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Glibenclamide Therapy in Hyperglycemia during Pregnancy and its Short and Long Term Implications

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Abstract

Objectives: This randomized controlled trial was conducted to evaluate efficacy and safety of glyburide (glibenclamide as available in India) compared to insulin for treatment of hyperglycaemia in pregnancy (HIP) including gestational diabetes mellitus and type-2 DM, with offspring follow up to 7-10 years for long-term consequences.

Materials and Methods: Total 80 cases of GDM diagnosed on OGTT (100 gm) by Carpenter-Coustan cut-offs and remained uncontrolled on MNT type-2 DM, between 12 to 34 weeks gestation, were enrolled after taking informed consent and randomized into two groups. Group-I (n=40) received oral glibenclamide and group-II (n=40) received Insulin. Glibenclamide therapy was considered failed if targets BS could not be achieved with maximum glibenclamide dose (20 mg) and patient was switched over to insulin.Primary outcome measures wereglycemic control and time taken for achieving normoglycemia and failure of therapy. Secondary outcomes were dose requirement, maternal hypoglycemia, fetal complications- macrosomia, intrauterine death (IUD), congenital malformations, neonatal hypoglycemia and neonatal intensive care unit (NICU) admission and long-term follow up of children born.

Results: Baseline profile of patients in both groups was comparable. In group I, 31 subjects required twice daily doses. Mean ±SD (range) of daily glibenclamide dose was 5.5±3.6 (2.5-17.5) mg. Mean glibenclamide dose was 3.75 for morning single dose, 3.55 mgfor evening single dose and 2.7 mgeach in patients requiring twice daily dose.In group-II the mean insulin required was 28.8 ± 9.6 (8-45) units in 4 divided dosages of approximately 6-7 units. There was no difference in the time taken to attain glycemic control in the two groups which was 17 days and 15.5 days in group I and II respectively (p=0.57).

At recruitment the mean HbA1c (in %) was 6.2±0.28 and 6.4±0.43(p=0.22) which reduced to 5.3±0.53 and 5.8±0.(p=0.01) at delivery in group I and group II respectively indicating better control of HbA1c levels with glibenclamide. None of the babies in group-I including two cases of type 2DM who continued glibenclamide in first trimesterhad any congenital malformation. In group II, two babies had congenital malformations:

BS-F was more significantly correlated to the control on nutrition alone vs treatment requirement. All patients with BS-F<95 mg/dL achieved normoglycemia on MNT and did not require pharmacologic treatment. Patients with BS-F >110 mg/dLcould not be controlled on diet alone throughout pregnacy. Fasting value <135 could not be controlled on diet initially also in GDM cases. Nutan GDM grading is proposed on basis of fasting blood sugar lavels.

Two cases (5%) had failure of therapy with glibenclamide and switched over to insulin therapy both had hypothyroidism. In group I, hypoglycemic attacks were seen in 4(10%) cases. In insulin group,

hypoglycemia was seen in 3 (7.5%) cases.

There were two IUD in group I, both had preeclampsia. One neonatal death occurred in group 2. Neonatal outcome was comparable in both groups. Offsprings of glibenclamide group showed no adverse consequences at 7-10 year follow up

Conclusions: Glibenclamide is comparable to insulin in treating diabetes in pregnancy with similar obstetrical, maternal or perinatal outcomes andis not associated with any long term adverseconsequences in the offspring.

Keywords: Gestational diabetes mellitus; glibenclamide; glyburide; insulin; glycemic control.

Introduction

Incidence of hyperglycemiain pregnancy (HIP) is increasing world over and has reached upto 27.5% in India[1] and includes gestational diabetes mellitus (GDM) and type 1 and 2 DM. The estimated prevalence of GDM in India is 16.5%.[2] Maternal hyperglycemia changes the intrauterine milieu,alters fetal physiology leading to long term metabolic problems like obesity, diabetes and cardiovascular diseases in the child.[3] This is an example of fetal origin of adult disease. Hence hyperglycemia in pregnancy puts two generations at risk.

Approximately 30-40% of pregnant women with hyperglycemiaremain uncontrolled on medical nutrition therapy (MNT) and exercise and require pharmacological treatment.[4] Insulin continues to be the first line therapyas iteffectively reduces adverse effects of hyperglycemia in pregnancy and does not cross placental barrier due to high molecular weight. Disadvantages of insulin include inconvenience of repeated injections, need of monitoring, lipid dystrophy at injection site and cost and storage difficulties. Therefore, finding an effective alternative to insulin is desirable for pregnant women.

