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Comparison of Glibenclamide and Insulin on Neonatal Outcomes in Pregnant Women with Gestational Diabetes

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ABSTRACT

Background: Untreated or poorly controlled gestational diabetes can cause serious complications for mother and newborn. Glibenclamide is rarely used in treating mothers with this disease. This study aimed at comparing the effect of glibenclamide and insulin on neonatal outcomes in women with gestational diabetes mellitus.

Methods: In this randomized controlled clinical trial, 249 pregnant women aged 18–45 years within the 11th–33rd weeks of gestation with gestational diabetes, single fetus pregnancy, and in need of hyperglycemia treatment were entered and grouped randomly as either glibenclamide or insulin. In the insulin group (n = 129), insulin was administered with an initial dose of 0.2 IU/kg subcutaneously twice per day, whereas in the glibenclamide group (n = 120), 1.25 mg oral glibenclamide was administered once daily and increased if needed.

Results: The results showed no significant difference in means age, gestational age, and body mass index between women in the two groups. In addition, there were no significant differences in the frequency of neonatal hypoglycemia, anomaly, hyperbilirubinemia, admission in Neonatal Intensive Care Unit (NICU), and neonatal respiratory distress between two groups. Macrosomia was lower in the glibenclamide group than the insulin group (3.3% vs. 13.2%, respectively, P = 0.005). Regression logistics model results showed that the type of treatment (odds ratio [OR]: 4.62; confidence interval [CI]: 1.45–14.02; P = 0.01) and gestational age at delivery (OR: 1.41; CI: 1.04–1.74; P = 0.01) were as predictor factors of macrosomia.

Conclusions: The results of this study revealed that glibenclamide is able to reduce the risk of fetal macrosomia without increasing neonatal anomalies, jaundice, hypocalcemia, infant respiratory distress, and NICU admission.

Keywords: Gestational diabetes, glibenclamide, insulin

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that occurred or is diagnosed for the first time during pregnancy. It affects approximately 3–6% of all pregnancies.[1] GDM is still a great problem for the mother and fetus and even in the best conditions, the risk of fetal malformations and mortality is 2–5 times higher than normal pregnancy.[2] Women with untreated gestational diabetes have a greater risk of developing some fetal,

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neonatal, and maternal outcomes. Congenital anomalies, macrosomia, hypoglycemia, respiratory distress syndrome, hypocalcemia, and hyperbilirubinemia are the neonatal consequences of this complication.[3-5]

It is very important to treat GDM during pregnancy. The use of insulin is a standard treatment of gestational diabetes because of its high effectiveness; also, it is believed that insulin does not cross the placental barrier because of its large molecular size.[6] Results from previous studies showed that anti-insulin antibody is produced in response to insulin transcription in pregnant women with GDM and insulin can cross the placenta as a part of the insulin-antibody complexes.[7-9] This autoimmune response to exogenous insulin can affect fetal development.[7] Furthermore, insulin injection has disadvantages such as fear, anxiety, repeated injections, the need for education, skills in dose adjustment and injection, the risk of hypoglycemia, more weight gain in pregnant women, and high costs.[10,11]

Several studies have investigated oral antidiabetic agents in the treatment of gestational diabetes and some of them used glibenclamide.[12-15] However, it is the second generation sulfonylureas that are commonly used in the treatment of diabetes.[16-19] As a result of similarity in the pathophysiology of gestational diabetes and type 2 diabetes, this drug was also considered in GDM. *In vitro* and clinical studies with very little placental transfer for this drug have been reported unlike other sulfonylureas. The mechanism that reduces the human placental transport of glibenclamide is unknown. A combination of extremely high protein binding and a relatively short elimination half-life might partially explain it.[6] This drug releases insulin from pancreatic beta cells by affecting potassium channels.[20,21] Furthermore, it reduces postprandial hyperglycemia by improving insulin secretion after meals.[16] In addition, it inhibits glucose production by the liver cells.[22,23] The results of a meta-analysis of research entitled "safety of glyburide for gestational diabetes" did not show any increase in perinatal complications.[24] The results of a study showed that glibenclamide can be used as the first blood sugar (BS) controller in pregnancy.[25] Zeng *et al*. also suggested that glibenclamide is effective in the treatment of women with gestational diabetes.[26] However, Balsells *et al*.[8] concluded that glibenclamide should be used as the last drug after insulin and metformin. Studies on glibenclamide, in the treatment of GDM, showed different neonatal outcomes. According to research carried out by Cheng *et al*.,[27] the risk of macrosomia in newborns (weighing more than 4 kg) and admission to the Neonatal Intensive Care Unit (NICU) was higher in glibenclamide than the insulin group. The results of some other studies found no difference in the incidence of neonatal hypoglycemia, increased risk of macrosomia, admission to the NICU, or fetal anomalies.[13,28,29] Due to the importance of this topic and the conflicting research results, this study was conducted to compare the effect of glibenclamide and insulin on neonatal outcomes in GDM.

