# COMPARISON BETWEEN METFORMIN AND INSULIN IN TREATMENT OF GESTATIONAL DIABETES MELLITUS AND EFFECT ON NEONATAL HYPOGLYCAEMIA

**Samra Ayub, Syed Raza Jaffar*, Ayesha Basharat, Waqas Ayub**, Naseer Ahmed Khan*****

Benazir Bhutto Hospital Rawalpindi Pakistan, *Armed Forces Institute of Pathology Rawalpindi Pakistan, **Holy Family Hospital Rawalpindi Pakistan, ***Combined Military Hospital Rawalpindi Pakistan

## ABSTRACT

***Objective:*** To compare the efficacy of metformin in the treatment of gestational diabetes mellitus (GDM) with insulin and to compare the frequency of hypoglycaemia in neonates of the mothers treated with metformin and insulin.

***Study Design:*** Randomized control trial to compare the efficacy of metformin with insulin in the treatment of GDM.

***Place and Duration of Study:*** Outpatient department and labour ward of Obstetric and Gynaecology department of Benazir Bhutto Hospital Rawalpindi from August 2012 to January 2013.

***Patients and Method:*** A total of 110 pregnant ladies with GDM diagnosed after 20 weeks of gestation were included and divided into group A and group B with 55 patients in each group. Group A patients were treated with insulin and group B with metformin. Plasma fasting glucose and two hours postprandial glucose levels were determined on weekly basis for four weeks after starting the treatment to determine the efficacy of insulin and metformin. At birth plasma glucose levels of all the neonates were carried out two hourly, and more frequently depending upon the requirement, during first 24 hours in both the groups to determine neonatal hypoglycaemia.

***Results:*** Fasting plasma glucose in group A and B were calculated as 5.96 ± 0.58 and 5.76 ± 0.46 mmol/L respectively ($p$=0.280), while two hours post-prandial plasma glucose levels were 7.34 ± 0.48 and 7.28 ± 0.58 mmol/L respectively ($p$=0.650). Efficacy in group A was 78.18% and in group B was 70.91% ($p$=0.381) while frequency of neonatal hypoglycaemia was calculated as 61.54% in group A and 41% in group B ($p$=0.113).

***Conclusion:*** The efficacy of metformin in treatment of gestational diabetes mellitus is similar as with insulin and the frequency of hypoglycemia in neonates of the mother treated with metformin and insulin is also similar.

**Keywords:** Gestational diabetes, Insulin, Metformin, Neonatal hypoglycaemia.

## INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as "carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy[1]. Prevalence of GDM is increasing, incidence being approximately 3% to 7% of all pregnancies[2-4]. The incidence of GDM increases in older and more obese pregnant women.

Gestational diabetes is a major cause of maternal morbidity, pregnancy complications and perinatal morbidity and mortality[5-7]. As the pregnancy advances, insulin sensitivity decreases in pregnant women[2]. Majority of pregnant women may also have β cell dysfunction due to chronic insulin resistance[8]. Such women develop GDM if there is inadequate insulin secretion to compensate for increased insulin resistance[2].

Lowering of plasma glucose level with lifestyle modification, special obstetrics care and if not controlled with addition of insulin improves perinatal outcome[9]. The percentage of GDM patients needing pharmacological treatment varies from 20% to 60% quoted by various studies[10]. Subcutaneous insulin therapy has been the mainstay of treatment of women with GDM not controlled by dietary modification. However treatment with insulin needs patient education and regular monitoring to ensure safe and effective administration.

**Correspondence:** Dr Syed Raza Jaffar, Classified Pathologist, Armed Forces Institute of Pathology Rawalpindi, Pakistan
*Email: drrazjaf61@gmail.com*
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Moreover this treatment is inconvenient and expensive because it requires refrigerated storage and skilled handling, which may not be always available in low resource countries[11]. Also there are risks of complications with insulin therapy like hypoglycemia and weight gain[10,12], faulty technique of subcuticular injections, noncompliance of patients to injections and neonatal effects like recurrent early neonatal hypoglycaemia.

