Comparison of Glyburide and Insulin in Women with Gestational Diabetes Mellitus and Associated Perinatal Outcome: a Randomized Clinical Trial

Masoomeh Mirzamoradi[1], Zahra Heidar[2], Ziba Faalpoor[3], Zahra Naeiji[3], and Razyeh Jamali[4]

[1] Department of Prenatology, Mahdieh Hospital, Infertility and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] Department of Infertility, Mahdieh Hospital, Infertility and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3] Department of Gynecology, Mahdieh Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4] Department of Medicine, School of Medicine, Shahed University of Medical Sciences, Tehran, Iran

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Abstract- Insulin is currently the drug of choice in treating patients with gestational diabetes mellitus but insulin is expensive, inconvenient to store and use and probably associated with more risks of asymptomatic hypoglycemia in comparison with some oral agents. This randomized clinical trial was conducted to evaluate the efficacy and safety of glyburide in patients with gestational diabetes mellitus in comparison with insulin therapy. Pregnant women aged between 18-45 years with singleton pregnancies and in their 24-36 weeks of gestation were assessed for eligibility. Women with gestational diabetes mellitus were randomly allocated to two insulin and glyburide groups and compared with maternal and neonatal outcome. Ninety-six women with gestational diabetes mellitus enrolled in the study. At screen and treated fasting and post-prandial blood glucose levels were similar in both groups. Time for beginning the treatment to control the glycemic index was 28.30 (±20.60) days in the insulin group and 22.56 (±18.86) in the glyburide group. There was no statistically significant difference in time-to-control the blood glucose level in two studied group. Time, between beginning the treatment of GDM and delivery, was 53.22 (±28.96) days in the insulin group and 56.67 (±30.47) in the glyburide group. There was no statistically significant difference between the times of treatment-to-delivery in two studied groups. There were no statistically significant differences between maternal and neonatal outcomes in two studied groups. Glyburide can effectively and safely control the glycemic index in women with gestational diabetes mellitus in comparison with insulin.

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Keywords: Glyburide; Insulin; Gestational Diabetes Mellitus; Treatment

Introduction

Impaired glucose tolerance first occurred or recognized in pregnancy which is named gestational diabetes mellitus (GDM) is a major public health concern all over the world because of its association with several perinatal complications like preterm labor, respiratory distress syndrome, macrosomia, hypoxemia and hypoglycemia in fetus and elevated blood pressure/preeclampsia and traumatic or cesarean delivery in mother (1). GDM has prevalence between 1-14% in different studies (2). Recent studies show that the prevalence of GDM has increased steadily between 10–100% in several race/ethnicity groups in recent years (may be due to the rise of maternal age or sedentary lifestyle, obesity rate and type 2 diabetes in general population) (3). Some studies have proposed that changing the current diagnostic criteria may even triple the prevalence of GDM in the same population (4).

Insulin therapy is currently the method of choice for treating patients with both type 1 and type 2 diabetes in pregnant women when diet therapy alone can't control the hyperglycemia. Insulin is effective in glycemic index control but has its disadvantages. It is expensive, inconvenient to store and use and according to some studies it is accompanied by more risks of asymptomatic

Corresponding Author: Z. Heidar
Department of Infertility, Mahdieh Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Tel: +98 21 66525327, Fax: +98 21 66525327, E-mail address: dr_zheidar@yahoo.com

hypoglycemia in comparison with oral agents (glyburide) (5).

Glyburide is a common oral anti-diabetic agent from sulfonylurea family that has been proposed in the late 1960s. A single dose of glyburide is absorbed within 1 hour and peaks in about 4 hours. It has a half-life of 10 hours and clears from plasma in about 24 hours (in non-diabetic persons) so its anti-glycemic effects can persist for 24 hours after a single dose administration (6). Although some controlled in vitro studies have shown that against the first-generation sulfonylureas (tolbutamide and chlorpropamide) glyburide can't cross the placental barriers significantly (7), concerns about its teratogenicity and neonatal adverse outcomes (severe prolonged hypoglycemia) make clinicians to be cautious about using it in pregnant women (8).

This randomized clinical trial was conducted to evaluate the efficacy and safety of glyburide in patients with GDM in comparison with injections of insulin.

Materials and Methods

Study design and setting

This randomized clinical trial with convenient recruitment of patients during March 2012-March 2013 was conducted in a tertiary teaching hospital with a total annual census of 45000 adult patients. Study was approved by the institutional ethics committee. Informed written consent was obtained from all patients, and the trial was registered with clinicaltrials.gov (Identifier: IRCT2013071010876N2).