With oral hypoglycemic agents, there are concerns of teratogenicity when used in the first trimester, delayed and poor glycemic control and fear of hypoglycemia. Metformin, although found effective and safe even in first trimester, required additional insulin therapy in approximately 46% cases.[5] There are concerns of crossing placental barrier and fat redistribution in baby.[6]

Sulphonylureas like chloropamide and tolbutamide, though evaluated in initial studies, were considered a contraindication during in pregnancy, as these could cross placenta and reach fetus. Since GDM is characterized by insulin resistance, as well as loss of first phaseinsulin secretion, glibenclamide (glyburide) has also been evaluated during pregnancy as it can correct both thesedefects and does not cross placenta inappreciable quantity.[7,8]

The first landmark trial for glibenclamide conducted by Langer et al compare dits efficacy with insulin for treating GDM and found no difference.[9] Further studies reported it as an effective treatment of GDM when started after 24 weeks.[10,11] When compared to metformin, glibenclamide has lesser failure rate as monotherapy.[12] Thus glibenclamide seems much more promising and if found safe and efficacious, it can be used as first line treatment of HIP which remains uncontrolled on MNT especially in developing countries as the drug is much cheaper, easily available and can obviate need of multiple daily injections and storage facility.

The present trial was conducted to evaluate efficacy and safety of glyburide (glibenclamide as available in India) compared to insulin for treatment of HIP including GDM, overt diabetes and type-2 DM. Also, patients and children were followed up to 7-10 years for long-term consequences.

Materials and Methods

This prospective randomized controlled trial was conducted in high risk pregnancy clinic in Department of Obstetrics and Gynaecology at All India Institute of Medical Sciences, New Delhi in 2010- 2013, after taking ethical clearancefrom institute'sEthics Committee.

Total 80 cases of HIP between 12 to 34 weeks of gestation who were uncontrolled on MNT, were enrolled after taking informed consent. Patients already on insulin therapy before 12 weeks gestation were also included once they were beyond 12 weeks. Type-1 DM and multiple gestation were excluded. GDM was diagnosed as per Carpenter and Coustan cut off values on 100 gm oral glucose tolerance test (OGTT): Fasting blood sugar (BS-F)>95mg/dL, BS-1hour >180mg/dL, BS-2hour >155mg/dL and BS-3hour>140mg/dL;if any two or more values were deranged.[13]

Detailed obstetric history, previous diabetic history and significant past history related to risk factors was taken. General physical and obstetrical examination was conducted. Routine antenatal investigations and HbA1c was done. Renal function test and fundus examination was done in type-II diabetes. First trimester and second trimester ultrasound including anomaly scan, fetal echo, were also done. Patients wereadvised MNT and 4-point blood sugar profile was evaluated a week later.

Patients of GDM who did not achieve target blood sugar (BS-F< 95mg/dL and BS-2hr< 120mg/dL) and patients of type-II DM after 12 weeks gestation (even if they were on insulin in first trimester) were randomized into two groups after 12 weeks in 1:1 ratio by computerized randomization table after taking informed consent. Group-I (n=40) received oral glibenclamide and group-II (n=40) received Insulin.

Glibenclamide was started as 1.25 mg once or twice daily,half an hour before breakfast or dinner Six-point blood sugar (BS) profile including BS-F, BS-2hr post-breakfast, pre-lunch, BS-2hr post-lunch, pre-dinner and BS-2hr post-dinner were measured twice weekly till normoglycemia was achieved. Glibenclamide dose was increased by 1.25-2.5 mg/day to amaximum of 10 mg twice-daily (total 20 mg) or reduced if hypoglycemia developed (BS <60 mg/dL). Therapy was considered failed if targets BS could not be achieved with maximum glibenclamide dose and patient was switched over to insulin.

Group-II was given regular insulin three times daily: pre-breakfast, pre-lunch and pre-dinner and intermediately-acting insulin at bed time; dose was based on the principle that 1 unit insulin lowers blood glucose by 30mg/dL.[14] Blood sugar monitoring was done every 48-72 hours after an increase indose. Once normoglycemia was attained, monitoring was done weekly.

All patients underwent HbA1c at baseline, then at delivery. Routine antenatal care was given to all patients including anomaly scan. Ultrasound for growth estimation was done at 32 weeks.

Primary outcome measures wereglycemic control and time taken for achieving normoglycemia, failure of therapy Secondary outcomes were dose requirement, maternal hypoglycemia, fetal complications-macrosomia, intrauterine death (IUD), congenital malformations, neonatal hypoglycemia and neonatal intensive care unit (NICU) admission.

Patients' delivery was planned at 38 weeks, either by induction or caesarean as indicated. Babies with birth weight >90th percentile were considered large for date(LGA). Macrosomia was defined as birth weight of ≥4000 gm. Neonates were monitored for hypoglycemia (BS<40 mg/dL); serum bilirubin and levels were also measured. NICU admission, congenital anomalies, birth injuries, and need for phototherapy were noted.Long-term follow-up after 7-10 years of delivery was done for any consequencein the offspring after glibenclamide exposure in utero andobesity, diabetes, cardiovascular disease, neuro-development were noted in children.

Statistical Analysis

Data was analyzed using SPSS version 19. The statistical techniques applied were student t-test (independent) to compare between two groups glycemic control and baby weight. The chi-square test was used for qualitative data such as the antenatal complications, perinatal complications. Mann Whitney test, 2way ANOVA followed by Bonferroni were used as appropriate. P-value <0.05 was considered significant.