Theoretically metformin is an alternative to insulin in the treatment of hyperglycaemia during pregnancy. It decreases hepatic gluconeogenesis and improves peripheral glucose uptake[13,14]. It does not induce hypoglycaemia and is not associated with increased weight gain. Oral metformin improves insulin sensitivity by activating adenosine monophosphate (AMP) Kinase[9], hypoglycaemia lowers hyperinsulinaemia[15] and decreases the requirement of insulin for insulin treatment. Evidence supporting the use of metformin in pregnancy is available from studies in patients with polycystic ovarian syndrome (PCOS), metformin has been used in the treatment of infertility secondary to PCOS[16]. There is no evidence of adverse fetal effects or increased risk of major malformations when metformin is used in pregnant women. In general the number of studies reporting on the use of metformin in women with GDM is still small.

Hypoglycaemia is the most common metabolic problem in neonates. A plasma glucose level of less than 30 mg/dl (1.65 mmol/L) in the first twenty four hours of birth and less than 45 mg/dl (2.5 mmol/L) thereafter constitutes hypoglycaemia in the newborn[17]. Neonates with hypoglycaemia may present with severe central nervous system and cardiopulmonary disturbances. The use of oral hypoglycaemic agents in pregnancy has been controversial because case reports and small sample studies have reported adverse effects like potential risks of neonatal hypoglycaemia and teratogenicity associated with placental transfer to the fetus[18,19]. Infact several studies with glyburide and metfomin showed similar or even better neonatal outcomes as compared to treatment with insulin[20-24].

The significance of this study is to explore the more effective control of glucose in GDM and decreased risk of early neonatal hypoglycaemia by using metformin as compared to insulin, so that any injectable drug can be replaced by an oral alternative.

## PATIENTS AND METHODS

This randomized control trial was carried out in the outpatient department (OPD) and labour ward of department of Obstetrics and Gynaecology of Benazir Bhutto hospital Rawalpindi from August 2012 to January 2013. Pregnant ladies between 15 to 45 years of age, diagnosed GDM after 20 weeks of gestation and with singleton foetus were included in the study. Cases with diabetes mellitus diagnosed before 20 weeks of gestation, contra indication to the use of metformin, foetal anomaly, gestational hypertension, foetal growth restriction and twin pregnancy were excluded.

By using consecutive non probability sampling, a total of 110 patients were included. All the selected patients were informed about the risk and benefits of the study and written informed consent was taken. They were included in the study with the permission of ethical committee. The selected cases were randomly divided into two groups, group A and group B, having 55 patients in each group using random number table. Group A was treated with insulin and group B with metformin. After an overnight fast, 2 ml of venous blood samples for each patient in both the groups were taken in fluoride bottles for fasting plasma glucose and two hours postprandial glucose levels (two hours after breakfast, lunch and dinner). These lab tests were repeated and results recorded weekly for four weeks after starting the treatment to determine the efficacy of insulin and metformin to control hyperglycaemia. Efficacy in this study means ability of insulin and metformin to control hyperglycaemia measured as fasting plasma glucose <5.5 mmol/L and two hour postprandial glucose level <7.2 mmol/L, samples taken one week apart having these

values on all four occasions over a period of one month were considered as effective.

Plasma glucose samples were analyzed using Beckman's Coulter fully automated chemistry analyzer CX-9, using Beckman's Coulter reagent kits on hexokinase principle and controls.

Patients showing no efficacy with metformin were put on insulin treatment. Patients showing efficacy with insulin and metformin (n=39 in each group) were followed till delivery. At birth, plasma glucose of neonates was recorded two hourly and more frequently depending upon the requirement during first twenty four hours. Data had been analyzed by using SPSS version 19. Mean and standard deviation (SD) were calculated for fasting plasma glucose and two hour postprandial plasma glucose level for both the groups and compared through independent sample's t-test. Frequency and percentage were calculated for efficacy of drug and neonatal hypoglycaemia and Chi square test was used to compare the efficacy of drugs and neonatal hypoglycaemia in the two groups, using *p* value <0.05 as significant.

## RESULTS

A total of 110 selected patients were between 18-45 years of age. Mean age in group A was 32.54 years (SD=3.64) and in group B, it was 33.21 years (SD=4.25), (*p*= 0.181).