Selection of participants

Pregnant women aged between 18-45 years with singleton pregnancies and in their 24-36 weeks of gestation were assessed for eligibility. Two-hour oral glucose tolerance test was performed between 24-28 weeks of pregnancy. If fasting blood glucose level was >95 mg/dl, first-hour post-prandial blood glucose level was > 180 or second hour post-prandial glucose level was >150 patient was considered to have GDM.

All patients with a diagnosis of GDM were referred to diet and nutrition clinic. These patients were instructed to have three meals and three snacks per day. Their diet was designed to provide 25kcal/kg for obese patients and 35kcal/kg for the non-obese ones, with 40%-45% of total calories from carbohydrates. Patients were educated about how to measure blood glucose with a glucometer. They were requested to measure and document their blood sugar level 4 times a day (after overnight fasting and 2 hours after meals). Patients were visited weekly, and their adherence to dietary regimen was evaluated. If the FBS and 2 hours postprandial blood sugar levels stayed above 90 and 120 mg/dl respectively it was considered that the diet therapy has failed, and the patient was included in the study.

We excluded patients with known previous diabetes mellitus, fetal anomalies/aneuploidy, vascular disorders, and substance/alcohol abuse.

Intervention

Pharmacologic intervention was indicated when standard dietary management did not consistently maintain the fasting plasma glucose at <90mg/dl or the 2 hours postprandial plasma glucose <120mg/dl. Included patients were randomly assigned to glyburide and insulin groups by block randomization method based on computer generated random blocks of four by using sequentially coded sealed opaque envelopes.

Patients assigned to glyburide group received starting dose of 1.25 mg glyburide (Glibenclamide-Minoo®, 5mg tablets, Iran) with morning meal. If necessary, the daily dose was increased to 1.25 mg every 3 to 7 days (up to 20 mg/day). If consuming 20 mg/day glyburide for two weeks could not control the glucose level, therapeutic regimen was switched to insulin therapy. More than 10 mg doses were administered in two divided daily doses.

Patients assigned to insulin group received initially o.4 unit/kg insulin (100 units vials, Exir Pharmaceutical Co, Iran) subcutaneously, 50% from NPH and 50% from the regular form and in divided doses. The insulin dose was adjusted every 2 days.

At the initial visit, a detailed history was obtained that included demographic data, ethnic background (as reported by the women) and a summary of past social, medical and obstetrical history. At each following visit, the care provider evaluated the blood glucose values and, when necessary, increased the dose of insulin or glyburide as needed to meet these goals. All patients were scheduled for routine prenatal care visits for mothers with GDM. Laboratory and radiologic assessments were done uniformly and according to routine standard protocols. A standard protocol for the management of labor and delivery was used for both treatment groups perinatal outcome both in mother and infant was documented.

Outcome measures

Primary outcome was effective glycemic index control. The goals of treatment were achievement of mean blood glucose level of 90 to 105 mg/dl, fasting

blood glucose level of 60 to 90 mg/dl, a pre-prandial blood glucose level of 90 to 95 mg/dl, 2 hours postprandial blood glucose level of less than 120 mg/dl.

Secondary outcome was the fetal/maternal outcome which was assessed by evaluating the occurrence rate of abnormally high or low newborn body weight including large for gestational age (more than 90% percentile of body weight according to gestational age), small for gestational age (less than 10% percentile of body weight according to gestational age), macrosomia (birth weight ≥ 4000g); hypoglycemia (fetal umbilical cord blood glucose level <40mg/dl); hyperbilirubinemia (total bilirubin>12 mg/dl in first 7 days of life), polycythemia (hematocrit>60%), hypocalcaemia (ionized calcium<8mg/dl in first 3 days of life); Neonatal Intensive Care Unit (NICU) admission, need for oxygen therapy for more than 1 hour after birth or need to assisted ventilation and intubation. Neonatal respiratory outcomes included the presence or absence of hyaline membrane disease and transient tachypnea (defined as respiratory distress in infants born near term that lasted for about three days). The diagnosis of hyaline membrane disease was based on the criteria of Corbet *et al.,* (9). Another secondary outcome was the occurrence of drugs' adverse effect especially hypoglycemic sign and symptoms of agitation, confusion, poor coordination, double vision, palpitation, cold sweating, headache, and, *etc*.