Results

During study period, total 177subjects hadhyperglycemia in pregnancy, among whom 15 were pre-diagnosed cases of type 2DM on oral hypoglycemic or insulin and 162 were GDM and were advised MNT. Twelve out 15 type-2 diabetic patients after 12 weeks gestation and 68/162 GDM patients not meeting glycemic targets on MNT (49 a week after initiation of MNTand 19 more in due course of pregnancywererandomized into the group I and II, with 40 patients in each group. Consort (Fig. 1). Baseline profile of patients in both groups was comparable. (Table 1).

Table:1 Baseline characteristic of patients in both groups

Characteristic	Group I (n=40)	Group II (n=40)	P value
Age (in Years) Mean ± SD (range)	30 ± 4.4 (23-42)	30 ± 3.9 (20-38)	0.45
BMI (kg/m2)	26.5± 2.2	27.6± 2.3	0.13
Primigravida n(%)	11(27.5%)	12(30%)	0.13
Multigravida n(%)	29(72.5%)	28(70%)	0.13
Previous Abortions n(%)	8(24%)	11(27.5)	0.31
Previous Preterm birth n(%)	6(15%)	10(25%)	0.53
Previous history of IUD* n(%)	3(7.5%)	7(12.5%)	0.20
Gestation age at initiation of therapy (in weeks) Mean±SD (Range)	22 ± 6.9 (12-32)	20.1 ± 9.3 (6-34)	0.75

*IUD- intrauterine death

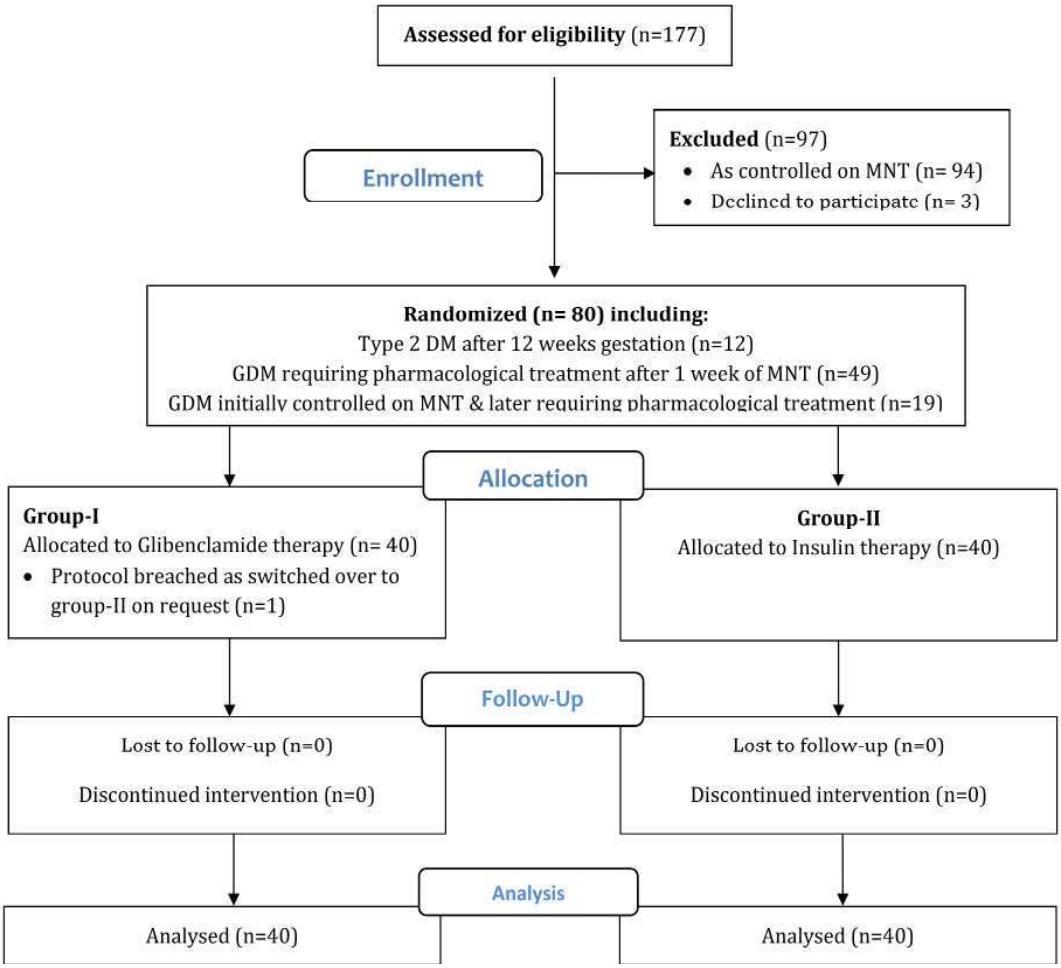


Fig.1: Consort Flow Diagram.

