METFORMIN OR INSULIN IN GESTATIONAL DIABETES-A CONUNDRUM

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ABSTRACT

Objective: To determine the effectiveness of metformin vs insulin for glycemic control in gestational diabetes mellitus.

Methodology: This study was done in the Department of Gynecology and Obstetrics, Saidu Teaching Hospital Swat from November 2019 to May 2020. Ethical approval was taken from the hospital ethical and research committee. A sample of 93 patients in each group was taken as per WHO sample size calculation software. All female patients with singleton pregnancies having gestational diabetes diagnosed for the first time in current pregnancy with an age limit from 16-40 Years were included in this study. The lottery method was used for dividing patients into two groups, group A (Metformin) and group B (Insulin). SPSS 23.0 was used for the data analysis using frequencies and percentages and the Chi-Square test was used to compare the efficacy of drugs between the two study groups. Efficacy was checked by measuring 1-hour postprandial sugar levels, i-e; more or less than 140mg/dl. A p-value less than or equal to 0.05 was considered statistically significant.

Results: Total number of patients was 186 (93 in each group). The mean age in group A was 28±3.76 years compared to 27±3.13 years in group B. Good glycemic control out of our total 186 patients (93 in each group) was achieved in 80%(n-74) in Group A compared to 90% (n-84) in Group B with a p-value was 0.0403.

Conclusion: The study concludes that metformin is non-inferior to insulin in controlling glucose levels in gestational diabetes mellitus.

Keywords: Gestational Diabetes Mellitus; Metformin; Insulin; Pregnancy

INTRODUCTION

Diabetes in pregnancy is one of the most important causes of perinatal and maternal morbidity.[1-3] Gestational diabetes occurred in 7-18% of all pregnancies[4] and its incidence is increasing day by day. According to WHO prediction, the worldwide prevalence of diabetes will increase 35% by 2025 and an additional 1-6% of women will develop gestational diabetes.[5] In Pakistan the true incidence is still to be determined because of the lack of screening for the disease but small hospital-based studies show a 3.2% risk of gestational diabetes and 1.9% for impaired glucose tolerance.[6]

Pregnancy itself is a potentially glucose intolerant condition due to increased resistance to insulin and this resistance increases as pregnancy advances.[7-9] In addition to the physiological changes of insulin resistance in pregnancy additional risk factors like obesity further increase the risk of gestational diabetes.[10-14]

The Oral Glucose Tolerance Test (OGTT) is used for the diagnosis of gestational diabetes while RBS and FBS are used to screen it.[15,16] Gestational diabetes is mostly treated with insulin therapy. The aim of therapy is to achieve optimal glycemic control. In addition to insulin studies now show that metformin is also used for glycemic control. It decreases glucose production by hepatocytes, decreases glucose absorption from the gut, and increases insulin sensitivity in the target cell. It is more cost-effective compared to insulin. Nowadays studies are going on for its safety and cost-effectiveness.

A study conducted in Brazil at Obstetrics Clinic das Clinicas Hospital, showed that mean pretreatment glucose level showed no difference in two groups with P value of 0.020. After the introduction of the drug, only 12 women (26.08%) out of 47 in the metformin group needed additional insulin remaining 73.92% responded to metformin for the control of glycemia.[12]

A study was conducted in Obstetrics and Gynecology department in PIMS (Pakistan Institute of Medical Sciences) Islamabad, in which 88.2% of patients were

effective to insulin compared to 79.4% for metformin for glucose control.[16]

As metformin reduces the psychological and financial burden of patients and hospital and prevalence of gestational diabetes has been seen to be rising over past several years so this study is conducted in tertiary care hospital to achieve strict glycemic control with metformin which is considered to be safe, non-invasive and effective alternative for the treatment of gestational diabetes.

METHODOLOGY

This randomized control trial study was conducted in Saidu Teaching Hospital, Department of Gynecology and Obstetrics from November 2019 to May 2020. Ethical Approval was taken from the hospital's ethical and research committee. The procedure was clarified to the patients and informed consent was taken from them in written form. A sample of 93 patients in each group as shown in consort diagram (Figure 1). The sample size was calculated by WHO Calculator. Proportion P1=73.92%[2] and proportion for control (Insulin) P2=88.2%.[8] Power of the test was 80% with a 5% level of significance, using nonprobability consecutive sampling with random allocation. This study inclusion criteria for all female patients with any age of gestation, with singleton pregnancy having an age limit from 16-40 years and gestational diabetes diagnosed for the first time, using OGTT in current pregnancy at booking or later on during 24 to 28 weeks and again in the third trimester if she is screen negative in first two trimesters, irrespective of risk factors as universal screening of all pregnant women is recommended.[4]

Type I and Type II diabetes mellitus, multiple pregnancies, Intolerant to metformin due to gastrointestinal side effects, and other medical conditions like, hypertension, hepatic disorders, renal impairment, and cardiac problems patients were excluded from the study to control bias, because all these factors have an impact on the feto-maternal outcome.