Data analysis

The sample size was calculated as 42 in each group based on Magdy *et al*., study, in which sample size was calculated by "n=2*Cp-power/d2" formula considering d (standardized difference) as 0.71 and Cp-power as 10.5 (a constant defined by values chosen for the *P*-value and power, 10.5 for P-value of 0.05 and power of 90%) (10).

Descriptive data are presented as minimum, maximum and mean (with a standard deviation). We used Student *t*-test or chi-square test to compare means. *P*-value <0.05 was considered statistically significant. All data analyzes were performed with SPSS version 16 (SPSS, Inc., Chicago, IL).

Results

Maternal data

One hundred and five patients were assessed for eligibility. Nine patients were excluded, and 96 patients were enrolled in the study. Thirty-seven were allocated to receive glyburide and 59 to receive insulin. Studied patients' flow is illustrated as CONSORT diagram in figure 1.

Mean age of patients was 30.75 ±5.07 with a minimum of 18 and maximum of 40 years old. Mean body mass index (BMI) in the glyburide group was 30.18 ±5.35 and 31.77 ±5.11 in the insulin group. The difference between mean BMI in two groups was not statistically significant (*P*=0.15). Gestational age at the time of diagnosing GDM and beginning the treatment and also at the time of neonatal birth had no statistically significant differences. Other baseline characteristics of two treatment groups are summarized in table 1.

Table 1. Basic Characteristics of studied patients

Variable		Glyburide (n=37)	Insulin (n=59)	*P*. value
Age, mean ± SD, years		29.50 ±4.06	31.18 ±5.01	0.009
BMI, NO (%)	**19-25**	8 (21.6)	8 (13.6)	0.42
	26-28	8 (21.6)	10 (16.9)	
	≥29	21(56.8)	41 (69.5)	
Parity, NO (%)	**Nulliparous**	15 (40.05)	18 (30.5)	0.31
	Multiparous	22 (59.5)	41 (69.5)	
Previous children birth weight, mean ± SD, years		3144.34±701.25	3021.12 ±934.35	0.58
Previous history of GDM		1 (2.07)	2 (3.38)	0.85
Previous delivery of the newborn with macrosomia		2 (5.40)	1 (1.70)	0.27
Familial history of GDM		2 (5.40)	3(5.08)	0.94
Gestational age, mean ±SD, days	**at GDM diagnosis**	194.89±29.54	193.59 (±20.01)	0.83
	at beginning of treatment	209.24±28.84	211.89 (±27.80)	0.65
	at time of delivery	265.91±13.53	265.11 ±8.83	0.18
Type of delivery, NO (%)	**Vaginal**	9 (24.3)	17 (28.80)	0.63
	Cesarean	28 (75.7)	42 (71.20)	

At screen and treated fasting and post-prandial blood glucose level was similar in two groups before and during treatment (Table 2). Mean administered glyburide dose was 2.5 ± 1.25 mg/day and mean administered insulin dose was 27.82 ± 25.55) units/day.