METHODS

Study design and participants

In this clinical trial study, 258 pregnant women who were referred to the gynecology clinics of Shabihkhani and Shahid Beheshti Hospital of Kashan for prenatal care were used as subjects. The criteria for selecting them included the following: 18–45 years, 11–33 weeks of gestation, absence of diabetes before pregnancy, singleton pregnancy, absence of known kidney, and hepatic, hematological, and/or cardiovascular disease. Women who experienced premature rupture of membranes, severe bleeding, or one of the above-mentioned diseases during the study were excluded from the study. Fasting BS (FBS) was checked in eligible women. For all women with FBS higher than 92, glucose tolerance test, FBS, and BS at 1, 2, and 3 h after drinking 100 g of glucose solution were requested. If two of these criteria (BS >95, 1 h >180, 2 h >155, and 3 h >140) were high, GDM was diagnosed.[30] Education for lifestyle change (exercise and diet) was performed for all the participants. After 1 week, FBS and postprandial glucose test were checked at 2 h after breakfast, lunch, and dinner. Patients were hospitalized if FBS and BS, 2 h after meal were >90 and >120, respectively.

Sample size was calculated based on the assumption that the hypoglycemia ratio in patients who received insulin and glibenclamide in a previous study were 0.08 and 0.20, respectively,[31] at 95% confidence and 80% power. It was determined that 129 patients were needed for each group.

Figure 1 presents the flow diagram of patient recruitment, showing that 258 eligible patients were randomized into the glibenclamide group (129 patients) and insulin group (129 patients).

Intervention and variable assessment

In enrolled patients, at first, HbA1c was measured and then treatment was started randomly. Block randomization was done for assignment of 2 groups to treatments.

In the insulin group, insulin was administered with an initial dose of 0.2 IU/kg.

Subcutaneously, twice per day 2/3 of the dose was prescribed in the morning and 1/3 in the evening; morning insulin included 2/3 of normal pressure hydrocephalus (NPH) and 1/3 regular, evening insulin included 1/2 NPH and 1/2 regular that increased every 3 days if necessary (1 unit regular insulin or NPH was added if BS increased by 10 mg/dl).

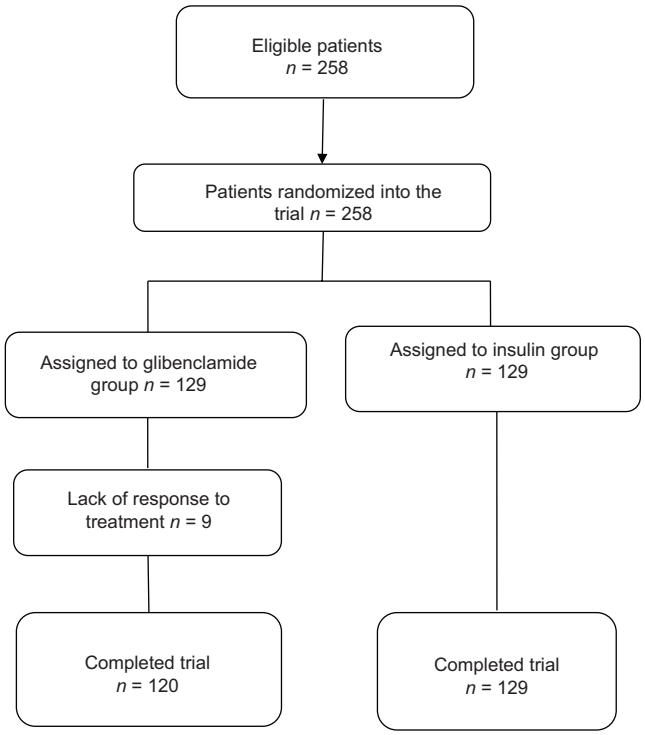

Figure 1: Flow diagram of participants through each stage of the study

In the glibenclamide group, 1.25 mg of oral glibenclamide was administered once daily and increased from 1.25 to 2.5 mg every 3 days to the maximum of 20 mg/day if needed. BS was assessed 4 times/day (fasting, 2 h after breakfast, 2 h after lunch, and 2 h after dinner). The purpose of treatment was to reduce fasting plasma glucose levels to <90 as well as decrease 2 h postprandial glucose to <120 mg/dl. The patients were discharged when BS reached normal levels by medication. Insulin therapy was started if BS was not normal after 2 weeks of taking the highest dose of glibenclamide. These patients were excluded from the study. FBS and BS 2 h after meal were assessed every 2 weeks in all eligible women and the dose of medication was adjusted.

