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Metformin versus Insulin for Gestational Diabetes: A Randomized Clinical Trial

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Abstract

Background: Insulin therapy is often started if medical nutritional therapy (MNT) fails to manage Gestational diabetes mellitus (GDM) which is associated with multiple injections and demands more patient compliance. So use of safe and effective oral agents may offer advantages over insulin. **Objectives:** To evaluate glycaemic control in women receiving metformin versus insulin for GDM, and to identify factors predicting the need for supplemental insulin in women initially treated with metformin. **Methods:** Women, 18 – 45 years at 20 –33 weeks of gestation with singleton pregnancy with GDM without satisfactory glycemic control on MNT for a minimum period of 1 week were randomised to receive either insulin or metformin. **Results:** There was no significant difference in mean pre-treatment glucose levels between two groups (P = 0.890). After randomizing, women received their respective intervention. Mean glucose level measured after glycaemic control showed, lower levels in the metformin group (P= .034). Also women under metformin presented less weight gain (P=.02) and a lower frequency of neonatal hypoglycaemia (P= .032). Thirteen women in the metformin group (31.7%) required supplemental insulin. Early gestational age at diagnosis and high BMI were identified as predictors of the need for supplemental insulin. **Conclusions:** Metformin appears to constitute safe and effective treatment option for GDM who do not have satisfactory glycemic control. It was found to provide adequate glycemic control with lower mean glucose level, less weight gain and a lower frequency of neonatal hypoglycaemia. Early gestational age at diagnosis and high BMI were predictors of the need for supplemental insulin therapy in women initially treated with metformin.

Key Words: Gestational Diabetes, Insulin, Metformin

INTRODUCTION

Gestational diabetes mellitus (GDM), affecting 5% of population, has classically been defined as any glucose intolerance first identified during pregnancy[1]. American Diabetes Association (ADA) defined it as "Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes"[2]. As per IADPSG criteria, women can be diagnosed to have GDM even in the first trimester, if fasting plasma glucose (FPG) is ≥ 5.1 mmol/L (92 mg/dL), but ≤ 7 mmol/L (126 mg/dL)[3].

Studies indicate that the severity of maternal and fetal complications is proportional to the level of maternal hyperglycemia[4-6]. The benefits of treating GDM with diet and insulin, if necessary, are well established[7,8]. However women who begin insulin require education to ensure the safe administration of insulin. So use of safe and effective oral agents may offer advantages over insulin because of their ease of use and lower cost.

Investigations on the use of metformin for the treatment of GDM have concluded that metformin seems to be an effective alternative for the treatment of GDM[9-12]. However, response to treatment in patients with gestational diabetes is highly dependent on patient characteristics.[13] Since Nepal is inhabited by mixture of different cast and

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ethnicity which is different from population in other part of the world, we need to test the response of metformin in GDM in our population. Thus this present study is conducted with primary aim to compare glycemic control in women who received metformin versus standard use of insulin for the treatment of GDM in our population. Our secondary objective was to compare neonatal outcome among women in two groups and identify factors that lead to need for insulin in women under metformin.

METHODS

This was a randomised controlled study done over two years from May 2016 to January 2018, involving women with diagnosed GDM not controlled with MNT for a minimum period of 1 week at BP Koirala Institute of Health sciences (BPKIHS), Dharan, Nepal. Women, 18-45 years, who were at 20-33 weeks of gestation having singleton pregnancy, were included. Women with contraindication to taking metformin, pre-pregnancy diagnosis of diabetes, any obstetrical indication for immediate vaginal or surgical delivery and having fetal congenital malformation were excluded. Total of 82 Women who met selection criteria were included in this study. Consent was taken from women before enrolling them to this study. This study was approved by Institutional Review Committee, BPKIHS (IRC/480/015).

After selection women were randomised using computer generated random number table into 2 groups, 41 in each. Women in Group 1, taken as cases, were started with Tab Metformin, 1500mg in 3 divided doses taken with food and increased to maximum of 2500mg depending upon glycemic control till the target blood sugar was met. Metformin was stopped if significant maternal conditions, such as severe preeclampsia, sepsis, or pregnancy cholestasis and also if fetal growth restriction developed. Women in Group 2, as control, received standard Insulin therapy as per our hospital protocol. They were typically started with combination of regular and intermediate acting insulin according to their weight and were adjusted to meet the target blood sugar. The target glucose reference values recommended by the ADA were used: fasting (95 mg/dL) and 2 hours after a meal (120 mg/dL) [14]. Women in group 1 who didn't tolerate metformin or who didn't achieve target glucose level were supplemented with insulin.