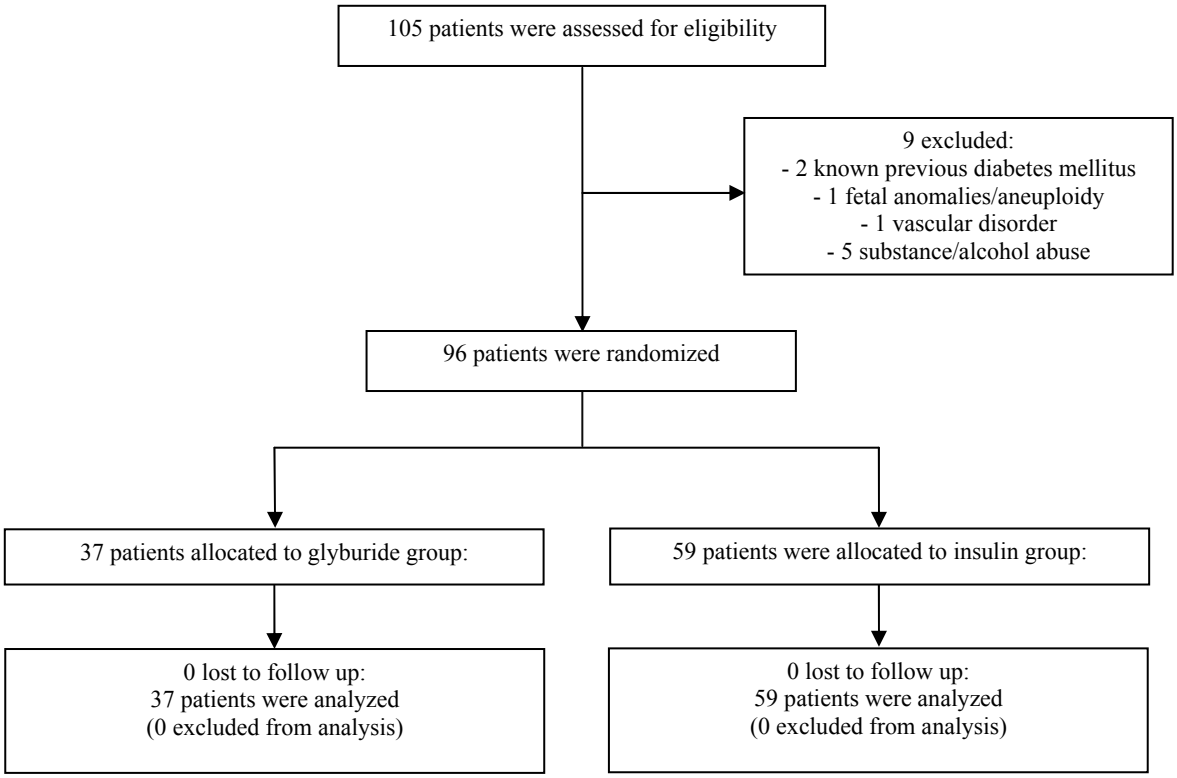

Table 2. At screen and treated blood glucose level in two studied groups

Variable		Glyburide (n=37)	Insulin (n=59)	*P*-value
At screen fasting blood glucose level, mean ± SD, mg/dl		109.83 ±68.99	112.15 ±19.39	0.72
At screen fasting blood glucose level, NO (%), mg/dl	**<95**	15 (40.5)	10 (16.9)	0.01
	≥95	22 (59.5)	49 (83.1)	
Treated fasting blood glucose level, mean ± SD, mg/dl		114.02 ±10.65	123.42 ±14.71	0.83
Treated post-prandial blood glucose level, mean ± SD, mg/dl		115.46 ±8.21	120.15 ±9.56	0.83
GTT results in 6 weeks after treatment, NO (%)	**Normal**	34 (91.9)	52 (88.1)	0.55
	Abnormal	3 (8.1)	7 (11.9)	

Time from beginning the treatment to control the glycemic index was 28.30 ± 20.60 days in the insulin group and 22.56 ± 18.86 in the glyburide group. There was no statistically significant difference in time-to-control the blood glucose level in two studied group (*P*=0.17). Time, between beginning the treatment of GDM and delivery, was 53.22 ± 28.96 days in the insulin group and 56.67 ± 30.47 in the glyburide group. There was no statistically significant difference between the time of treatment-to-delivery in two studied groups (*P*=0.57).

In all studied patients, glyburide could control the glycemic index, and no patient was switched to insulin therapy regimen.

The incidence of preeclampsia in the insulin group was higher than glyburide group (13.6% versus 8.1) but this difference was not statistically significant (*P*= 0.41). Cesarean section and vaginal delivery also had similar distribution in two studied groups. The indications for cesarean section (like beginning the labor pain in woman with previous cesarean section, amniotic fluid leak, fetal distress, cord presentation and etc.) had also similar frequencies in both groups (*P*. value=0.29).

Neonatal data

Mean birth weight was 3215 ± 506.47 in insulin received patients and 3236.75 ± 536.53) in glyburide received group. There was no statistically significant difference in birth weights between two groups (*P*= 0.84). Eleven neonates needed NICU admission. All NICU admissions were due to respiratory distress syndrome. One (1.7%) patient in the insulin group and 1 (2.7%) in the glyburide group needed endotracheal intubation. There was not statistically significant difference in need to endotracheal intubation between two studied groups (*P*= 0.73). Intubated neonate in the glyburide group (2.7%) needed surfactant. There were no cases of hypoglycemia, hypocalcemia and polycythemia in both groups. Another neonatal outcome related is summarized in Table 3.