Neonatal outcomes included Apgar scores, macrosomia (birth weight >4000 g), hypoglycemia (blood glucose <40 mg/dl), hypocalcemia (calcium <7 mg/dl in the first 3 days after birth), hyperbilirubinemia (bilirubin >12 mg/dl in the first 7 days after birth),[32] fetal anomalies, respiratory distress, and neonatal unit hospitalization were recorded.

The bilirubin and serum calcium of the infants were measured using a machine in Shahid Beheshti Hospital laboratory. Birth weight was assessed using standard scales of SECA brand; a glucometer was used to check the BS of newborns every 30 min during the first 3 h after birth. All newborns were examined immediately after birth for respiratory distress (need for respiratory support at least 4 h during the first 24 h after birth), major and minor anomalies, and admission to the NICU. Furthermore, all infants were checked for jaundice within 1 week after birth. The questionnaire and checklist were completed by examining the subjects and observation of their laboratory tests.

Statistical analyses

Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to evaluate data distribution. The differences of quantitative, normally distributed data in two groups were assessed by independent *t*-test (body mass index [BMI], age, and gestational age at the point of entry into the study). For data that were not normally distributed, the Mann–Whitney U-test statistics were used (gestational age at delivery, Hba1c, FBS after treatment, and BS 2 h after meal). Chi-square or Fisher exact test was used for qualitative data to compare the two groups.

To determine the factors related to macrosomia, the independent sample *t*-test (age, BMI, and parity), Mann–Whitney U-test (HbA1c, FBS, gestational age at delivery, and BS 2 h after meal) and Chi-square test (sex of newborn and type of treatment) were used as a univariate analysis. Thereafter, multivariate analysis was performed using logistic regression to assess predictor factors of macrosomia. The variables were entered in regression logistic models if their $P < 0.25$ in univariate analysis (FBS, gestational age at delivery, and type of treatment) and backward modeling was performed. A $P < 0.05$ was considered statistically significant in all tests.

Ethics

This study was approved by the Ethics Committee of Kashan University of Medical Sciences on 08.26.2013 by the code 2062/1/5/29. The research began after obtaining written informed consent from the hospital's officials. The aim of the study, the benefits, effectiveness, and possible side effects of two treatment methods were explained by the researchers before the trial began and written consent was obtained from all the patients. This study is registered in the Iranian Registry of Clinical Trials (IRCT) as trial number: IRCT2013102315045N2.

RESULTS

A total of 258 pregnant women were studied in the insulin group (129) and glibenclamide group (129). In the glibenclamide group, 9 did not respond to treatments; this led to the introduction of insulin therapy. Therefore, it was analyzed on 249 patients. The mothers' characteristics in both groups are shown in Table 1. The findings of this table showed no significant difference between the two groups in age, BMI, and gestational age [Table 1].

Table 2 shows neonatal outcomes in the insulin and glibenclamide groups. The findings showed no significant

Table 1: Baseline patient characteristics in glibenclamide and insulin groups

Variable	Mean±SD		*P*
	Glibenclamide (*n*=120)	Insulin (*n*=129)	
Age[a] (year)	30.69±7.194	29.98±7.033	0.43
BMI[b] in the first trimester	21.94±2.800	22.59±3.094	0.44
Gestational age at the entry into the study[a]	24.89±3.90	24.48±4.51	0.44
Gestational age at delivery[c]	38.36±2.06	36.91±2.28	0.64
HbA1c[c]	5.98±0.82	6.13±0.83	0.26
FBS after treatment[c]	84.85±5.26	83.75±6.77	0.38
Blood sugar 2 h after meal[c]	114.38±81.74	107.14±7.99	0.95

[a]Independent *t*-test was performed, [b]Body mass index, [c]Mann-Whitney U-test was performed. FBS=Fasting blood sugar, HbAlc=Glycated hemoglobin, SD=Standard deviation

