A comparison of Glibenclamide/Metformin Combination and Insulin for the Management of the Diabetes Mellitusn during singleton Pregnancy

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Abstract: Background: To study the efficacy and safety of glibenclamide/metformin combination as a treatment option for pregnant women with either gestational diabetes or type-2 diabetes mellitus compared to conventional insulin therapy. **Methods:** Ninety pregnant women with singleton pregnancies (69 women with gestational diabetes & 21 with type-2 diabetes mellitus) were included. They were randomly allocated to receive either glibenclamide/metformin combination or insulin. The primary end point was the achievement of the desired level of glycemic control. The presence or absence of maternal, fetal and/or neonatal complications was measured as secondary end points. **Results:** There were no differences between the oral hypoglycemic-treated group and insulin-treated group as regard the mean blood glucose levels. It was 125.64 ± 18.15 mg/dL in the former group where it was 124.62 ± 9.29 mg/dL in the latter one. There was no significant difference as regard the amniotic fluid volume, gestational age at delivery and mode of delivery. Also, there were no significant difference between the two groups as regard fetal outcomes; the perinatal mortality was 7.1% in oral hypoglycemic group compared to 4.8% in insulin group, and the rate of congenital anomalies was 4.9% in oral group compared to 9.5% in insulin group. Also there was no statistically significant difference as regard neonatal birth weight, neonatal umbilical blood glucose, incidence and duration of admission to NICU. **Conclusion:** The treatment of gestational diabetes and type-2 diabetes mellitus pregnant ladies with Glibenclamide/ metformin combination or insulin seems to be equivalent for both the mother and newborns.

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1. Introduction

Gestational diabetes mellitus (GDM) refers to diabetes diagnosed in the second or third trimester of pregnancy that is not clearly either type 1 or type 2 diabetes [1].

Very tight glycemic control is the main requirement for improvement of pregnancy outcome in diabetic ladies [2]. Insulin is the only approved pharmacological therapy to control hyperglycemia during pregnancy [3,4]. To achieve tight glycemic control required during pregnancy by the use of insulin, the pregnant lady has to have multiple insulin injections of insulin pump. In developing countries lack of both affordability and education are the main barriers to achieve this level of tight glycemic control by insulin use. The use of oral therapy to control glycemia during pregnancy, if possible, would be an excellent alternative to overcome these barriers.

Problems with the use of oral treatment of DM in pregnancy result from the ability of many antidiabetic oral agents to cross the placenta and cause fetal hyperinsulinemia. The fear of the possible teratogenic effects of oral antidiabetic drugs is another obstacle to their use in pregnancy. In 1991, Elliott et al. demonstrated experimentally that minimal glyburide was detectable crossing the placenta in an in vitro placental perfusion model [5]. In 2000, Langer et al. published the results of their controlled randomized clinical trial; where glyburide was compared with insulin in treatment of diabetes mellitus [6]. Reanalysis of the results of this study revealed that the use of large dose of Glyburide >10 mgm was accompanied with a trend to increased neonatal size [7].

Metformin is safe in pregnancy and women with gestational diabetes treated with metformin have less weight gain during pregnancy than those treated with insulin. Babies born to women treated with metformin have been found to develop less visceral fat, making them less prone to insulin resistance in later life. [8].

Gastrointestinal upset can cause severe discomfort; it is most common when metformin is first administered, or when the dose is increased. The discomfort can often be avoided by beginning at a low dose (1.0 to 1.7 grams per day) and increasing the dose gradually but even with low doses 5% of people may be unable to tolerate metformin. Use of slow- or extended-release preparations may improve

tolerability [9]. Metformin on the other hand, in spite of its significant ability to cross the placenta, does not cause hyperinsulinemia and was reported to be effective and safe in several clinical studies [10-16]. However, most of the published studies are small and retrospective.

Aim of the Study

To compare Glibenclamide/Metformin combination with insulin in treatment of diabetes mellitus during pregnancy; whether gestational or type-2.

2. Patient and Methods

Study design

Randomized controlled clinical trial.

This study was conducted on women attending outpatient clinic of obstetrics and gynecology department, Al Azhar university hospital.

Inclusion criteria

• Gestational Diabetes Mellitus (GDM): diagnosed according to WHO criteria by using Oral Glucose Tolerance Test (OGTT) that consists of glucose load of 75 g and a blood sample was measured 2 hrs later. The diagnosis of GDM was established if plasma glucose level was more than 140 mg/dL [17].

• Type 2 diabetes: where the beginning of the recruitment was before pregnancy.

Exclusion criteria

• Women with preexisting type 1 diabetes mellitus.

• Women with history of diabetic ketoacidosis.

• Multi-fetal pregnancy.

• Hypersensitivity to the used medications.

• Underlying vascular disease or medical condition known to affect fetal growth or drug clearance such as: chronic hypertension, systemic lupus erythematosis, chronic renal insufficiency, hepatic disease, antiphospholipid antibody syndrome or thrombophilia.

• Fetal anomalies identified on ultrasound prior to initiation of therapy.

• Diagnosis of GDM made after 32 weeks gestation.

• Patient refusal.