Mean gestational age in group A was 29.21 weeks (SD=2.57) and in group B was 30.45 weeks (SD=2.58), (*p*=0.73).

Mean fasting plasma glucose level in group A was 5.96 mmol / L (SD=0.58) and in group B was 5.76 mmol / L (SD=0.46), (*p*=0.28).

Mean two hours postprandial plasma glucose in group A was 7.34 mmol / L (SD=0.48) and in group B it was 7.28 mmol / L (SD=0.52), (*p*=0.65).

Efficacy was 78.18% (n=43) in group A and it was 70.91% (n=39) in group B (*p*=0.381), (Table-1).

**Table-1: Efficacy of Insulin and metformin in group A and group B (n=110).**

| Efficacy | Group A (n=55) | | Group B (n=55) | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| Yes | 43 | 78.18 | 39 | 70.91 |
| No | 12 | 21.82 | 16 | 29.09 |

*p*=0.381

**Table-2: Frequency of neonatal hypoglycaemia in group A and group B (n=78).**

| Neonatal hypoglycemia | Group A (n=39) | | Group B (n=39) | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| Yes | 24 | 61.54 | 16 | 41 |
| No | 15 | 38.46 | 23 | 59 |

*p*=0.113

A total of 61.54% (n=24) neonates in group A and 41% (n=16) nonates in group B had hypoglycaemia while 38.46% (n=15) in group A and 59% (n=23) in group B neonates had no hypoglycaemia (*p*=0.113), (Table-2).

## DISCUSSION

Keistina Tertti and co-workers[2] compared maternal and neonatal outcomes in patients with gestational diabetes mellitus (GDM) treated with metformin with those treated with insulin, or diet alone and recorded that there were no differences between the metformin treated group and the other two groups in terms of maternal outcomes. In the diagnostic 2-hour oral glucose tolerance test, glucose values were slightly, but significantly, higher in the insulin group than in the metformin group (*p*=<0.003). Eighteen percent of mothers treated with metformin needed supplementary insulin therapy. The incidence of neonatal hypoglycemia was higher in the insulin group than in the metformin group (*p*=<0.03) and concluded that these retrospective data suggest that metformin is as effective as insulin in controlling gestational diabetes[2]. Our study also

supported the findings of this study that metformin is as effective as insulin in treating GDM, but the incidence of neonatal hypoglycaemia was similar in both the insulin and metformin group in our study ($p$=0.113) which is contrary to the result of the study by Keistina and colleagues ($p$=<0.03).Twenty nine percent of the patients in the metformin group (group B) of our study needed and given supplementary insulin therapy.

In the study by Rowan and colleagues[25] the rate of neonatal hypoglycemia was similar but the rate of severe hypoglycemia was lower in the metformin group compared to the insulin group. Since the incidence of neonatal hypoglycemia was similar in insulin and metformin groups in our study, therefore, it supports the result of the study by Rowan and colleagues[25].

Prospective randomized studies have recently demonstrated that effective treatment of hyperglycemia in women with GDM can reduce adverse perinatal outcomes[26]. The main purpose of treatment is to prevent fetal hyperinsulinaemia and fetal macrosomia by reducing maternal glucose levels[27]. This is initially attempted by dietary and exercise counseling, but women often require additional treatment, which has traditionally been insulin[28]. The percentage of GDM patients needing pharmacological treatment varies from 20% to 60% by various studies[10,29]. However, the disadvantages of insulin for pregnant women, like other patients needing insulin, include the need to give injections, risk of hypoglycemia and risk of excessive weight gain[29,30].

Advantages of metformin are its ease of administration and its low cost. This is beneficial in resource-poor populations like ours while disadvantages of insulin are problems of storage, the inconvenience of daily injections besides increase in appetite and weight. Dosing of metformin is standardized, unlike insulin, and can be managed by obstetric specialists without the help of general physician. Metformin do not cause hypoglycemia.

## CONCLUSION

We concluded that the efficacy of metformin in treatment of gestational diabetes mellitus is similar as with insulin and the frequency of hypoglycemia in neonates of the mother treated with metformin and insulin is also similar.

## CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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