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# A Comparison of Insulin and Glibenclamide in the Treatment of Gestational Diabetes Mellitus

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## ABSTRACT

**Background and objectives:** *Gestational Diabetes Mellitus is an important medical disorder in pregnancy which is amenable to treatment thereby improving the maternal and neonatal morbidities to a great extent. Insulin has been the gold standard for management of GDM but has many demerits as far as patient acceptance and compliance are concerned. Oral hypoglycemic agents if proven safe can revolutionise the treatment of GDM. The present study aims to compare the efficacy of insulin and glibenclamide in the treatment of GDM and also to analyse the maternal and neonatal outcomes.*

**Methods:** *It is a prospective observational study carried out in our institution. 100 antenatal patients diagnosed as GDM by standard criteria were recruited and randomized to two study arms of 50 each. Group A was started on insulin and Group B was started on glibenclamide upto a maximum dose of 20 mg per day. Capillary blood glucose levels were monitored and patients were followed up till delivery and neonatal outcomes also were analysed.*

**Results:** *One week after starting treatment 72% of Group A and 68% of Group B achieved target levels of blood glucose and the difference was not statistically different. Before delivery 88% in Group A and 86% in Group B had values within normal range. The reduction in fasting blood glucose levels in glibenclamide group before delivery was statistically significant. The incidence of maternal and neonatal morbidities was comparable in both the groups.8% of patients had treatment failure with glibenclamide and were switched over to insulin.*

**Conclusion:** *Glibenclamide appears to be an effective treatment agent in GDM with maternal and neonatal outcomes comparable with insulin. Studies involving more number of patients are still needed before glibenclamide can be considered as an effective alternative to insulin.*

**Keywords:** *Gestational diabetes mellitus, Insulin, Glibenclamide, Target blood glucose levels, Maternal and neonatal morbidities*

## INTRODUCTION

Gestational Diabetes Mellitus(GDM) is a very common disease that is detected among the pregnant women of our country. The incidence is on the rise and the effective control of blood glucose levels helps to reduce the associated maternal and neonatal morbidities to a great extent. Insulin has been the gold standard in the management of GDM because of its efficacy and also its safety as it does not cross the placenta. Oral hypoglycaemic agents have many advantages over insulin as far as patient acceptance and compliance are considered. Till recently oral hypoglycaemic agents were not used in pregnancy for the management of GDM because of the concerns about their safety and efficacy in pregnancy. A randomised controlled trial published in 2000 had proved that glibenclamide is a safe alternative to insulin in the treatment of GDM. Langer's study of 404 patients was preceded by placental perfusion study which showed that there was no transplacental transportation of glyburide. Since 2000, numerous studies of level 1 and level 2 evidence have produced similar findings. 80% of GDM patients treated with glyburide achieve glycaemic control with no risk to the mother and the baby. This is a giant leap forward for those providing primary obstetric care. The option of treating GDM with oral medication is a wonderful development that goes a long way in optimising the blood glucose levels of these patients even in low resource settings. This study is intended to compare the efficacy of insulin and glibenclamide in controlling the maternal blood glucose levels in women with Gestational Diabetes Mellitus. It also analyses the maternal and neonatal outcomes in both the treatment groups

## MATERIALS AND METHODS

We have conducted a prospective observational study at our tertiary care hospital among women attending the antenatal department. The women included were of age between 20 and 40 years with singleton gestation between 24 and 34 weeks. Those women with pregestational diabetes or any other medical disorders were excluded. The women who met the inclusion criteria were screened for GDM with a 1 hour, 50 gm oral glucose challenge test at 24 to 28 weeks of gestation. Women with plasma glucose concentrations between 140 and 200 mg/dl after the glucose challenge test were subjected to a 100 gm oral glucose tolerance test. GDM was diagnosed if the plasma glucose concentration after the 1 hour,50 gm oral glucose challenge test was greater than 200mg/dl or if two or more of the 100gm oral glucose tolerance test values were abnormal using the Carpenter and

Coustan's[1] criteria (fasting 95 mg/dl, 1 hour 180 mg/dl, 2hour 155 mg/dl and 3 hour 140 mg/dl). Upon diagnosis, women were advised dietary recommendations which included three meals and four snacks daily of which 40 to45% of the calories comprised of carbohydrates. Exercise usually walking for 20 minutes per day was also advised. After 2 weeks of dietary therapy capillary glucose monitoring was obtained. Failure of dietary therapy was defined as FBS greater than 90mg/dl and 2 hour PPBS greater than 120 mg/dl. These patients were subjected to two arms. Women in the insulin arm were designated as Group A and those in the glibenclamide arm were designated as Group B. Glibenclamide was started on a dose of 2.5 mg per day and was then increased at weekly increments of 2.5 mg upto a maximum of 20 mg per day as 10 mg b.i.d dosage. An increase of glibenclamide dosage was recommended when the capillary blood glucose levels were above the desired levels(FBS>90 mg/dl and PPBS >120 mg/dl). Glibenclamide failure was defined as capillary blood glucose levels above the desired range while on maximum dosage for 1 week.