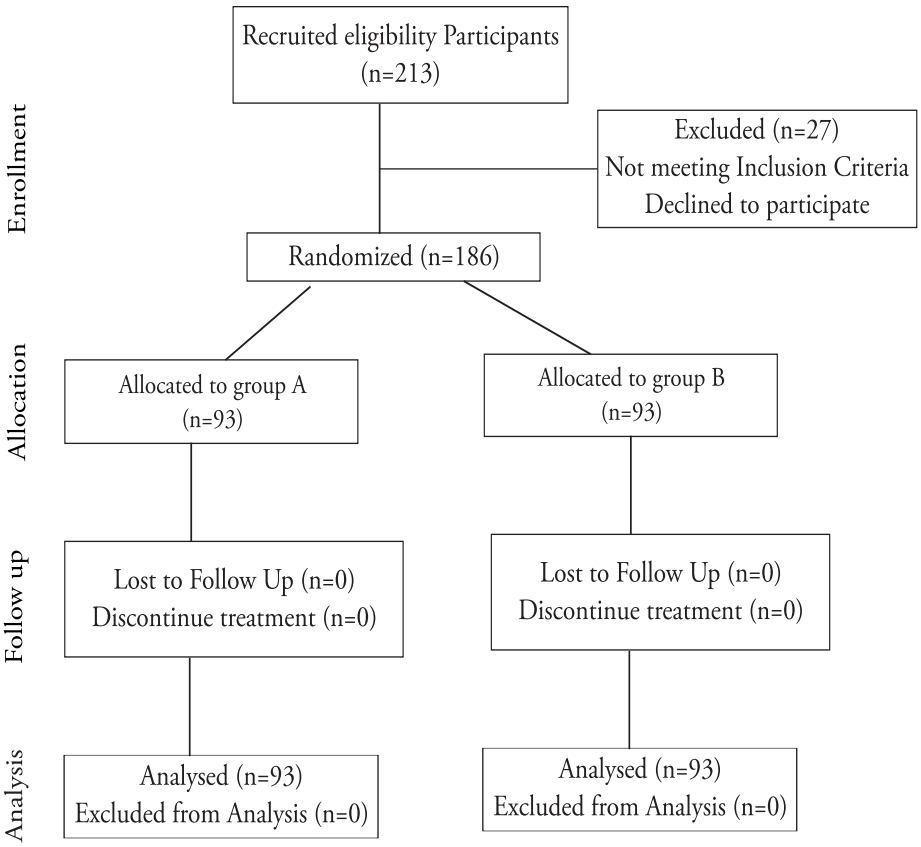

Figure 1: CONSORT diagram showing the flow of participants through each stage of the trial

Gestational diabetes was explained as, Fasting Blood sugar level of >100mg/dl and 01 hours postprandial blood sugar of >140mg/dl.[14] After the diagnosis of gestational diabetes patients were divided into 2 groups (Group A Metformin and Group B Insulin) by utilizing the lottery method. Medicines were obtained by their brand name from a local pharmacy (Tablet Glucophage, Humulin R, Humulin N) to control biasness. Metformin was started at a dose of 500mg twice a day in the morning and evening between meals. The dose of metformin can be increased typically over a period of one to two weeks to 500mg three times a day and then to a maximum daily dose of 2550mg i-e; 850mg three times a day to achieve the glycemic control i-e; FBS <95mg/dl and RBS <140 mg/dl till delivery of the baby.[14] Those patients with poor desirable glycemic control were also recorded. Initially, patients were admitted once sugar control was achieved then patients were followed in OPD on two weekly basis with FBS and RBS. If targets were not achieved then their dose was adjusted to get target levels. In group B intermediate and short-acting insulin were started as per the weight of the patient. The dose was adjusted till the patient achieves glycemic control.[9] Patients remained admitted for blood glucose monitoring for a couple of days until targets were achieved and were followed in OPD on fortnightly basis with FBS and RBS. If targets were not achieved then their dose was adjusted to get desired levels. Blood for testing sugar levels was obtained from the veins of patients in both groups by an experienced nurse after an overnight fast of 8 hours at 6:00 AM in a gel tube and was sent to the hospital laboratory. Blood sugar

was checked by hexokinase or glucose oxidase method by an experienced laboratory technician. Patients were instructed to take their lunch at 1:00 pm and dinner at 9:00 PM. Similarly, 1-hour post lunch and post dinner venous blood samples were obtained at 2:00 PM and 10:00 PM respectively and were sent to the laboratory in the same way. Pre-designed proforma was used to record the data.