At study entry, background maternal demographic data, medical history, family history, obstetric history, medication intake through pregnancy, early pregnancy data, and any pregnancy complications were recorded. Paternal demographic data and height and weight were also recorded. Fetal ultrasound growth within 2 weeks before or 1 week after study entry was documented. During the study, women were asked to continue measuring capillary glucose levels fasting and 2 hour after the start of each meal regularly weekly, self by glucometer as per instructions and report to the investigator. At delivery, pregnancy complications, indication for induction (if performed), mode of delivery, and complications are recorded from the hospital notes. Detailed neonatal morbidity is also recorded. Trained personnel performed anthropometric and blood sugar measurements on the baby within 48 h of birth.

Numerical variables were compared by the Student t test or Mann-Whitney test. The $\chi 2$ test, Fisher exact test or likelihood ratio tests were used to compare categorical variables. In addition, logistic regression analysis was performed to predict the need for supplemental insulin in women initially treated with metformin.

RESULTS

In this study 82 women were enrolled and they were randomised into two groups with 41 in each group. The demographic and clinical characters in two groups were recorded at enrolment. This shows similar pattern as shown in Table-1. It includes age, body mass index (BMI) at enrolment, gestational week and parity. We also recorded fasting blood sugar after overnight fasting and post prandial as well as mean pre-treatment blood glucose level and glycated haemoglobin at enrolment. Also blood test was done for liver function as well as renal function at enrolment to make sure this result does

not preclude the use of metformin. There was no significant difference in mean pre-treatment glucose levels between two groups (P = 0.890). Also the glycated haemoglobin was similar in both the group. After enrolment in the study, patients were randomised into two groups as described in methods. After randomizing, women received their respective intervention.

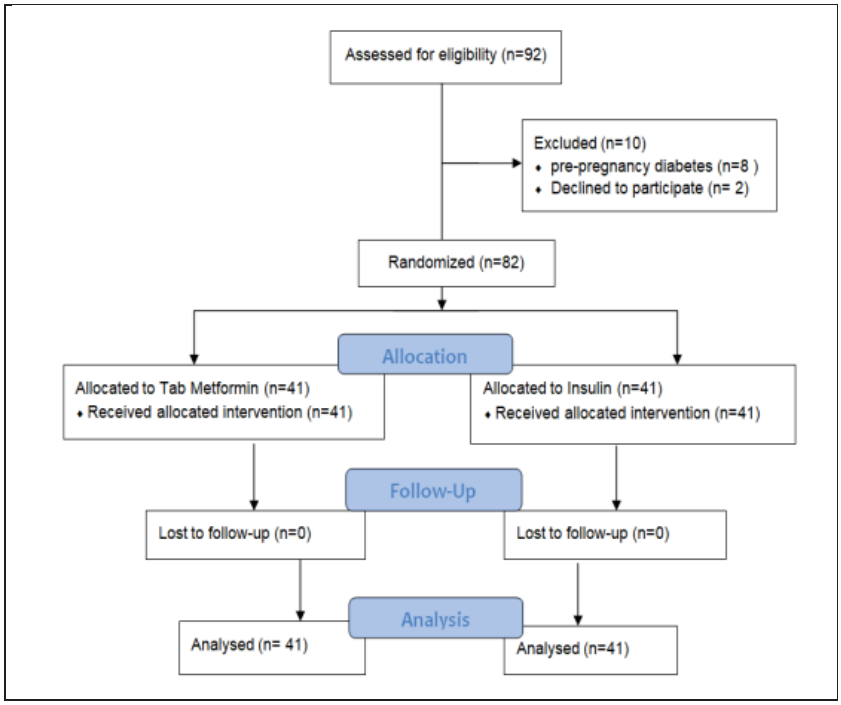

Figure1. Enrollment of Subjects.

Table.1 Baseline maternal Characterstics

Character	Metformin (41)	Insulin (41)
Age (yrs)	33.4±5.4	33.0±5.3
BMI at enrolment	35.1±7.2	34.6±8.3
Period of gestation (weeks)	30.3±3.2	31.2±3.1
Nulliparous(%)	31.7	31.9
Glycated haemoglobin	5.7±0.2	5.8±0.8

Less weight gain was observed in women in group 1 compared to group 2 between the start of medication treatment and delivery (group 1: 0.53 ±2.52 kg vsgroup 2: 2.3 ± 2.77 kg; P = .002). There was no difference in the two groups in terms of frequency of preeclampsia, prematurity and operative delivery.
None of the women discontinued the study protocol (figure 1). Only 10 women in metformin group reported some side effects, most frequent being gastrointestinal effects like nausea and occasional increase frequency of bowel movements. But all of them continued with the treatment protocol. Out of 41 women in group 1, 13 (31.7%) required supplemental insulin to achieve target glycemic control. Regarding glucose control, the mean glucose level measured after glycemic control showed, lower levels in the metformin group (P= .034) compared to insulin group. (Table 3)

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Table 3 Mean blood glucose level after treatment.