Comparison of GTT values in women diagnosed with GDM and controlled on MNT vs. pharmacological therapy is given in Table-2.

All patients with BS-F<95 mg/dLachieved normoglycemia on MNT and did not require pharmacologic treatment initially. Patients with BS-F >110 mg/dL could not be controlled on diet alonethroughout pregnancy. BS-F was more significantly correlated to the control on nutrition alone vs treatment requirement. Fasting value>134 could not be controlled on diet initially also in

Table 2: Comparison of GTT values in women diagnosed with GDM and controlled on MNT vs. pharmacological therapy n=162.

OGTT (100 gm) values*	GDM controlled on MNT N=94	GDM controlled on pharmacological therapy N=49	P Value	GDM initially controlled on MNT, later required pharmacological therapy n=19	P Value
BS-F Mean ± SD (Range)	94 ± 8 (86-110)	123 ± 20 (111-167)	0.0001	108 ±11 (96-134)	0.01
BS-1h Mean ± SD (Range)	170 ± 21 (123-199)	197 ± 32 (140-275)	0.01	172 ± 14 (136-220)	0.93
BS-2h Mean ± SD (Range)	141 ± 28 (94-176)	165 ± 32 (132-230)	0.001	155 ± 24 (130-172)	0.14
BS-3h Mean ± SD (Range)	120 ± 26 (89-165)	148 ± 22 (108-187)	0.01	130 ± 15 (120-147)	0.25

*Carpenter Coustan Cut offs, Type 2 diabetes not included

GDM cases. Post Glucose 1, 2 and 3h values were not significantly correlated to the glycemic control. All patients with BS-F<95 mg/dLachieved normoglycemia on MNT and did not require pharmacologic treatment initially. Patients with BS-F >110 mg/dL could not be controlled on diet alonethroughout pregnancy. BS-F was more significantly correlated to the control on nutrition alone vs treatment requirement. Fasting value>134 could not be controlled on diet initially also in GDM cases. Post Glucose 1, 2 and 3h values were not significantly correlated to the glycemic control.

In group I, total 31 subjects required twice daily doses. Mean ±SD (range) of daily glibenclamide dose was 5.5±3.6 (2.5-17.5) mg. Mean glibenclamidedose was 3.75 for morning single dose, 3.55 mg for evening single dose and 2.7 mg each in patients requiring twice daily dose. Pattern of fall of blood sugar in first week with starting doses of 1.25 and 2.5 mg is shown in Table-3. Total 16 (40%) patients required one or more dose increments with 2/3rd patients requiring increments between 26-32 weeks gestation.

Table 3: Pattern of fall in blood sugar in first week with glibenclamide.

Starting Dose	Dose 1.25 mg	Pre-meals (mg/dL)	Postmeals (mg/dL
	At Recruitment	119.1±12.4	143.67± 15.98
1.25 mg	After 1 week	104.1±6.87	130.17±11.3
	Fall in sugar levels in 1 week	15 (12.6% fall)	13.5 (9.3%)
	At Recruitment	134.14±9.5	149.76±14.1
2.5 mg (1.25 mg twice daily)	After 1 week	111.09± 6.14	122.05±9.2
	Fall in sugar levels in 1 week	23.05 (14.5% fall)	27.71 (18.5%)

In group-II the mean insulin required was 28.8±9.6 (8-45) units in 4 divided dosages of approximately 6-7 units. There was no difference in the time taken to attain glycemic control in the two groups which was 17 days and 15.5 daysin group I and II respectively (p=0.57). Mean blood sugar levels at the treatment initiation and at delivery were comparable in group I and II as shown in Table 4.

Table 4: Blood glucose levels in two groups at Drug initiation and at delivery.

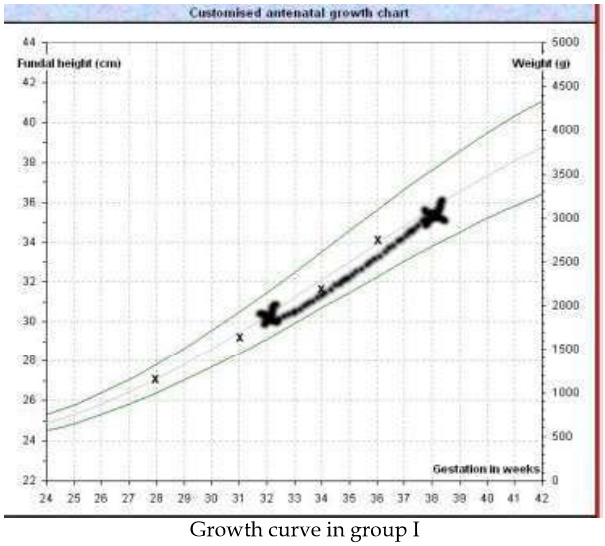
Blood sugar (In mg/dL)	At Drug Initiation			At Delivery		
	Group Glibenclamide Mean ± SD (Range)	Group II Insulin Mean ± SD (Range)	P Value	Group I Glibenclamide Mean ± SD (Range)	Group II Insulin Mean ± SD (Range)	P Value
Fasting	121.6±13.8 (96-150)	136.1±36.5 (111-260)	0.11	84.5±8 (76-110)	84.2±5.5 (76-98)	0.91
2-h post Breakfast	139 ± 29 (94-213)	152.3±24.5 (126-195)	0.14	89.4±7.9 (77-102)	91.2±11.5 (88-112)	0.56
Pre-lunch	138.8±23.7 (98-188)	147.2±20.1 (118-178)	0.24	85.4±7.1 (75-103)	90.4-7.4 (77-104)	0.03
2-h post-lunch	154.4± 20.4 (112-183)	167±25.2 (133-242)	0.09	91.4-10.8 (70-112)	94.7-10.1 (79-117)	0.32
Pre-dinner	139±28.4 (94-169)	149.8±20.8 (110-176)	0.18	90.9±8.4 (76-102)	92.1±9.8 (75-111)	0.69
2-h post-dinner	165±28.9 (126-213)	167.7±20.2 (137-206)	0.73	99.8±11.9 (80-133)	103.6-10.4 (87-118)	0.30

