) (n = 50)		P
	No	%	No	%	
Non-complicated	32	64	40	80	**>0.05**
Polyhydramnios	4	8	2	4	**>0.05**
Macrosomia	3	6	3	6	**>0.05**
IUGR	**3**	**6**	**0**	**0**	**>0.05**

The weight of the neonate was statistically different on both groups. The weight was lower on glibenclamide group (3600 (2750-4250) on insulin group compared to 3250 (2500-3750) on glibenclamide group), but the blood sugar of the neonate was comparable on both groups (62.0(50-75) on glibenclamide group compared to 66.0 (55-80) on insulin group), and also the rate of admission to ICU and perinatal mortality and neonatal hypoglycemia was comparable on both groups **(Table 4)**.

Table (4): Comparison of neonatal outcome of both groups

Groups / Parameters	Glipenclamide Group (A) (n = 50)		Insulin Group (B) (n = 50)		P
Weight of the neonate	3250 (2500-3750)		3600 (2750-4250)		<**0.001**
Blood sugar of the neonate	62.0(50-75)		66.0 (55-80)		**>0.05**
	No	**Ratio**	**No**	**Ratio**	**P**
Admission to ICU	3	6 %	5	10 %	**>0.05**
Perinatal mortality	1	2 %	0	0 %	**>0.05**
Neonatal hypoglycemia	1	2 %	2	4 %	**>0.05**

DISCUSSION

Glibenclamide dose was variable. About 44% of patients were controlled on a dose of 2.5 mg, 36% of patients were controlled on a dose of 5 mg, 4% of patients were controlled on a dose of 7.5 mg and 16% of patietns reached maximum dose of glibenclamide (10 mg) and failed to attain glycemic control. They were shifted to insulin and removed from our study. These results were comparable to the study made by *Brown et al. (2017).*

Glibenclamide failure in our study in patients who failed to attain glycemic control after receiving the maximum dose of glyburide was 16%. The results were comparable to the result of the study made by *Behrashi et al. (2016)* as 16%. The failure rate was lower in the study made by *Glover et al. (2016)* as 4%.

The maternal age, gravidity, parity and gestational age at discovery of gestational diabetes were comparable in both groups. *Rao et al. (2017)* determined the efficacy of the glibenclamide versus insulin in achieving the adequate glycemic control. The age of the patients ranged from 23 to 33 years. The mean age in glibenclamide group was 27.32 (SD±2.84) where as in insulin group was 26.30 (SD±3.01).

The fasting and postprandial blood sugars after reaching the appropriate dose

of treatment were comparable in both groups. These results were in agreement with *Behrashi et al. (2016)* who compared glibenclamide and insulin as regard maternal blood glucose. *Kalra et al. (2013)* achieved plasma blood glucose level of fasting 82 mg/dl and postprandial 107 mg/dl in glibenclamide group and fasting 89 mg/dl and postprandial 111mg/dl.

The birth weight was different between the two groups in the current study. It was lower in glibenclamide group. This agreed with *Moore (2010)* and *Behrashi et al. (2016).*

The incidence of perinatal mortality in our study was 2% and 0% in oral hypglycemic group and insulin group respectively. There was only one case of sudden IUFD in insulin group at the 37th week of gestation. The cause was unexplained. Our result was comparable to the study made by *Goh et al. (2011)* who reported one IUFD in the insulin group who had Budd Chiari syndrome but disagreed with *Moore (2010)* who reported on IUFD in each group, probably with congenital anomalies as causative.

The neonatal blood glucose in the present work was comparable in both groups. *Rao et al. (2017)* showed the mean plasma glucose level before delivery. In glibenclamide group, fasting was 87.62 mg/dl, postprandial was 116.44 mg/dl, before lunch was 95.62 mg/dl, after lunch was 115.80 mg/dl, before dinner was 91.96 mg/dl and after dinner was 116.64 mg/dl, 3AM was 84.42mg/dl and next day fasting was 86.30mg/dl in comparison with insulin where fasting was 85.54 mg/dl, postprandial was 114.14 mg/dl, before lunch was 87.08 mg/dl, after lunch was 112.82 mg/dl, before dinner was 86.76 mg/dl and after dinner was 114.18 mg/dl,3AM was 81.16 mg/dl and next day fasting was 86.72 mg/dl. It is statistically significant.

The incidence of neonatal hypoglycemia was lower in oral hypoglycemic group (occurred in 2% in oral hypoglycemic group and was 4% in insulin group), but the differences were not statistically significant. Our results disagreed with *Sénat et al. (2018)* who found that the incidence of neonatal hypoglycemia was higher in oral hypoglycemic group, 12.2% in oral hypoglycemic group and were comparable to 7.2% in insulin group.

Both groups were comparable as regards admission to Neonatal Care Unit (NCU). About 6% of neonates admitted in oral hypoglycemic group, whereas 10% admitted in insulin group. The most common indications in both groups were hypoglycemia and respiratory distress. Our results are in agreement with *Sénat et al. (2018)* who found higher frequency of admission in insulin group and longer duration of admission (2.3% versus 2.4% in glibenclamide and insulin group respectively).