Table 2: Comparison of neonatal outcomes of glibenclamide and insulin groups

Neonatal outcome	Glibenclamide (*n*=120)	Insulin (*n*=129)	*P*
Apgar score 1 min after birth, median (quartiles)[a]	9 (9-9)	9 (9-9)	0.22
Apgar score 5 min after birth, median (quartiles)[a]	10 (9-10)	10 (9-10)	0.92
Fetal macrosomia, *n* (%)[b]			
No	116 (96.7)	112 (868)	0.005
Yes	4 (3.3)	17 (13.2)	
Hypoglycemia, *n* (%)[c]			
No	118 (98.3)	122 (94.6)	0.17
Yes	2 (1.7)	7 (5.4)	
Hypocalcemia, *n* (%)[c]			
No	120 (100)	127 (98.4)	0.5
Yes	0 (0.0)	2 (1.6)	
Fetal distress, *n* (%)[c]			
No	118 (98.3)	125 (96.9)	0.68
Yes	2 (1.7)	4 (3.1)	
Hyperbilirubinemia, *n* (%)[b]			
No	109 (90.8)	118 (91.5)	0.86
Yes	11 (9.2)	11 (8.5)	
Anomaly, *n* (%)[c]			
No	120 (0.0)	129 (98.4)	0.5
Yes	0 (0.0)	2 (1.6)	
NICU admission, *n* (%)[b]			
No	116 (96.7)	121 (93.8)	0.29
Yes	4 (3.3)	8 (6.2)	

[a]Mann-Whitney U-test was performed, [b]Chi-square test was performed, [c]Fisher exact test was performed. NICU=Neonatal Intensive Care Unit

difference in Apgar score, hypoglycemia, hypocalcemia, fetal distress, hyperbilirubinemia, anomaly, and NICU admission between the two groups. Fetal macrosomia in the insulin group was higher than the glibenclamide group ($P = 0.005$) (odds ratio: 0.227, confidence interval: 0.074–0.696). The mean weights of infants in the insulin and glibenclamide groups were 3700.77 ± 329.18 and 3433.29 ± 344.61 g, respectively. Independent *t*-test showed a significant difference in birth weight between two groups ($P = 0.001$). In this study, 50.4% of infants in the insulin group and 46.7% in the glibenclamide group were male. Chi-square test showed no significant difference in gender between the two groups. No injuries occurred to infants during the birth process. A comparison of other neonatal variables is shown in Table 2.

The findings in Table 2 showed that the prevalence of macrosomia was different in the two groups, and univariate analysis was performed based on the predictor factors of macrosomia. Findings showed that gestational age at delivery ($P = 0.01$) and types of treatment were associated with macrosomia ($P = 0.005$) [Table 3].

Multivariate analysis was performed using logistic regression to assess predictor factors of macrosomia. The variables were entered in regression logistic models if their $P < 0.25$ in univariate analysis (FBS, gestational age at delivery, and type of treatment). Logistics test results showed that the type of treatment and gestational age at delivery were predictor factors of macrosomia; such that a one unit increase in gestational age at delivery was associated with a 1.35-fold increase in macrosomia. In addition, a one unit increase in the use of insulin was associated with a 4.5-fold increase in macrosomia [Table 4].

DISCUSSION

In this study, neonatal outcomes were examined in glibenclamide and insulin therapy in GDM. The result indicated that the neonatal hypoglycemia was less in the glibenclamide group than insulin, but there was no statistically significant difference between the two groups. This finding was similar to the results of Gilson and Murphy[18] Other studies reported a higher incidence of neonatal hypoglycemia in the glibenclamide group when compared with the insulin group, but the difference between the groups was not significant.[18,19,31,32] In a retrospective study by Ramos *et al.*,[14] hypoglycemia was significantly higher in the glibenclamide group than the insulin group. This difference may be related to the level of glycemic control in patients in the various studies.

The results of this study showed that the incidence of macrosomia in the glibenclamide group was significantly less than the group receiving insulin ($P = 0.005$). In some studies, no significant difference was observed between insulin and glibenclamide groups in the prevalence of macrosomia.[13,14,29,31] Balsells *et al.*[15] in a meta-analysis study showed that glibenclamide was associated with a higher birth weight and macrosomia. In another study, macrosomia risk (weighing more than 4 kg) was

Table 3: Univariate analysis based on predictor factors of macrosomia

Variables	Macrosomia		*P*
	Yes	No	
HbA1c (mean±SD)[a]	6.31±0.79	6.03±0.83	0.26
Maternal age (mean±SD)[b]	31.71±7.64	30.18±7.05	0.34
BMI (mean±SD)[b]	22.18±2.56	22.29±3.00	0.88
FBS (mean±SD)[a]	85.76±6.81	84.14±6.03	0.24
Gestational age at delivery (mean±SD)[a]	37.95±2.25	36.77±2.14	0.01
Para (mean±SD)[b]	1.38±0.60	1.42±0.62	0.78
Blood sugar 2 h after meal (mean±SD)[a]	107.57±8.25	110.91±59.55	0.87
Group[c], *n* (%)			
Insulin	17 (81)	112 (49.1)	0.005
Glibenclamide	4 (19)	116 (50.9)	
Sex of newborn[c], *n* (%)			
Male	9 (42.9)	112 (49.1)	0.58
Female	12 (57.1)	116 (50.9)	