At recruitment the mean HbA1c (in%) was 6.2±0.28 and 6.4±0.43 (p=0.22) which reduced to 5.3±0.53 and 5.8±0.(p=0.01) at delivery in group I and group II respectively indicating better control of HbA1c levels with glibenclamide.

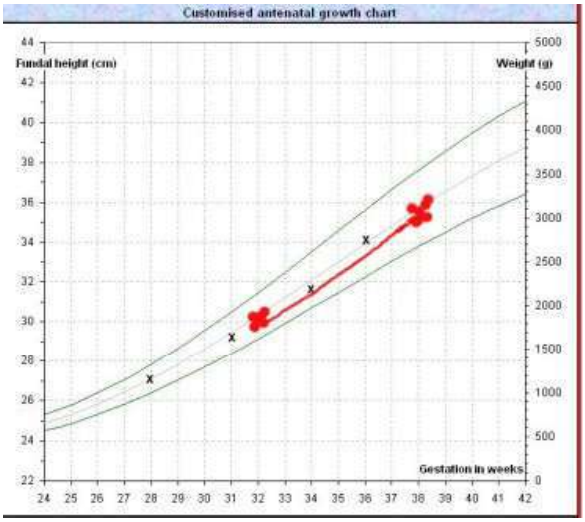
Two cases (5%) had failure of therapy with glibenclamide and switched over to insulin therapy. Ironically, one of these two cases diagnosed early in pregnancy, had intermittent hypoglycemic attacks yet normoglycemia was not achieved. One case had protocol violation as initially allocated to glibenclamide group, she was switched over to insulin on her request. In group-II one patient remained hyperglycemic despite 69 units of insulin.

Adding metformin 500mg twice daily with insulin could control the sugar levels in this patient.

In group I, hypoglycemic attacks were seen in 4(10%) cases including the patient who had to be switched over to insulin due to failed response; the other three developed hypoglycemia between 27 to 32 weeks gestation approximately 3-5 weeks after starting therapy and could be controlled on lowering the dose along with diet modification. In insulin group, hypoglycemia was seen in 3(7.5%) cases.



Growth curve in group I



Growth curve in group II

Fig.2: Comparison of intrauterine fetal growth pattern in the two groups

Growth parameters on ultrasound were comparable in the two groups (Figure 2). Mild polyhydramnios was detected in two cases in group II at 32-week scan.None of the babies in group-I,including the two cases of type 2DM who continued glibenclamide in first trimester,had any congenital malformations. In group II, two babies had congenital malformations: one had cardiac defects and anal atresia detected at 28 weeks gestation, cordocentesis revealed normal karyotype, patient had preterm delivery and baby died immediately. The other baby had atrial septal defect.

There were two IUD in group I: one was a known case of preeclampsia, oligohydramnios and fetal growth restriction and subsequently had fetal demise at 33 weeks gestation. The other was the case who was switched over to insulin due to failed response to glibenclamide; she developed gestational hypertension, was advised hospitalization but was noncompliant and came at 37 weeks with history of diminished fetal movements and IUD was detected.There was one neonatal death in group 2. Maternal and fetal outcome is depicted in table 5.

The period of gestation at delivery was similar in the two groups, 37.6±0.57 (32-38.6) weeks in group I

Table 5: Maternal and perinatal outcomes in the two groups.

