

# Comparison of Metformin with Insulin in the Management of Gestational Diabetes

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## ABSTRACT

**Objective:** Purpose of this study is to determine the efficacy of metformin as opposed to insulin in management of gestational diabetes mellitus.

**Study Design:** Randomized control trial.

**Place and Duration of study:** This study was conducted at the Gynecology and Obstetrics, Lady Wellington Hospital, Lahore from May 2016 to March 2017.

**Materials and Methods:** Ethical approval was obtained from Hospital Ethics Committee. Sample was calculated using non probability consecutive sampling technique. Total 770 Patients were randomly divided into two equal groups, group M (metformin) and Group I (insulin). Glycemic control, mode of delivery and associated medical complication were recognized as possible maternal outcomes while congenital anomalies (if any), macrosomia, hypoglycemia, hyperbilirubinemia were the neonatal outcomes assessed by clinical and laboratory investigations. These outcomes were subjected to statistical analysis by using computer software SPSS version 23. Percentages were calculated for dichotomous variables and range, mean and standard deviation was calculated for continuous data. Chi square and t-test were applied to compare the two groups. P value less than 0.05 was considered as significant.

**Results:** Overall 100% (n=770) female patients were included, in this study; divided into two equal groups 50% (n=385) in each i.e. metformin (Group M) and insulin (Group I). Significant difference was found between age (p=0.000), gravidity (p=0.012), gestational age (p=0.000), BMI in early pregnancy (p=0.000), FBS at entry (p=0.000), FBS after treatment (p=0.000), HbA1c at entry (p=0.000), HbA1c after treatment (p=0.000), in groups. Association was found between Preeclampsia (p=0.000), Pre-term birth (p=0.000), Neonatal birth weight >4 (p=0.002), neonatal hypoglycemia (p=0.000), in groups.

**Conclusion:** This study concludes that metformin is as much effective as insulin in management of gestational diabetes mellitus. Metformin when used securely can prove effective as it does not cause any congenital anomalies or maternal or neonatal complications. But insulin still remains the gold standard for treatment of gestational diabetes mellitus.

**Key Words:** Diabetes Mellitus, Gestational Diabetes, Metformin, Insulin, Pregnancy

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## INTRODUCTION

Glucose intolerance of any level with onset or first identified during the pregnancy can be called as gestational diabetes<sup>1</sup>. Overall morbidity of gestational diabetes is increasing with passing time. According to an estimate, 1 to 14% of all the pregnancies are complicated by gestational diabetes, which of course depends upon the size of the population under study, type of classification and diagnostic tests used<sup>2</sup>. Gestational diabetes is thought to have both short and

long term outcomes which affect both mother and newly born child<sup>3</sup>. Out of the complications faced by the pregnant mother most common are preeclampsia, increased risk of developing diabetes mellitus type 2 after pregnancy and cesarean section. In case of neonatal morbidities, risk of neonatal loss becomes greater; there is also risk of still birth and congenital abnormalities, all because of excess glucose transfer from mother to fetus. Macrosomia is another major complication which can lead to shoulder dystocia during transvaginal birth, presenting a risk for instrumental deliveries, C-section and neonatal hypoglycemia later<sup>4</sup>. Intrauterine hyperglycemic environment may cause this condition to pass on to the children of the mother who is suffering from gestational diabetes<sup>5</sup>. That is why the aim of management of gestational diabetes is to control the glycemic levels and hence reduce the horrible post-pregnancy outcomes<sup>6</sup>.

Possible treatments to reduce these complications can be enlisted as, exercise<sup>7</sup>, diet modifications, insulin and

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oral hypoglycemic conditions. Up till now, insulin therapy has been considered as gold standard for treatment of gestational diabetes as diet modification with or without exercise is not enough to resolve this grave problem<sup>8</sup>. Although insulin is the treatment of choice but it does come with some side effects like weight gain, several injections per day and a risk of developing hypoglycemia<sup>9</sup>. So adjustments are made according to the BMI, lifestyle of the patient and blood glucose level. In other words, a detailed guidance is necessary regarding change in insulin dosages, so that self administration can be ensured to be safe. As expected, oral insulin therapy is much more satisfying and preferable in women with gestational diabetes, until its safe and effective.