Table 3. Neonatal Outcomes

Variable		Glyburide (n=37)	Insulin (n=59)	*P*-value
Neonatal birth weight, g	1000-2000	1 (2.7)	0 (0.0)	0.34
	2000-3000	9 (24.3)	22 (37.3)	
	3000-4000	25 (67.6)	33 (55.9)	
	>4000	2 (5.4)	4 (6.8)	
Neonatal APGAR score	Normal	37 (100)	58 (98.3)	0.42
	Abnormal	0 (0.0)	1 (1.7)	
Limb anomaly, NO (%)		0 (0.0)	1 (1.77)	0.01
Need to phototherapy, NO (%)	Yes	26 (70.3)	46 (78)	0.49
	No	11 (29.6)	13 (22)	
NICU admission, NO (%)		4 (10.8)	7 (11.9)	0.78
Mean NICU admission time, Mean ±SD, days		13.5 ±16.44	6.5 ±4.31	0.93

Discussion

Our study showed that glyburide can effectively control the blood glucose level in pregnant women with GDM as fasting and post-prandial blood glucose levels were similar in patients treated with glyburide and patients treated with insulin (as the treatment of choice). Time, from beginning the treatment to control the glycemic index, had also no statistically significant difference in patients treated with glyburide and patients treated with insulin. Our study showed also glyburide has an acceptable level of safety for glycemic index control in pregnant women with GDM as according to our results there is no statistically significant differences between maternal and neonatal outcomes between glyburide and insulin groups.

Although previous studies had shown that sulfonylurea agents can cross placental barrier easily, some recent pharmacodynamics studies show that minimal amounts of glyburide cross the placenta in in-vitro perfusion and this low level of glyburide is not harmful to fetus (11-12). Our results are compatible with other studies which have shown a similar efficacy and safety profile for glyburide and insulin-like the study of Anjalakshi *et al.,* (13) who showed that glycemic index control and neonatal birth weight were similar in patients receiving glyburide and insulin and the study of Kremer *et al.,* who evaluated 73 glyburide-treated pregnant women and showed that 81% of them had acceptable glycemic index control (14). Chmait *et al*., has also showed that glyburide has the failure rate as low as 19% in controlling the blood glucose level in pregnant women with GDM (15).

Our results about the safety of glyburide in pregnancy are in contrast with some other studies like the study of Jcobson *et al*., in 2005. We found no statistically significant difference between neonatal and maternal complications of GDM while Jcobson *et al*., (16) showed that some maternal/neonatal complications like pre-eclampsia and phototherapy requirement are more common in glyburide group in comparison with insulin group, but in same study the birth weight and prevalence of macrosomia were similar in patients receiving glyburide and patients receiving insulin. There

also other studies concluding the use of glyburide are inadvisable in pregnancy because of its possible maternal/neonatal adverse effects (17). This while the retrospective study of Conway *et al.,* on 75 glyburide - treated patients showed also a good glycemic control in 84% of the subjects with glyburide (16% were switched to insulin), similar rate of fetal macrosomia and mean birth weight and lower rate of required intravenous glucose infusions in the nursery in neonates from mothers treated with glyburide (18). Another case-control study by Fines et al reported that ponderal index (a measure of infant adiposity) was statistically significant lower glyburide-treated patients because the glyburide could provide a tighter glycemic control when compared with insulin (19).

There are also limited studies that show a better safety profile glyburide than insulin. For example, Holt *et al.,* who showed in their study that glyburide can control the blood glucose level, as well as insulin, while providing a better neonatal outcome in women receiving glyburide. In their study maternal outcome, especially the rate of pre-eclampsia and episodes of hypoglycemia were similar in patients receiving glyburide or insulin (20).

Considering the limitations and complications of insulin-therapy, providing a safe and effective alternative will be promising. Glyburide can be an acceptable alternative according to some clinical trials and retrospective studies which have found a tighter blood glucose control with fewer hypoglycemic episodes and similar neonatal and maternal outcomes in glyburide -treated patients in comparison with insulin but it is also reported that up to 20% of GDM patients (especially those with higher levels of blood glucose) fail to respond well to glyburide. It seems that the data about glyburide is a little conflicting yet, and complementary studies are needed better to clarify the cost and benefits of this therapeutic protocol. As a review on 9 studies, including a total of 745 glyburide-exposed pregnancies and 637 insulin-exposed pregnancies, showed that the use of glyburide was not associated with risk of macrosomia, differences in birth weight, rate of large for gestational age, differences in gestational age at birth, ICU admission, increased risk of neonatal hypoglycemia but concludes that because the most available studies are not well-designed randomized trials and potential teratogenicity of oral anti-diabetic agents, the effectiveness and safety of glyburide require further evaluation (21).

In summary, it is concluded that glyburide can effectively and safely control the glycemic index in women with gestational diabetes mellitus.

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