If glibenclamide failure was noted, therapy was discontinued and patients were switched over to insulin. Demographic data, pertinent medical and obstetric history, weekly glucose values and the delivery and neonatal outcomes were recorded in a datasheet. Foetal surveillance was started at 28 weeks with daily foetal movement count. Non stress test and amniotic fluid index were done weekly from 34 weeks. All patients were routinely screened with an ultrasonogram for growth at 30 to 32 weeks of gestation and again at 36 to 38 weeks of gestation mainly to assess macrosomia and polyhydramnios. Patients were allowed to deliver at 40 weeks if blood glucose levels were well controlled or earlier if they developed any complications. The neonatal outcomes analysed included macrosomia(birth weight >4 kg),respiratory distress(defined as need for at least 4 hours of respiratory support with supplemental oxygen or continuous positive airway pressure, or intermittent positive pressure ventilation during the first 24 hours after delivery),neonatal hypoglycaemia (blood glucose level <40 mg/dl), hyperbilirubinemia (serum bilirubin >12 mg/dl), preterm birth (<37 weeks of gestation), hypocalcemia (serum calcium <7 mg/dl and hypomagnesemia (serum magnesium level <1.5 mg/dl). The data was summarized as frequencies or percentages for categorical variables and as means and standard deviations and inter quantile ranges for continuous variables, depending on the distribution. Differences between the treatment groups were compared by the chi-square for categorical variables and a two sample t-test for continuous variables. Two-tailed calculations were used to rule out a significant difference in either groups. Analyses were performed with SPSS software, version17 for windows.

## OBSERVATIONS AND RESULTS

100 women were recruited who fulfilled the inclusion criteria.

**Table 1** shows the age distribution of the study p opulation in both groups. The age of the patients in this study ranged from 22 to 36 years with a mean age of 28.04+/- SD(3.34) years. The mean age in Group A was 27.86(SD+/-3.58) where as in Group B was 28.22(SD+/-3.12).

**Table 1**

| Age Distribution | | |
|---|---|---|
| **Age (Yrs)** | **Group A N=50 # of patients (%)** | **Group B N=50 # of patients (%)** |
| <25 | 9 (18) | 14(28) |
| 25-30 | 33 (66) | 29(58) |
| >30 | 8 (16) | 7(14) |

**Table 2** shows the BMI distribution of the study population. The mean BMI was 28.04+/-SD(3.34).The mean BMI in Group A was 28.28(SD+/-3.76) and in Group B was 27.76 (SD+/- 3.99).

**Table 2**

| BMI | GROUP A N = 50 # OF PATIENTS (%) | GROUP B N = 50 #OF PATIENTS (%) |
|---|---|---|
| 18-24 | 12 (24) | 8 (16) |
| 25-30 | 23 (46) | 30 (60) |
| > 30 | 15 (30) | 12 (24) |

**Table 3** shows the incidence of family history of Diabetes Mellitus in both the groups (46% in Group A and 36% in Group B).

**Table 3**

| FAMILY HISTORY of DM | | |
|---|---|---|
| **FAMILY HISTORY** | **GROUP A** | **GROUP B** |
| | N =50 | N =50 |
| PRESENT | 23 (46) | 18 (36) |
| ABSENT | 27 (54) | 32 (64) |

**Table 4** shows the HbA1C value at the time of recruitment. The mean HbA1C value in the study was 6.23 SD +/- (3.97).In Group A the mean value of HbA1C was 6.6(SD+/-5.57) and in Group B was 6.1(SD+/-0.66).There was no statistically significant difference between the two groups(p value 0.28) >0.05

**Table 4**

| HbA1c at recruitment | | |
|---|---|---|
| HbA1c | **Gp A N =50 # of pts** | **Gp B N =50 # of pts** |
| <6 | 19 (38) | 25 (50) |
| 6.1-7 | 26 (52) | 23 (46) |
| >7 | 5 (10) | 2 (4) |

**Table 5** shows the number of patients who got blood glucose levels controlled within 1 week of starting treatment.72% had control achieved in 1 week in Group A and 68% in Group B.