Parameter	Group I	Group II	P-value
Maternal Outcomes			
Preeclampsia n (%)	9(22.5%)	7(17.5%)	0.5
Preterm labour n (%)	3(7.5 %)	3(7.5%)	1.0
Perinatal loss n (%)	2(5%)	1(2.5%)	0.6
Caesarean delivery n (%)	8(20%)	14 (35%)	0.5
Hypoglycemia	4(7.5%)	3(12.5%)	
Polyhydramnios	0(0%)	2(10%)	0.49
Perinatal Outcomes			
Weight (kg) Mean±SD Range	3.052±0.45 (2.2-4.2)	3.014±0.39 (1.8-3.52)	0.77
Glucose (mg/dL) Mean±SD Range	83.9±8.5 (68-98)	86.2±5.5 (76-96)	0.32
Bilirubin (mg/dL) Mean±SD Range	8.06±0.82 (7-9)	8.8±1.19 (7-12)	0.027
Birth Asphyxia n (%)	1(2.5%)	1(2.5%)	0.31
Neonatal hypoglycemia n (%)	2(5%)	0(0%)	0.49
Phototherapy n (%)	4(10%)	4(10%)	1.0
Malformations. n (%)	0(0%)	2(5%)	0.49
NICU admission n (%)	3(7.5)	2(5%)	0.31
Perinatal loss n (%)	2(5%)	1(2.5%)	0,66

and 37.67±0.49 (30-38.7) weeks in group II (p=0.30). Physiological jaundice occurred in 4 and 3 cases in group I and II respectively.

Total 12/40 (40%) women of glibenclamide group could be contacted telephonically for long term follow-up of offspring. All children were doing well with normal physical and neurobehavioral development at age varying between 7-10 years and none had obesity, diabetes or any late onset malformation.

Discussion

This trial was conducted to compare oral hypoglycemic agent glibenclamide with gold standard insulin therapy; irrespective of any cut-off for blood sugar levels and with inclusion of type II diabetes also in the study. This was in contrast to most previous studies on GDM with glibenclamide where lower BS-F, usually <140mg/dL were the inclusion criteria.[9,15] The dose requirement, duration to attain glycemic control, any adverse effect of drug, failure of therapy and need for insulin therapy were noted.

Hyperglycemic state during pregnancy not only affects the perinatal outcome but also has long term consequences on offspring. Even mildly deranged blood sugar also needs treatment as evident by studies which have shown that normoglycemia improves perinatal outcomes even in mild GDM or even when only one BS value is deranged.[16] Though insulin therapy remains the gold standard, oral treatment can be more convenient and cheaper for treating hyperglycemia of pregnancy if proven effective and safe in terms of in-utero glibenclamide exposure on fetal, neonatal or child's health. In the present study, long term follow up was also conducted for babies born to mothers receiving glibenclamide for any long term consequences.

Based on our results, an attempt has been made to grade baseline hyperglycemia during pregnancy so as to assess the probability of achieving glycemic targets with diet therapy and requirement of pharmacologic therapy. High baseline fasting blood sugar values correlated to the requirement of pharmacological treatment in this study with no correlation with the post glucose GTT values. Hence, this grading may avoid losing time with diet therapy alone in cases who are probable candidates for additional pharmacological treatment as reflected by high fasting blood sugar levels.

From our results, it can be inferred that a fasting blood glucose <95mg/dl may not require pharmacological treatment and is likely to be controlled on diet therapy alone; while fasting level >110mg/dL is unlikely to be controlled on diet alone, hence require more close monitoring. Also FBS >135 mg/dL is unlikely to be controlled on diet alone, hence can be considered directly for pharmacological therapy instead of prior diet to minimize the time to achieve glycemic control and can avoid unnecessarydelay of 1-2 weeks due to managing with diet alone before starting insulin/ oral hypoglycemics. We propose grading of GDM on basis of fasting blood sugaras (FBS) as follows:

Grading of GDM (Nutan GDM grading)

- Grade 1: (Minimal) FBS; <95mg%-will achieve glycemic control on MNT throughout pregnancy.
- Grade 2: (Mild) FBS:95-110mg%-Initially controlled on MNT but later may require pharmacotherapy in due course during pregnancy.
- Grade 3: (Moderate) FBS>110-134mg%-pharmacotherapy will be required initially or later if MNT helped in achieving glycemic control for some time.
- Grade 4: (Severe) FBS≥135 mg%-Pharmacotherapy will be required to achieve glycemic control since beginning.

Glibenclamide dose requirement

In our study the minimum dose of glibenclamide required for achieving glycemic targets was 2.5mg/day, and the mean daily dose required was 4.5 (range 2.5-17.5) mg. Approximately one-third cases (35%) cases were controlled with upto 2.5 mg daily dose and two-thirds (65%) with upto 5.0 mg daily dose; and overall total 80% women could be controlled with <10 mg daily dose. None of our patients required 20 mg/day which is considered the maximum dose allowed. The reported starting doses of glibenclamide varies from as low as 0.625mg/day[17] to 1.25[18] and 2.5 mg/day[16] though efficacy of lower doses on glycemic control is not mentioned in literature. In our study also, none of the patients were controlled on 1.25 mg daily dose, hence we suggest that glibenclamide therapy can be initiated with 2.5mg/day which can expedite glycemic control by 4-7 days. Lower dose of 1.25 mg can be tried if OGTT has only one very marginally raised value.