Pretreatment blood glucose	Fasting	2 Hr- post prandial	P value
Metformin	102.15 ±21.96	120.61 ± 22.63	0.890
Insulin	100.87 ±15.05	123.72 ± 19.4	
Post-treatment blood glucose			
Metformin	90.09 ± 16.29	106.87 ±11.16	0.034
Insulin	88.35 ± 7.45	111.43 ± 8.84	

Neonatal outcome

No significant differences between the 2 groups were observed regarding thefollowingimmediate neonatal outcomes: gestational age at birth (group 1: 38.33 ± 1.45weeks vs group 2: 38.24 ±1.53 weeks; P = 0.776), 1-minute Apgar score (group1: 9 [0-10] vs group 2: 9 [4-10]; P =.980), 5-minute Apgar score (group 1: 10[0-10] vs group 2: 10 [0-10]; P =.188) and newborn weight (group 1: 3143.7 ± 446.6 g vs group 2: 3237.6 ± 586.8 g; P =.390) (Table 2). There were no fetuses with macrosomia in the group metformin vs 3 (7.3%) cases in the insulin group (P =.342). A lower frequency of neonatal hypoglycaemia was observed in cases treated with metformin (3/41, 7.3%) compared with newborns from the insulin group (10/41, 24.3%) (P = .042).

Table 2 – Neonatal outcome

Variables	Metformin	Insulin	P value
Gestational age at birth (weeks)	38.33 ± 1.45	38.24 ±1.53	0.776
1-minute Apgar score	9 [0-10]	9 [4-10]	0.980
5-minute Apgar score	10(0-10)	10(0-10)	0.188
Newborn weight	3143.7 ± 446.6 g	3237.6 ± 586.8 g	0.390

Early gestational age at diagnosis (odds ratio.0.78; 95%confidence interval, 0.52-0.97;P = .02) and high BMI were identified as predictors of the need for insulin by logistic regression analysis.

DISCUSSSION

As per the primary objective of this study we were able to evaluate glycemic control in both the groups of women. The mean glucose level measuredafterglycemic control showed, lower levels in the metformin group (P= .034) compared to insulin group (Table 3). Similarresults were shown in the study by Spaulonci CP et al. They also demonstrated that lower level of blood sugar was observed especiallyafter dinner[12]. Less weight gain observed in women of group 1 compared to group 2 between the start of medication treatment and delivery (group 1: 0.53 ±2.52 kg vsgroup 2: 2.3 ± 2.77 kg; P = .002) in our study was again comparable to other similar study [10,12]. Also as comparable to Spaulonci CP et al[12] and Rowan et al 10, there was no difference in the two groups in terms of frequency of preeclampsia, prematurity and operative delivery.

In the present study, only [10] (24.3%) women in metformin group reported some side effects, but all of them continued with the treatment protocol. Twenty-one (45.65%) of the 46 womenwho received metformin reported someside effect in the study by Spaulonci CP et al [12]which is similar to our study. Out of 41 women in group [1, 13] (31.7%) required supplemental insulin to achieve target glycemic control. This is more that that reported by Spaulonci CP et al [12] who reported [12] (26.08%) women in metformin group requiring supplemental insulin. In the study by Rowan et al [10] 46.3% of women taking metforminrequired supplemental insulin. These

differencesmay be because of difference in ethnicity and characteristic of population as diabetes widely varies among different population.

Regarding immediate neonatal outcomes like gestational age at birth, 1,5-minute Apgar score and newborn weight, our study showed no significant differences between the 2 groups. There were no fetus with macrosomia in the group metformin vs 3 (7.3%) cases in the insulin group (P = .342). In the study by Rowan et al [10]the primary outcome, a composite of neonatal hypoglycemia, respiratory dis¬tress, need for phototherapy, birth trauma, 5-minute Apgar score lower than [7], or pre¬maturity, occurred with similar frequency in the 2 groups (32% in each group) where 733 women were randomised to metformin versus insulin. Our study also demonstrated lower frequency of neonatal hypoglycaemia in cases treated with metformin (3/41, 7.3%) compared with newborns from the metformin group (10/41, 24.3%) (P = .042) which was comparable to other studies [10,12]. As per the literature review our women with early gestational age at diagnosis and high BMI were identified as predictors of the need for insulin.

The strength of this study is that all women were followed up till delivery. Our group of women included all different caste of Nepal so the results can be implemented to all. Major limitations are we don't have any records of level of glycemic control at home because of poor patient compliance and Cord blood has not been stored for assessment of insulin and c peptide.

CONCLUSION

The primary objective of this study was to evaluate glycemic control in women with GDM treated with metformin or insulin.Metformin appears to constitute safe and effective treatment option for GDM who do not have satisfactory glycemic control with MNT. It was found to provide adequate glycemic control with lower mean glucose level, less weight gain and a lower frequency of neonatal hypoglycemia. Early gestational age at diagnosis and high BMI were predictors of the need for supplemental insulin therapy in women initially treated with metformin

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Journal of Diabetes and Endocrinology Association of Nepal

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