**Table 5**

| Plasma glucose levels after starting treatment | | |
|---|---|---|
| | **Group A N=50 # of patients (%)** | **Group B N=50 # of patients (%)** |
| Controlled | 36(72) | 34(68) |
| Uncontrolled | 14(28) | 16(32) |

**Table 6** shows the mean fasting and 2 hour postprandial blood glucose levels in both the groups 1 week after starting the treatment. The difference was not statistically significant. The number of patients who could attain target blood glucose levels before delivery in both the groups were as follows(88% in Group A and 86% in Group B).

**Table 6**

| Plasma glucose levels after start of treatment | | | |
|---|---|---|---|
| | **GROUP A N=50 Mean (+/-SD)** | **GROUP B N=50 Mean (+/-SD)** | **p value** |
| FBS | 95.80 (17.48) | 90.28 (13.21) | 0.07 |
| PPBS | 123.1 (29.78) | 122.52 (26.29) | 0.91 |

**Table 7** shows the mean fasting and postprandial blood glucose levels before delivery. The difference between the two groups in fasting blood glucose levels was statistically significant (p value 0.002) whereas the difference between the two groups in post prandial blood glucose levels was not statistically significant (p value 0.115)

**Table 7**

| Mean Blood Levels Before Delivery | | | |
|---|---|---|---|
| | **GROUP A MEAN (+/-)** | **GROUP B MEAN(+/-)** | **P VALUE** |
| FBS | 89.26 (12.1) | 82.58 (8.19) | 0.002 |
| PPBS | 111.48 (12.1) | 107.3 (13.90) | 0.115 |

**Table 8** compares the plasma glucose levels between the two groups. The difference between the two groups in the reduction in fasting blood glucose levels before delivery alone was statistically significant.

**Table 8**

COMPARISON OF BLOOD LEVELS BTWN THE TWO GROUPS

| **Mean** | **Plasma Levels Before Treatment** | | **P VALUE** |
|---|---|---|---|
| | **GROUP A** | **GROUP B** | |
| FBS | 106 | 105 | 0.65 |
| PPBS | 140 | 141 | 0.67 |

**Table 8**

| Plasma Levels 1 Wk After Rx | | P value |
|---|---|---|
| **GROUP A** | **GROUP B** | |
| 95 | 90 | 0.078 |
| 123 | 122 | 0.918 |

**Table 8**

| Plasma Levels Before Delivery | | P VALUE |
|---|---|---|
| **GROUP A** | **GROUP B** | |
| 89 | 82 | 0.002 |
| 111 | 107 | 0.115 |

**Table 9** compares the gestational age at the time of delivery. There was no statistically significant difference between the two groups regarding the gestational age at termination of pregnancy( p value 0.73). 80% of the patients carried the pregnancy to term.30% of the study population had spontaneous onset of labour and70% had induction of labour.

**Table 9**

| AGE AT DELIVERY | | |
|---|---|---|
| **GA IN WKS** | **GROUP A N =50** | **GROUP B** |
| <34 | 2 (4) | 1 (2) |
| 34-37 | 7 (14) | 9 (18) |
| >37 | 41( 82) | 40 (80) |

**Table 10** compares the different maternal morbidities between the two groups. Operative delivery tops the list.

**Table 10**

| MATERNAL MORBIDITY | | |
|---|---|---|
| **OUTCOME** | **GROUP A** | **GROUP B** |
| INFECTION | 16(32) | 12 (24) |
| PIH | 4 (8) | 2 (4) |
| OPER.DEL | 21 (42) | 16 (24) |
| PRETERM D | 7 (14) | 8 (16) |
| POLYHYDR | 6(12) | 2 (4) |

**Table 11** shows the mode of delivery among patients in the two groups.63% had vaginal delivery and 37% had operative delivery.

**Table 11**

| MODE OF DELIVERY | GROUP A # (%) | GROUP B # (%) |
|---|---|---|
| SVD | 26 (52) | 28 (56) |
| AVD | 3 (6) | 6 (12) |
| EL.LSCS | 12(24) | 9 (18) |
| EMER.LSCS | 9 (18) | 7(14) |

**Table12** shows the indications for LSCS in both the groups.

**Table 12**

| INDN. FOR LSCS | GROUP A # (%) | GROUP B # (%) |
|---|---|---|
| CPD | 3 (6) | 1 (2) |
| PREV.LSCS | 10 (20) | 8 (16) |
| FOETAL DISTRESS | 4 (8) | 5 (10) |
| PRECIOUS PREGNANCY | 1 (2) | 1 (2) |
| FAILED INDUCTION | 2 (4) | 0 (0) |
| MALPRESENTATION | 1 (2) | 0 (0) |
| OTHERS | 0 (0) | 1 (2) |

**Table 13** compares the neonatal outcomes between the two groups. Hyperbilirubinemia, prematurity and hypoglycemia were the common morbidities encountered. There was no statistically significant difference between the two groups with regard to the neonatal outcomes.