All women who agree to participate in the study, by informed written consent, were randomly allocated into two equal groups. The 1st group received Glibenclamide/Metformin combination; the beginning dose was 2.5 mg Glibenclamide and 500 mg Metformin orally with the morning meal. The dosage was increased gradually according to blood glucose level to a maximum daily dose of 10 mg Glibenclamide and 2 gm Metformin. If this maximum daily dose of the combination did not result in achieving the target values for two week period, insulin was given [6].

The second group received standard insulin 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 [6].

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 [6] The most recent randomized controlled trial, conducted in 2013, demonstrated that using a low carbohydrate diet (40%) did not reduce the insulin requirement but that it had a favorable impact on maternal weight gain. [14].

The sample size was analyzed using Statistical Program for Social Science (SPSS) version 22.0. Quantitative data were expressed as mean± standard deviation (SD) or Median (IQR). Qualitative data were expressed as frequency and percentage.

Method of randomization

Patients were serially ranked. Random tables were used to randomize those patients into two equal groups (using Glibenclamide/ metformin was labeled as letter “A”, and the patents who used insulin therapy was labeled as letter “B”. Both “A” and “B” labels were put in the opaque envelops according to serial ranking obtained from the random tables. After counseling women about the nature of the study and after obtaining a written consent, the corresponding serial envelop was opened and the patient then received the corresponding drug according to the type of label inside “A” or “B”.

The goals of treatment was the achievement of a mean blood glucose concentration of 90 to 105 mg per deciliter (5.0 to 5.9 mmol per liter), a fasting blood glucose concentration of 60 to 90 mg per deciliter (3.4 to 5.0 mmol per liter), a pre-prandial blood glucose concentration of 80 to 95 mg per deciliter (4.5 to 5.3 mmol per liter), and a postprandial blood glucose concentration of less than 120 mg per deciliter (6.7 mmol per liter) and hemoglobin A1c levels of less than 6.0% [2,6].

After establishment of optimum dose in both groups, the patients were followed up for:

• Weekly fasting and after two hour blood glucose level

• Development of polyhydramnios.

• Assessment of fetal wellbeing.

Upon admission for delivery both groups were compared as regard:

• Gestational age at delivery

• Mode of delivery.
• Serum glycosylated hemoglobin A1C.
• Birth weight: macrosomia was defined as birth weight 4000 gm or more [6,18].
• Fetal umbilical cord blood glucose level.
• Neonatal hyperbillirubinemia which was defined as a total bilirubin 12 mg/dl or more within the first 7 days of the birth.
• Admission to Neonatal Intensive Care Unit (NICU), and the duration of the admission.
• Neonatal outcome.

The results were statistically analyzed using independent sample student's t-Test to compare numerical value & chi-square test or Fisher exact test to compare categorical data. P-value <0.05 was considered statistically significant.

3. Results

90 patient devided into two group each had 45 patient, 6 patient were excluded 3 from each because in oral hypoglycemic drugs received group 1 moved away, 2 not continue in follow up, and another group were received insulin therapy 3 not continue in follow up.

Eighty-four patients were included in this study; forty-two patients received oral hypoglycemic in the form of glibenclamide/ metformin and the other forty-two patients received insulin therapy as a comparison group.

The following table shows that both groups were comparable at the time of recruitment **(Table 1).**

Table 1: Clinical characteristics of patients included in the study at admission (mean ± SD).

	Oral hypoglycemic group	**Insulin group**	***p*-value**
Age	33.19 ± 4.94	32.14 ± 5.73	0.189
Number of previous pregnancies	3.72 ± 1.79	3.17 ± 1.98	0.097
Gestational age	22.14 ± 7.33	24.48 ± 6.33	0.063
Glycosylated HbA1c	6.88 ± 0.62	6.96 ± 0.53	0.258

There was no statistically significant difference between the two groups as regard mean maternal blood glucose, amniotic fluid index, glycosylated HbA1c before delivery and reduction in glycosylated HbA1c (**Table 2).**

There was no statistically significant difference between two groups as regard fetal birth weight, fetal blood glucose, neonatal jaundice, neonatal hypoglycemia, admission to NICU, duration of admission to NICU, Perinatal mortality and congenital malformations (**Table 3**).

Table 2: Effect of treatment and degree of control of diabetes (mean ± SD).

	Oral hypoglycemic Group	**Insulin group**	***p*-value**
Mean maternal blood glucose	125.64 ± 18.15	124.62±9.29	0.374
Amniotic fluid index	17.05 ± 2.91	17.67 ± 2.85	0.167
Gestational age at delivery	38.05 ± 1.89	38.26 ± 1.24	0.272
Glycosylated HbA1c before delivery	5.54 ± 0.64	5.43 ± 0.49	0.205
Reduction in glycosylated HBA 1c	1.34 ± 0.77	1.53 ± 0.73	0.130

Table 3: Neonatal outcomes in both groups.