[a]Mann-Whitney U-test was performed, [b]Independent *t*-test was performed, [c]Chi-square test was performed. SD=Standard deviation; BMI=Body mass index, FBS=Fasting blood sugar, HbAlc=Glycated hemoglobin

Table 4: The predictor factors of macrosomia based on the result of logistic regression models at birth

	B	SE	Significant	OR	95.0% CI	
					Lower	Upper
Groups* (insulin and glibenclamide)	1.51	0.58	0.01	4.62	1.45	14.02
Gestational age at delivery	0.30	0.04	0.01	1.41	1.04	1.74
FBS	0.06	0.04	0.16	1.06	0.98	1.14

*Glibenclamide group was reference. *B*=Regression coefficient, SE=Standard error, OR=Odds ratio, CI=Confidence intervals, FBS=Fasting blood sugar

higher in the glibenclamide group than the insulin group.[26,27] In this study, glycemic control was desirable with glibenclamide dose modification. Since uncontrolled diabetes can lead to fetal macrosomia,[33] perhaps the higher rate of macrosomia was due to higher BS levels in Cheng's study as compared to the current study.

Findings of this study showed that there was no statistically significant difference between the two groups in the prevalence of hypocalcemia, respiratory distress, and neonatal jaundice. The findings of this study are similar to other studies.[14,29,31,32,34]

In this study, two neonates in the insulin group had anomalies, one heart disease, and one polydactyly. There was no anomaly in glibenclamide group. Fisher exact test did not reveal significant differences between groups. In the study, treatment was started after organogenesis, when gestational age had reached 12 weeks or more. Therefore, it may be that the incidence of abnormalities has been related with the type of treatment. Ramos *et al.*[14] reported greater incidence of congenital anomalies in patients treated with glibenclamide than the insulin group. There were no neonatal anomalies in glibenclamide and insulin groups in Zangeneh *et al.*'s[29] trial study. Data in Homko *et al.*'s study indicated that risk of major congenital abnormalities may be related to maternal glycemic control before and during pregnancy.[35]

The results of the current study showed that NICU admission was more in the insulin group (8 vs. 4). Chi-square test showed no statistically significant difference between groups related to admission. Other studies reported similar results.[14,36] In Zangeneh *et al.*'s[29] study, none of the infants were hospitalized. Jacobson *et al.*[31] reported higher NICU admission rates in the group receiving insulin as compared to the group treated with glibenclamide and this difference was significant ($P < 0.001$). In Cheng *et al.*'s[27] study, NICU admission was more in infants of mothers taking glibenclamide than the group receiving insulin.

In general, the findings of this study showed that using glibenclamide for the treatment of gestational diabetes does not have side effects on newborns. This was corroborated in the study carried out by Elliott *et al.*[37] In their study, they observed that very low levels of second-generation sulfonylureas could pass through the placenta. They also observed that glibenclamide had the lowest concentration in infants' umbilical cord blood of diabetic mothers under treatment.[37] The reason behind this observation was the strong tendency of the drug to bind to proteins (it is reported as 99.9%) and a very short half-life of 4–6 h.[28,38]

In another study carried out by Kraemer *et al.*, to remove the binding effect of glibenclamide to proteins, they found that by removing albumin, blood levels of glibenclamide in umbilical cord still remained undetectable. They concluded that a specific pump actively pumps glibenclamide into the maternal blood against the direction of fetal blood concentration.[6,38] This pump, with the two above-mentioned mechanisms, has made glibenclamide a suitable drug for the treatment of gestational diabetes with minimal transmission to the fetus.

Limitation and suggestions

This study did not assess the amount of drugs used in each patient, length of NICU stay for infants, and the cause of hospitalization.

It is recommended that future studies consider the effects of each dose of drug used in neonatal outcomes. In addition, the cause of NICU admission in each group should be evaluated.

CONCLUSIONS

From the results and findings of this study, glibenclamide was able to reduce the risk of macrosomia without

increasing anomalies, jaundice, neonatal hypocalcemia, respiratory distress, and admission to the NICU. Therefore, glibenclamide can be an excellent alternative for insulin in the treatment of GDM.

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Conflicts of interest
There are no conflicts of interest.

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