**Table 13**

| NEONATAL OUTCOME | GROUP A | GROUP B | P VALUE |
|---|---|---|---|
| Preterm | 9 (18) | 10(20) | NIL |
| Macrosomia | 4 (8) | 1(2) | 0.37 |
| Hyperbilirubinemia | 10 (20) | 14(28) | 1 |
| Respiratory distress | 2 (4) | 3 (6) | 1 |
| Hypoglycemia | 6 (12) | 4 (8) | 0.74 |
| Hypocalcemia | 1 (2) | 0 (0) | NIL |

**Table 14** shows the distribution of birthweight in neonates among the two groups. The mean birthweight in Group A was 3.1 kg and in Group B was 2.9 kg. The difference in birthweight was not statistically significant (p value 0.35). The minimum and maximum dose requirements of insulin were 4 IU/day and 30 IU/day respectively in Group A and those of glibenclamide were 2.5 mg/day and 20 mg/day respectively. The dose received in Group B was as follows (2.5 mg-8%; 5 mg-6%; 7.5 mg-6%; 10 mg-44%; 15 mg-20%;20 mg-16%)

**Table 14**

| Birth Weight Distribution in two Groups | | |
|---|---|---|
| **Weight In KGS** | **Group A** | **Group B** |
| <2.5 | 5 (10) | 9(18) |
| 2.6-3.5 | 31 (62) | 32(64) |
| 3.6-3.9 | 10 (20) | 8(16) |
| >4 | 4 (8) | 1 (2) |

**Table 15** shows the mean dosage in both the groups. (INSULIN-14.6 IU/day and GLIBENCLAMIDE-10.5mg/day).The mean duration of treatment for patients in both the groups was 8 weeks.

Among the 100 patients studied, 24(48%) in Group A were admitted as inpatients to achieve glycaemic control. In Group B, 20(40%) were admitted as inpatients among which 4(8%) were admitted to switch over to insulin therapy due to failure of glibenclamide therapy.

**Table 15**

| MEAN DOSE REQUIREMENT | | |
|---|---|---|
| | **GROUP A** | **GROUP B** |
| MEAN DOSE | 14.6 IU/DAY | 10.5 MG/DAY |

**Table 16** shows the incidence of switch over in multiple studies[7,8,9]. 1 patient in Group B had symptoms of hypoglycaemia.

**Table 16**

| SWITCH OVER TO INSULIN | | |
|---|---|---|
| **AUTHOR** | **GLIBENCLAMIDE THERAPY # OF PATIENTS** | **SWITCH OVER TO INS** |
| Convey et al | 75 | 16% |
| Kremer and Duff | 73 | 19% |
| Chmait et al | 69 | 19% |
| Jacobson et al | 236 | 12% |
| Langer et al | 201 | 4% |
| Present study | 50 | 8% |

19 patients in Group A and 11 patients in Group B were given corticosteroid cover(2 doses of injection betamethasone 12 mg IM 24 hours apart) due to their high risk for preterm delivery. In Group A 52% achieved target blood glucose levels in 1 week. 34% took 2 weeks and14% took 4 weeks to optimize their blood glucose levels. In Group B 56% achieved target blood glucose levels within 1 week. 24% took 2 weeks and12% took 4 weeks to optimize their blood glucose levels.8% switched over to insulin.

## DISCUSSION

Glucose intolerance during pregnancy can be of varying severity. Early diagnosis, adequate treatment and follow-up are vital in successfully managing these patients. The mean age of the study population is 28.42+/-4.48 years. When the maternal age is above 30 years, there is increased incidence of GDM.BMI more than 30 is also associated with increased incidence of GDM. Multiparous women were more affected than primigravidae in the study but the association was not statistically significant. A family history of Diabetes Mellitus was present in 41% of patients. There was a significant association between the family history of diabetes and the

occurrence of glucose intolerance in present pregnancy. In a study conducted by Abha et al [2], history of GDM in the previous pregnancy was the most common factor associated with glucose intolerance in subsequent pregnancies. In the present study both arms of the study population were equally matched for age, parity, BMI, family history of DM and gestational age at delivery.