	Oral hypoglycemic group	**Insulin group**	***p*-value**
Birth weight	3507.1 ± 462.5	3527.4 ± 489.4	0.424
Fetal umbilical cord blood glucose	60.49 ± 12.87	59.52 ± 11.33	0.361
Neonatal hypoglycemia	5 (12.1%)	4 (9.5%)	0.695
Neonatal jaundice	18 (43.8%)	20 (47.6%)	0.620
Admission to Neonatal Intensive Care Unit (NICU	26 (63.4%)	29 (69%)	0.432
Duration of admission to NICU	3.31 ± 1.77	3.45 ± 2.67	0.412
Perinatal mortality	3 (7.1%)	2 (4.8%)	0.320
Congenital malformations	2 (4.9%)	4 (9.5%)	0.249

Discussion

In the current study glibenclamide/metformin combination was comparable to insulin treatment as regard mean maternal blood glucose, amniotic fluid volume, glycosylated HbA1c before delivery and reduction in glycosylated HbA1c. These results are in agreement with langer et al. who used only glibenclamide in comparison with insulin [6]. Also in

agreement with Jacobson et al. and Ramos et al. in their retrospective studies comparing glibenclamideand insulin; as regard maternal blood glucose [18, 19]. On the other hand, results of the current study agreeing with studies comparing metformin only with insulin like that of Janet et al. in their prospective study in gestational diabetes (MIG trial) and also with that of Hickman et al. [20, 21]. In all these studies only one oral hypoglycemic drug was used compared to two drug combination in our study but the maximum dose in some of these studies of glibenclamide was 20 mg compared to 10 mg in our study.

The birth weight was comparable between the two groups in the current study (3507.1 ± 462.5 gm in oral hypoglycemic group versus 3527.4 ± 489.4 gm in insulin group). This was resembling the results of Jacobson et al. (3661 ± 629, 3559 ± 650 for glibenclamide and insulin respectively) and with Ramos et al. (3420 ± 786, 3524 ± 548 for glibenclamide and insulin respectively) [18,19]. Also our results agree with study comparing metformin and insulin such as Janet et al. (3372 ± 572, 3413 ± 569 for metformin and insulin respectively) and Kristiina et al. (3671 ± 598, 3759 ± 642 for metformin and insulin respectively). Langer et al. found that birth weight was comparable between glibenclamide and insulin treatment but the birth weight in both groups was slightly lower than our results (3256 ± 543, 33194 ± 598 for glibenclamide and insulin respectively) [6,20,22].

The umbilical blood glucose was comparable in both groups (60.49 ± 12.87 mg/dl in oral hypoglycemic group versus 59.52 ± 11.33 mg/dl in insulin group). This agrees with Jean et al. who compared metformin and glibenclamide (57.9 ± 20.3 versus 54.7 ± 15.4 respectively) [23]. Neonatal hypoglycemia occurred in 12.1% in oral hypoglycemic group and was comparable to 9.5% in insulin group. These results agree with Langer et al. whereas neonatal hypoglycemia encountered in 9% in glibenclamide group and 12 % in insulin group and agree with Janet et al. (15.2% versus 18.6% with metformin and insulin respectively) [6,20]. However our results disagree with Ramos et al. they reported increased risk of neonatal hypoglycemia in the glibenclamide group 34% compared 14% in insulin group [19]. This can be explained by retrospective nature of this study and there was no maximum dose for glibenclamide. In our study the maximum dose of glibenclamide was 10 mg in addition of using metformin in combination to glibenclamide to decrease the dose of glibenclamide.

Both groups were comparable as regards admission to Neonatal Intensive Care Unit (NICU). About 63% of neonates admitted in oral hypoglycemic group whereas 69% admitted in insulin group. This agree with Kristiina et al. (42.2% versus 62.2% in metformin & insulin group respectively), Janet et al. (18.7% versus 21.1% in metformin & insulin group respectively) [20-22]. Also duration of admission was similar in our study (3.31 ± 1.77 days versus 3.45 ± 2.67 days in oral hypoglycemic & insulin group respectively). This agree with Kristiina et al. (2.4 days versus 3.9 days), However our results not agree with & Jacobson et al. who found higher frequency of admission in insulin group & longer duration of admission (15% versus 24%, P=0.008), (4.3 days versus 8.01 days, P=0.008) in glibenclamide & insulin group respectively [18,22]. The explanation of this difference in this retrospective study that insulin group had a higher mean body mass index & a significantly higher mean fasting blood glucose before treatment.

Both groups were comparable as regard congenital malformation & perinatal mortality. About 4.9%, 7.1% respectively in oral hypoglycemic group in comparison to 9.5%, 4.8% in insulin group. These results agree with Janet et al. who reported similar rate of congenital malformations between metformin & insulin group (3.1% versus 4.9% respectively) [20]. Also it agrees with Langer et al. who reported nearly the same rate of congenital malformation (2%) & perinatal mortality (1%) between glibenclamide & insulin groups [6]. The above two studies include only gestational diabetes cases.

Conclusion

The use of the Glibenclamide/metformin combination appears as attractive alternative to traditional insulin treatment in controlling diabetes during pregnancy. It has advantage of being cheaper, more easily to administer & more accepted by patients especially in developing countries. Further studies are needed before wide spread use of oral hypoglycemic for pregnant ladies.

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