Oral hypoglycemic drugs should also be considered especially in order to identify their effect on the final outcomes in both mothers and neonates. Metformin is first line of drug in the management of type 2 diabetes mellitus<sup>10</sup> and can be considered as another possible treatment option for gestational diabetes. But studies have shown a mother to fetus transfer of almost 10 to 16% in case of metformin<sup>11</sup> which poses a great risk to both mother and the fetus as chances of adverse effects in mothers and birth defects in newborn increases significantly. This is the reason metformin has not been used widely in gestational diabetes management.

Multiple studies have been performed in past in order to determine the efficacy and safety of metformin in management of gestational diabetes but most of these studies were cross-sectional and had smaller sample size which does not sufficiently describe the effect of metformin on maternal and neonatal outcomes. Thus, in this study our aim is to compare the efficacy of metformin with insulin therapy in gestational diabetes management, in terms of maternal and neonatal outcomes. Reference for this study was taken from a recent study performed by Hesham Borg et al<sup>12</sup>.

## MATERIALS AND METHODS

The study took place in department of Gynecology and Obstetrics, Lady Wellington Hospital, Lahore, from May 2016 to August 2017. Study design is Randomized control trial. Ethical approval was obtained from Hospital Ethics Committee. Sample was calculated using non probability consecutive sampling technique, using the reference study by Hesham Borg et al. Confidence level was taken as 95% and power of study as 80% and mean and standard deviation of outcome variable postprandial blood sugar level was used to calculate the sample size. As a result 770 patients were taken as the required sample size for our study. Total no. of 770 patients was included in the study. Inclusion criteria described by Carpenter and Coustan was used to select the patients of gestational diabetes, according to which, blood glucose level must be, fasting  $> 95$  mg/dl, at 1hr  $> 180$  mg/dl, at 2h  $> 155$  mg/dl and at 3h

$> 146$  mg/dl, along with hospital criteria to start insulin therapy. Those patients who were in labor, had contradiction against metformin or with fetal anomalies, preeclampsia, gestational hypertension, ruptured membranes or fetal growth restrictions were excluded from the study. Informed consent was taken from the patients before involving them into the study. Patients were randomly divided into two equal groups, group M (metformin) and Group I (insulin). Metformin was given to patients of group M as 500 mg dose/day orally in morning and increased by 500 mg per week if required. Mixed human suspension of insulin was given as 0.7 U/kg of body weight subcutaneously two times a day and was also increased as per requirement. Weekly examination of the patients was scheduled which involved, history taking, general physical examination and fasting blood sugar and postprandial blood sugar (glycemic profile). Weekly visit involved dose adjustments if required and provision of standard obstetric care. Basic facilities were provided at antenatal clinic level including ultrasound examination. Ultrasound examination was performed at first visit and then at 16 to 19 weeks (2<sup>nd</sup> visit) and then monthly after 28 weeks of gestation. Glycemic control, mode of delivery and associated medical complication were recognized as possible maternal outcomes while congenital anomalies (if any), macrosomia, hypoglycemia, hyperbilirubinemia were the neonatal outcomes assessed by clinical and laboratory investigations. These outcomes were subjected to statistical analysis by using computer software SPSS version 23. Percentages were calculated for dichotomous variables and range, mean and standard deviation was calculated for continuous data. Chi square and t-test were applied to compare the two groups. P value less than 0.05 was considered as significant.

## RESULTS

Overall 100% (n=770) female patients were included, in this study; divided into two equal groups 50% (n=385) in each i.e. metformin (Group M) and insulin (Group I). The mean age, gravidity, parity, gestational age, BMI in early pregnancy and BMI during treatment of the patients of group M was  $24.92 \pm 2.57$  years,  $2.57 \pm 1.17$ ,  $1.48 \pm 0.66$ ,  $27.94 \pm 2.57$  weeks,  $22.08 \pm 2.98$  kg/m<sup>2</sup> and  $31.88 \pm 2.26$  kg/m<sup>2</sup> respectively. While, the mean age, gravidity, parity, gestational age, BMI in early pregnancy and BMI during treatment of the patients of group I was  $28.01 \pm 2.53$  years,  $2.35 \pm 1.19$ ,  $1.41 \pm 1.06$ ,  $29.92 \pm 2.27$  weeks,  $23.82 \pm 2.81$  kg/m<sup>2</sup> and  $32.05 \pm 1.89$  kg/m<sup>2</sup> respectively. (Table 1).