Both groups were comparable as regard perinatal mortality. About 2% in oral hypoglycemic group in comparison to 0% in insulin group. These results agreed with *Glover et al. (2016)* who reported nearly the same rate of perinatal mortality (1%) between glibenclamide and insulin groups. The above study included only gestational diabetic cases.

The mode of delivery was comparable in both groups (28% of women underwent vaginal delivery in glibenclamide group

and 22% of women underwent vaginal delivery in insulin group, 72% and 78% of women underwent cesarean delivery in glibenclamide and insulin groups respectively). These results agreed with *Mirzamoradi et al. (2015)* who found that 24.3% of women underwent vaginal delivery in glibenclamide group, and 28.8% of women underwent vaginal delivery in insulin group, 75.7% and 71.2% of women underwent cesarean delivery in glibenclamide and insulin groups respectively.

The gestational age at delivery was comparable in both groups. The results were comparable to a study made in Sohag University, Egypt, by *Mohamed et al. (2014)* who found that there is no difference in both groups as regard gestational age at delivery (38.05 in hypoglycemic group compared to 38.26 in insulin group).

The incidence of complications during delivery was found only in insulin group. There was only one case of shoulder dystochia and managed conservatively. The incidence of macrosomia was equal in both groups (6% on glibenclamide and insulin groups). This result agreed with the study formed by *Behrashi et al. (2016)* who found that the incidence of macrosomia was comparable in both groups (25% in both groups), but the rate of incidence was higher.

The incidence of maternal complications during pregnancy was comparable in both groups (2% in insulin group and 6% in glibenclamide group), but the incidence of preeclampsia was higher in glibenclamide group. Three cases of preeclampsia were recorded in glibenclamide group, but the differences were not statistically significant. *Rao et al. (2017)* concluded that glibenclamide is effective as insulin in achieving adequate glycemic control with no significant maternal and fetal morbidity and mortality.

CONCLUSION

Glibenclamide appeared to be a simple, safe, inexpensive, convenient and attractive alternative to insulin for the treatment of gestational diabetes mellitus on women who failed to attain glycemic control on diet only. The noninvasive, cost-effective, potential friendly regimen lends itself more readily to potential patient compliance although potentially avoiding the need for self-injection, the rate of discontinuation in a non-research setting warrants investigation into alternative administration protocols to improve compliance.

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دراسة تأثير الجليبنكلاميد مقارنة بالإنسولين على سكرى الحمل

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خلفيـــة البحـــث: يتـيح سـكرى الحمـل سـكري الحمـل فرصـه مهمـه مـن اجـل تشـخيص وفرض الخطط العلاجيه للوقايه من مرض السكرى.

الهـــدف مـــن البحـــث: تقـيم كفـاءة الجليبنكلاميـد فـى عـلاج سـكرى الحمـل مقارنـة بالانسولين فى النصف الثانى من الحمل.

المريضـــات وطـــرق البحـــث: هـذه الدراسـة المقارنـة التجريبيـة المسـتقبلية تمـت علـى 100 سـيده مـن المتـرددات علـى عيـادة متابعـة الحمـل بمستشـفى الأحـرار التعليمـى, الزقـازيق فـى الفتـره مـن يوليـو 2017 حتـى مـارس 2020, وتـم اختيـار المريضـات وتقسـيمهم عشـوائيا الـى مجمـوعتين متسـاويتين. المجموعـة الأولـى (أ) تلقـت عقـار جليبنكلاميـد بجرعـة 2.5-5 مجـم مـرة أو مـرتين فـي اليـوم بجرعـة قصـوى تبلـغ 10 مجـم / يـوم والمجموعـة الثانيـة (ب) تلقـت عـلاج الإنسـولين. وكانـت الجرعـات عبـاره عـن جـرعتين مختلطتـين تحـت الجلـد مـن الأنسـولين متوسـط المفعـول وقصـير المفعـول يعطـى قبـل الإفطـار والعشـاء. وكانـت جرعـة البدايـة 0.7 وحـدة لكـل كيلوجرام من وزن الجسم وتزداد أسبوعياً.

نتـائج البحـث: كانـت طريقـة الـولادة قابلـه للمقارنـة فـي كلتـا المجمـوعتين (28 ٪ مـن النسـاء خضـعن للـولادة المهبليـة فـي مجموعـة جليبينكلاميـد و 22 ٪ مـن النسـاء خضـعن للـولادة المهبليـة فـي مجموعـة الإنسـولين و72 ٪ و78 ٪ مـن النسـاء خضـعن للـولادة القيصـرية فـي مجموعـات جليبينكلاميـد والأنسـولين علـى التـوالي). كـان عمـر الحمل عند الولادة قابلاً للمقارنة في كلتا المجموعتين.

الاســـتنتاج: يعتبـــر الجليبنكلاميـــد بـــديلاً بســـيطا وآمنـــا وغيـــر مكلـــف ومـــريح كعـــلاج لســكري الحمــل علــى النســاء اللــواتي فشــلن فــي تحقيــق الــتحكم فــي نســبة الســكر فــي الــدم عن طريق النظام الغذائي فقط.