In first landmark study by Langer et al, 55% subjects were controlled with 2.5-5 mg daily dose similar to the present study though their mean daily dose was higher 9.2±6.7 mg with 20% subjects

receivingmaximum dose of 20 mg[16]. This might be due to higher (70 %) number of obese women with BMI >30kg/m^2 in that study. Lesser mean dose in our study might be because only 30% subjects on glibenclamide had BMI >28kg/m^2 which is comparable to the mean dose 5.6±4.6 mg reported in another.[15]

Glibenclamide dose frequency

We observed that 9 subjects could be controlled with only once daily dose while 31 subjects required twice daily dosing. The reported drug half-life of glibenclamide is 10 hours[19] and once or twice daily dosage can be predetermined based on the glycemic profile. Only morning dose for only high post lunch value and only evening dose for only post dinner value of blood sugars may suffice. F-BS also contributes in planning the dosages, if it fasting blood glucose is <105, morning dose, >105-115 evening or >115-125 mg% the subject is likely to need BD dose, >125 should always be started with bd doses of glibenclamide.Thus, twice daily schedule is required when all the pre-meals and post-meals blood glucose values are raised, whereas once daily schedule may be tried when some of the profile value are in normal range.

Glycemic control in relation to glibenclamide dose:

Fall in blood sugar levels was observed with 13 -15 mg/dL and 25-28mg/dL in 1.25 and with 2.5 mg glibenclamide respectively thus about 10-12 mg/dL fall in blood sugar was observed by 1mg dose and dose can be initiated accordingly without losing much time in controlling blood sugar.Time taken to attain targeted blood sugar values was similar in group I and II.

Another observation was an increase in the required dose predominantly at 26-32 weeks gestation by 1.25 to 5 mg in glibenclamide. The increment in insulin dose was also observed almost at same gestation.

Glycemic control

Glibenclamide was found as efficacious as insulin in attaining normoglycemia. with better control in pre-lunch blood sugar (p 0.03) and HbA1c (p 0.01). Langer observed glycemic control in 82% and 88% with glibenclamide and insulin respectively. Reported response rate by other authors ranges from 81-96%.[15,16,20] Which is similar to 93.5% found in the present study.

Fines et al reported a tighter glycemic control in the glibenclamide group when compared with the insulin (mean daily average plasma glucose levels were 115.4±10.1 and 128.0±18.6 in glibenclamide and insulin group respectively p=0.008). All glucose values obtained were at least 12mg/dl lower in glibenclamide versus insulin subjects (p<0.05) (89). Most of studies have shown similar or better control with glibenclamide.

Glibenclamide Failure

In the present study, 3(5%) patients were not controlled on glibenclamide and were switched over to insulin therapy. One (2.5%) patient on glibenclamide opted for insulin at 32 weeks gestation, hence was considered a breach of protocol and not as drug failure. Reported failure rate is 4-19% with glibenclamide[21,22,23] especially if BS-F was >115mg/dL.[12]

Factors reported for failure are high BMI >30kg/m^2, high fasting blood glucose >105mg/dl, earlier onset of GDM.[20] And higher values of >200 mg/dl in OGTT (71) thesis. The two patients who had failed response in our study were having hypothyroidism but it's difficult to speculate hypothyroidism as one of the factors for failed response.

Maternal and perinatal outcomes

In our study maternal outcomes including maternal hypoglycaemia, gestational age at delivery and birth weight were comparable in both groups. Langer et al reported ten times higher hypoglycaemia with insulin therapy than glibenclamide (p0.03)[16], though hypoglycemia is reported more with glibenclamide than insulin (0.2% vs 0.08%) (p0.001) by Jacobson et al.[15] One patient in glibenclamide groupdeveloped macrosomia in our study; her ultrasound at 32 weeks gestation showed corresponding growth parameters, she stopped glibenclamide herself after her follow-up visit at 32 weeks, and was started on insulin therapy in next antenatal visit after a week. It took about two weeks to control sugar levels again, this transient poor glycemic control in the switch-over period rather than the drug itself probably led to macrosomia. Comparable occurrence of macrosomia is reported by Jacobson et al in 24% vs. 25% in glibenclamide and insulin group respectively.[15] Kremer reported macrosomia in 19% cases despite good control with glibenclamide[24] and Conway found macrosomia in 11.1% vs. 8.3% (p=1.0) in successfully treated vs.patients with failure.[22] Fines et al reported >4000g birth weight in five neonates in glibenclamide compared to nine in insulin group (p=0.2)[25], Hence no study found more

macrosomia with glibenclamide therapy. Changing treatments especially in the third trimester may not be a good idea if good glycaemic control is already achieved by one treatment.