The Mean  $\pm$  S.D FBS at entry, FBS after treatment, 2hPPBS at entry, 2hPPBS after treatment, HbA1c at entry and HbA1c after treatment of the patients of group M was  $130.06 \pm 10.34$  mg/dl,  $82.28 \pm 5.51$  mg/dl,  $175.18 \pm 7.89$  mg/dl,  $111.94 \pm 7.02$  mg/dl,  $5.73 \pm 0.54$

mg/dl and  $5.08 \pm 0.42$  mg/dl respectively. While, the Mean $\pm$ S.D FBS at entry, FBS after treatment, 2hPPBS at entry, 2hPPBS after treatment, HBA1c at entry and HBA1c after treatment of the patients of group I was  $122.37 \pm 9.94$  mg/dl,  $76.88 \pm 7.75$  mg/dl,  $174.46 \pm 6.02$  mg/dl,  $112.34 \pm 5.02$  mg/dl,  $6.15 \pm 0.59$  mg/dl and  $5.71 \pm 0.49$  mg/dl respectively.

**Table No.1: Demographic Variables**

Variable	Metformin n=(385) Group A	Insulin n=(385) (Group B)	Test of Sig.
Age	$24.92 \pm 2.57$ years	$28.01 \pm 2.53$ years	$t = -16.80$ $p = 0.000$
Gravidity	$2.57 \pm 1.17$	$2.35 \pm 1.19$	$t = 2.53$ $p = 0.012$
Parity	$1.48 \pm 0.66$	$1.41 \pm 1.06$	$t = 1.05$ $p = 0.293$
Gestational Age	$27.94 \pm 2.57$ weeks	$29.92 \pm 2.27$ weeks	$t = -11.30$ $p = 0.000$
BMI in early pregnancy	$22.08 \pm 2.98$ kg/m <sup>2</sup>	$23.82 \pm 2.81$ kg/m <sup>2</sup>	$t = -8.323$ $p = 0.000$
BMI during treatment	$31.88 \pm 2.26$ kg/m <sup>2</sup>	$32.05 \pm 1.89$ kg/m <sup>2</sup>	$t = -1.10$ $p = 0.271$

**Table No.2: Comparison between groups with respect to pattern of blood sugar level, maternal and neonatal complications and mode of delivery**

Variable	Metformin n=(385) Group A	Insulin n=(385) (Group B)	Test of Sig.
FBS at entry	$130.06 \pm 10.34$ mg/dl	$122.37 \pm 9.94$ mg/dl	$t = 10.53$ $p = 0.000$
FBS after treatment	$82.28 \pm 5.51$ mg/dl	$76.88 \pm 7.75$ mg/dl	$t = 11.15$ $p = 0.000$
2hPPBS at entry	$175.18 \pm 7.89$ mg/dl	$174.46 \pm 6.02$ mg/dl	$t = 1.42$ $p = 0.157$
2hPPBS after treatment	$111.94 \pm 7.02$ mg/dl	$112.34 \pm 5.02$ mg/dl	$t = -0.909$ $p = 0.364$
HBA1c at entry	$5.73 \pm 0.54$ mg/dl	$6.15 \pm 0.59$ mg/dl	$t = -10.04$ $p = 0.000$
HBA1c after treatment	$5.08 \pm 0.42$ mg/dl	$5.71 \pm 0.49$ mg/dl	$t = -19.11$ $p = 0.000$
Gestational HTN	7.3% (n=28)	8.1% (n=31)	$\chi^2 = 0.165$ $p = 0.684$
Pre- eclampsia	4.4% (n=17)	15.6% (n=60)	$\chi^2 = 26.68$ $P = 0.000$
Pre-term birth	2.6% (n=10)	12.5% (n=48)	$\chi^2 = 26.93$ $P = 0.000$
Mode of delivery	CS 40.8% (n=157), NVD 59.2% (n=228)	CS 36.1% (n=139), NVD 63.9% (n=246)	$\chi^2 = 1.778$ $P = 0.182$
Neonatal birth weight >4	10.9% (n=42)	18.7% (n=72)	$\chi^2 = 9.27$ $P = 0.002$
Neonatal hypogly- cemia	28.3% (n=109)	52.5% (n=202)	$\chi^2 = 46.65$ $P = 0.000$
Neonatal Jaundice	51.2% (n=197)	39.7% (n=153)	$\chi^2 = 10.14$ $P = 0.001$