Data analysis was done by using SPSS 23.0 version. We used mean ± standard deviation (SD) for quantitative variables like age and used frequencies and percentages for categorical variables like glycemic control, and to compare the efficacy of both the drugs, chi-square test was used and p-value of 0.05 was considered statistically significant. Efficacy was stratified among age and glycemic control to see an effect.

RESULTS

A total of 186 patients, 93 patients were allocated to each group. In Group A, we had 70 (75%) patients in the age range of 20-30 years, and 23 (25%) patients were in the age range of 31-40 years. The mean age of patients in group A was 28.0 ± 3.76 years. Whereas in Group B 67 (72%) patients were in the age range 20-30 years, and 26(28%) patients were in the age range 31-40 years. The mean age of patients in group B was 27.0 ± 3.13 years.

The stratification of efficacy with respect to age is given in table 1. This stratification will help in a better understanding of the efficacy of either treatment across different age groups. The status of glycemic control between the two groups is given in Table 2.

DISCUSSION

In this study, Group A showed a mean age of 28 ± 3.76 years and Group B showed a mean age of 27± 3.13 years. Metformin was effective in 74 (80%) of patients and was not effective in 19 (20%) of patients. Whereas Insulin was effective in 84 (90%) of patients and was not effective in 9 (10%) of patients.

Similar results were found in another study conducted by Juan et al[7] in which they compared average fasting and postprandial glucose levels. In their study, glucose levels, though statistically insignificant, were higher in the insulin group as compared to the metformin group in fasting glycemic control and in postprandial glycemic control. The average postprandial glucose levels in the first week were significantly lower in the metformin group compared to that of the insulin but no significant difference was observed in HbA1c levels between the two groups at 36 to 37 weeks gestation.

A study was conducted by Waheed et al[16] showed similar results where the mean ages of the group A (receiving insulin) and group B (receiving metformin) were 29.82 and 29.35 years, respectively. Both the groups had 34 patients each. After one-month fasting blood sugar levels were within the normal range in 64.7% (n=22) patients in the A group and in 79.4% (n=27) patients in the B group ($p > 0.05$). They followed the patients till term and found that fasting blood sugar level at term were within normal range in 88.2% (n=30) patients in A group and 79.4% (n=27) in B group ($p > 0.05$). Similarly post prandial blood sugar levels were compared, which was controlled after 1 month in 73.5% (n=25) patients in A group and in 70.6% (n=24) patients in B group. Group A was treated with Metformin and Insulin was given to Group B. When patients reached term, postprandial blood sugar level were within normal limits in 82.4% (n=28) patients in group A and 79.4% (n=27) patients group B. They compared HbA1c levels after treatment which showed that it was within normal range in 79.4% (n=27) patients in A group and in 82.3% (n=28) patients of B group. So metformin was equally effective to insulin in controlling gestational diabetes. In all these studies, the sample sizes were small but their results are similar to current study done on larger sample size so metformin was equally effective to insulin in controlling gestational diabetes with less discomfort, more cost-effectiveness, and compliance.

Table 1: Stratification of efficacy with respect to age

Age (Years)	Efficacy	Group (A)	Group (B)	P value
20-30	Effective	58	61	0.1562
	Not effective	12	6	
31-40	Effective	16	23	0.1014
	Not effective	7	3	

Table 2: Glycemic control (n=186)

Glycemic Control (1 hour Post Prandial)	Group (A) metformin	Group Insulin (B)
≤140 mg/dl	74 (80%)	84 (90%)
>140 mg/dl	19 (20%)	9 (10%)

*P value is 0.0403

CONCLUSION

Our study concludes that metformin is more effective to insulin in terms of glucose control in gestational diabetes mellitus. As this was a single center, smaller sample size randomized study, so we recommend a multi-central, having larger sample size randomized study to further validate our study findings.

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Author's Contribution

SA conceived the idea and designed the study. SP contributed in data collection and performed the statistical analysis. FS and PN helped in writing the manuscript and critically reviewed it. TI helped in data analysis. SH helped with the bibliography. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.