Neonatal hypoglycemia is the main concern while treating diabetes with drugs. Two cases of neonatal hypoglycemia were noted in our study with glibenclamide and none with insulin (P 0.49). Other studies have also reported comparable hypoglycemia.[15,22] Langer reported hypoglycemia in 9% and 6% neonates in glibenclamide and insulin groupsrespectivelywhich was also statistically comparable.[9] No congenital malformation was detected in glibenclamide whereas 2 cases had glibenclamide in first trimester inadvertently. Rather in insulin therapy 2 cases had malformation. These were type 2 DM and early onset GDM and inadequate control before or early pregnancy is the cause. In Langer's study 5 subject (2%) in Glibenclamide group and 4 subjects (2%) in Insulin group had congenital anomaly. Studies have reported no statistical significance in the difference of polycythemia, hypocalcemia, respiratory complications or any other neonatal complications in treatments. Congenital anomaly was seen in four babies (2%) each in both groups in Jacobson's study. Other neonatal complications were also similar in the two study groups. Thus, the neonatal complications observed in our study were in agreement to the other studies .There were two IUD in glibenclamide, both had preeclampsia.

Many meta-analyses have evaluated the efficacy and safety of oral hypoglycemics with insulin in GDM patients and have shown that metformin glyburide and insulin all are suitable for GDM but highlighting few nuances of each option.[26-28] Metformin was the fastest to achieve glucose control, and had favourable pregnancy outcomes.[27] Neonatal hypoglycemia was associated more with glibenclamide (glyburide) therapy[26,28] although NICU admissions remained the same and there was no neonatal hypocalcemia and congenital anomalies,[26] However, high neonatal birth weight and macrosomia was reported.[28] Metformin was found more effective in obese GDM[28] whereas glibenclamide was reported as more suitable for non-obese GDM.[26] Glibenclamide had the highest rate of average glucose control.[27] We found hypothyroidism as one factor who failed on glyburide therapy.

Long term safety in offspring is always debated for oral hypoglycemics. In metformin there is ambiguous state of knowledge, there may be modification of epigenetic due to metabolic effects, leading to permanent adverse changes. There are concerns of some neuro-developmental delay in these babies, though not largely prooven. Some has reported poor linguistic skills.[29] Risk of fat redistribution.with lesser visceral distribution.[30] Author (Agarwal N) has also observed lesser buccal fat in neonates who had metformin exposure in utero. For glibenclamide, long term consequences in offspring are not extensively studied. In the limited patients for whom long term follow-up is available in the our study, no remarkable long-term adverse effects were observed in offspring born to mothers treated with glibenclamide for GDM.

Though insulin continues to be the ADA recommended first-line therapy for GDM[31,32], there definitely is a place for oral hypoglycemics because of obvious advantages of convenience of oral route, lesser cost, easy storage, less frequent dosing especially in women having reluctance for injections. with similar efficacy though metformin is the most studied drug during pregnancy, two-fifth of these women require switch over to insulin therapy. Here glibenclamide can fill the void as it has comparable glycemic control to insulin.

Small sample size is the limitation of this study, also long-term follow-up was not available for all the women. We found hypothyroidism as one factor who failed on glyburide therapy. Further larger trials may be undertaken to evaluate hypothyroidism as a predictor for failure of therapy and for long term implications of in-utero exposure.

Conclusion

Glibenclamide is comparable to insulin in treating diabetes in pregnancy with similar obstetrical, maternal or perinatal outcomes and is not associated with any long term adverse consequences in the offspring.

Key points for glibenclamide therapy:

1. Glibenclamide seems to have similar control on the baseline blood glucose levels compared to insulin .
2. If any one value of GTT with is as follows; fasting>110 mg%, more likely to require pharmacotherapy despite diet control initially. FBS >135mg%, the patient can be directly started on pharmacological therapy thus saving valuable time.
3. Glibenclamide may be started with 2.5 mg daily dose. Duration taken by glibenclamide to attain glycaemic control is about 3 weeks which is similar to that of insulin..

4. Glibenclamide also has the advantage that a single dose of the drug may be sufficient. If the fasting blood glucose value <105mg/dL only post lunch values are high only morning dose of glibenclamide may be given, If post dinner is high only evening dose may suffice. Twice daily dosing of glibenclamide is required. to produce glycaemic control in a majority of subjects.
5. The dose increments of glibenclamide required in later gestation around 28-32 weeks gestation similar to insulin. Increments can be calculated with the estimate that 1.25 mg glibenclamide lowersblood sugar by approximately 13.5 mg/dL to prevent hypoglycaemia.
6. Safety and efficacy of glibenclamide is not proven in the first trimester. Further studies are warranted in this direction to bring out more evidence in support of this drug which may revolutionize the management of hyperglycemia in pregnancy.
7. Glibenclamide therapy may not be suitable in cases with hypothyroidism and preeclampsia.

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Author contributions

All authors contributed in the patient management and follow-up. NA conceptualized the study and was chief investigator of study. RPM was responsible for the acquisition of clinical data, and obtaining informed consent. NA comprehended all insights in glibenclamide therapy and GDM gradingafter fine and detailed analysis of data. NAand VK were responsible for manuscript writing and it's critical editing.

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