Gestational HTN 7.3% (n=28) and 8.1% (n=31), preeclampsia 4.4% (n=17) and 15.6% (n=60), pre-term birth 2.6% (n=10) and 12.5% (n=48), mode of delivery CS 40.8% (n=157), NVD 59.2% (n=228) and CS 36.1% (n=139), NVD 63.9% (n=246), neonatal birth weight >4 10.9% (n=42) and 18.7% (n=72), neonatal hypoglycemia 28.3% (n=109) and 52.5% (n=202), neonatal Jaundice 51.2% (n=197) and 39.7% (n=153), were noted for the group M and I respectively. (Table 2).

Significant difference was found between age ( $p = 0.000$ ), gravidity ( $p = 0.012$ ), gestational age ( $p = 0.000$ ), BMI in early pregnancy ( $p = 0.000$ ), FBS at entry ( $p = 0.000$ ), FBS after treatment ( $p = 0.000$ ), HBA1c at entry ( $p = 0.000$ ), HBA1c after treatment ( $p = 0.000$ ), in groups. Association was found between Preeclampsia ( $p = 0.000$ ), Pre-term birth ( $p = 0.000$ ), Neonatal birth weight >4 ( $p = 0.002$ ), neonatal hypoglycemia ( $p = 0.000$ ), in groups. (Table 2).

## DISCUSSION

Prevalence of gestational diabetes varies within different races and it depends upon diagnostic tests used for its diagnosis. Use of a specific diagnostic criterion and a certain ethnic background suggests that gestational diabetes incidence varies from 2 to 8%<sup>13</sup>. Gestational diabetes has been reported to associate with many maternal and perinatal complications including, preeclampsia, macrosomia, shoulder dystocia, hypoglycemia, cesarean section, birth injuries and respiratory distress syndrome<sup>14,15</sup>. Multiple studies have shown that risk of these complication rises with the rise in blood glucose level and that these complications can be prevented by proper management of hyperglycemia which is the major finding of gestational diabetes<sup>16, 17</sup>. Recommendations regarding diagnosis and management of gestational diabetes are derived from American College of Obstetricians and Gynecologists and American Diabetes Association in attempt to avoid these unpleasant outcomes<sup>18,19</sup>.

Women suffering from gestational diabetes who were unable to be treated with diet modifications and exercise recommendations are traditionally treated by insulin therapy<sup>20</sup>. But insulin therapy carries risk of weight gain, difficulty for pregnant women as multiple injections are required daily and also there is risk of developing hypoglycemia. Therefore metformin is considered as a replacement therapy and it is also effective in gestational diabetes<sup>21</sup>. There are no risks of developing hypoglycemia and gaining of weight with use of metformin and metformin acts by preventing peripheral insulin resistance and diminishing gluconeogenesis in liver<sup>22</sup>.

According to a meta-analysis, there was no risk of major congenital anomalies associated with metformin. Other studies also gave the conclusion that oral hypoglycemic agents when compared with insulin are

not much different from insulin therapy in terms of maternal or neonatal outcomes, in women with gestational diabetes<sup>23,17</sup>.

A study by Rai et al.<sup>24</sup> demonstrated that although insulin showed slightly better results, even then the difference was not statistically significant ( $p=0.08-0.069$ ). In this study it was also found that adjusted glucose levels were significantly reduced in group of patients treated with metformin as compared to those treated with insulin ( $p<0.001-0.003$ ) after treating for one week. In other words metformin was uniform in controlling glucose level in comparison to insulin. But drawback of this particular prospective study was that sample size was not large enough.

Ija's H et al.<sup>25</sup> demonstrated that among the patients treated with metformin 32% required additional insulin to reach the normal blood glucose level. The observations suggest that women who needed additional insulin were mostly more obese, required earlier medical treatment and had higher fasting blood sugar levels as compared to the women who only required metformin to reach normal glucose levels. These findings suggest that these women had higher insulin resistance.

## CONCLUSION

This study concludes that metformin is as much effective as insulin in management of gestational diabetes mellitus. Metformin when used securely can prove effective as it does not cause any congenital anomalies or maternal or neonatal complications. But insulin still remains the gold standard for treatment of gestational diabetes mellitus.

### Author's Contribution:

Concept & Design of Study:	Rao Muhammad Akram Khan
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**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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