Glibenclamide is a common oral hypoglycaemic agent which gets absorbed within 1 hour and peaks in about 4 hours. It has a half life of 10 hours and gets cleared from plasma in about 24 hours with anti glycaemic effects persisting upto 24 hours after single dose administration[3]. Glibenclamide does not cross the placental barriers significantly [4].

There are several randomised controlled trials comparing insulin and glibenclamide. They were conducted in diverse countries and populations. Langer et al[5] conducted the study in U.S.A in 2000, involving 404 participants following a 3 hour OGTT. Bertini et al[6] conducted the study in Brazil in 2005 with 70 patients following a 75 gm WHO OGTT. Anjalakshi et al[7] conducted the study in India in 2006 with 26 participants following 75 gm WHO OGTT. The trials also compared different treatment interventions. The recent studies include those conducted by Mukopadhyay etal[8], Tempe et al[9] and Masoomeh etal[10].

In the present study 50 patients had received insulin and 50 patients received glibenclamide. 4 patients (8%) in the glibenclamide group were switched over to insulin.87% could achieve the values within the specified range. In the primary analysis of the present study, it was found that 88% of the insulin treated and 86% of the glibenclamide treated patients achieved the target levels of glycaemic control. In the current study the success rate for achieving established levels of glycaemic control is similar in insulin and glibenclamide treated patients. As the recommended threshold for initiation of pharmacological therapy is FBS >90 mg/dl and 2 hour PPBS> 120 mg/dl ,for majority of patients glibenclamide therapy could be the drug of choice when diet or exercise failed.

Langer[5] and colleagues reported from the largest RCT involving 404 patients that there was no statistically significant difference in the mean fasting or two hour postprandial blood glucose levels between those taking insulin or glibenclamide. A smaller RCT by Anjalakshi et al[7] also reported similar findings. There was difference in the gestational age at recruitment among the studies. The present study had patients recruited between 24 and 28 weeks of gestation whereas Langer et al[5] had patients recruited between 11 and 13 weeks.

In the present study 37% of patients underwent operative delivery, the most common indications being previous LSCS and foetal distress. 42% in the insulin arm and 32% in the glibenclamide arm had LSCS done.Langer[5] had reported similar LSCS rates among the patients of both groups(24% in insulin arm and 23% in glibenclamide arm). Bertini et al[6] reported similar incidence of LSCS among patients of both arms(44% in insulin arm versus 50% in glibenclamide arm).

In the present study hyperbilirubinemia and hypoglycemia were the most common neonatal morbidities. In the present study macrosomia was more common in the insulin group. This was associated with high BMI and positive family history. The study by Jacobson et al[11] showed that the incidence of macrosomia was higher and this could be attributed to the characteristics of the study population. Langer[5] reported no statistically significant difference between the two groups regarding the percentage of neonates with hypoglycaemia (6% versus 9%) whereas Bertini et al[6] and Lain et al[12] reported a statistically significant higher proportion of infants with macrosomia and hypoglycaemia in the glyburide group(33%) compared to the insulin group(4%).

As all the women were treated with glibenclamide after organogenesis. the rate of anomalies reported were similar between the two groups and also similar to women without GDM. No cases of neonatal death, intrauterine foetal demise, lethal anomalies or exchange transfusions were reported in both the groups.

According to Masoomeh et al[10] glyburide could achieve fasting and post prandial blood glucose levels comparable to insulin. Time from initiation of treatment to control of blood glucose levels had no statistically significant difference between both the treatment arms. The maternal and neonatal morbidities in both the groups also did not show any statistically significant difference. ACOG practice bulletin on Gestational Diabetes Mellitus 2013[13] indicates that the current data shows no adverse short term effects of therapy with oral hypoglycaemic agents on maternal and neonatal health, but long term outcomes have yet to be studied.

In the present study 8% of patients needed switch over to insulin to attain target blood glucose levels. This was 4% in Langer et al's[5] study. The patients started on glibenclamide maintained the desired blood glucose levels while on it. Those who were destined to fail glibenclamide therapy had significantly higher fasting and 2 hour postprandial blood glucose levels and were outside the desired levels while on treatment also. Their mean duration of glibenclamide therapy was 6 to 8 weeks.

The present study also showed that glibenclamide therapy is much more cost effective than insulin therapy. Glibenclamide also has better patient acceptance as it is orally administered when compared to insulin with parenteral administration.

## CONCLUSION

Glibenclamide seems to be an effective drug in the treatment of pregnant women with GDM, with maternal and neonatal morbidities comparable to those of insulin. However further sufficiently powered and randomized clinical studies are still needed, which address variety of issues including long term follow up of children, to determine the role of glibenclamide as an alternative to insulin in the treatment of women with Gestational Diabetes Mellitus.

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