Original Article

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Comparison of Metformin and Insulin in the Management of Non-Obese Gestational Diabetes Mellitus Patients

Naimatullah Khan, Waheed Iqbal, Heema, Nizamuddin, Syed Hasnain Ali Shah, Noor Ul Ain

ABSTRACT

Objective: This study will aim to determine the effects of metformin and insulin in the management of non-obese GDM.

Study Design and setting: This Cohort study was carried out in the department of gynecology, Healthways Hospital Khyber Pakhtunkhwa (KPK) Pakistan. The duration of the study was 6 months started from May 2024 to Dec 2024.

Methodology: Total 160 GDM patients were recruited which were divided equally in to two groups. To one group metformin 500mg thrice daily were prescribed while insulin (mixtard 70/30) was prescribed to insulin group. The target fasting blood sugar (FBS) was set <95mg/dl. All the patients were followed for 2 months with FBS after 1st week, 2nd week, 14 days and 1 month interval**.**

Results: In metformin group, 32.5% patients were in 1st trimester, 41.25% were in 2nd trimester while 41.25% were in 3rd trimester while in insulin group the frequency of 1st, 2nd and 3rd trimester was 33.75%, 52.5% and 13.75% respectively. The mean age, BMI and FBS in metformin group were 26.74±3.5 years, 24.18±2.21 and 135.16±9.74 mg/dl respectively. There were no statistical differences observed between mean values of both group with p-values 0.96, 0.73 and 0.87 respectively. However, in insulin group there was statistically significant difference achieved in controlling the FBS after two months with p-value 0.04.

Conclusion: Insulin significantly controls the FBS but metformin also shows comparable results. Thus, metformin is a good first line drug in terms of cost and compliance to GDM patients especially in financially deprived area.

Keywords: Gestational Diabetes Mellitus, Hyperglycemia, Insulin, Metformin

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Naimatullah Khan
PhD Scholar, Department of Pharmacology
Khyber Medical University
Email: orakzai76@gmail.com

Waheed Iqbal
PhD Scholar, Department of Pharmacology
Khyber Medical University
Email: waheediqbal22@gmail.com

Heema
PhD Scholar, Department of Pharmacology
Khyber Medical University
Email: heema123dr@gmail.com

Nizamuddin
PhD Scholar, Department of Pharmacology
Khyber Medical University
Email:drnizam99@yahoo.com

Syed Hasnain ali Shah
PhD Scholar, Department of Pharmacology
Khyber Medical University
Email: drhasnain80@yahoo.com

Noor Ul Ain
PhD Scholar, Department of Pharmacology
Khyber Medical University

Email: nurulain.afandi@abasyn.edu.pk

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is referred to as hyperglycemia among women during pregnancy.[1] There is also increase probability of type 2 diabetes mellitus after pregnancy. GDM not only poses threats at maternal level but also there is an increased risk of adverse outcomes at fetal level as well. At maternal level, there is an increased risk of caesarean section (C-section), macrosomia, preeclampsia and intrauterine growth retardation. The fetal abnormalities are not limited to delay brain maturity, lower intelligence that normal delivered babies, language impairments and poor attention.[2] Thus an early diagnosis and treatment prevent both mother and child from adverse outcomes.[3] Unlike obese women with GDM, in whom insulin resistance predominates, GDM in lean women is believed to result primarily from impaired insulin secretion. The risk factors related to the development of GDM included family history of diabetes, low physical activity, advanced maternal age, BMI >30kg/m^2, inadequate diet and antenatal depression were reported by many researchers around the world.[4] This pathophysiological distinction underscores the need to evaluate whether management strategies should differ based on BMI.[5] Globally, the prevalence of GDM ranges from approximately 1% to 14%. Higher rates are

observed in populations with risk factors such as advanced maternal age, obesity, and specific ethnicities. Regional data indicate variability, with some regions reporting as low as 1–2%, while others, especially in South Asia and the Middle East, report a prevalence exceeding 10%. According to a study published in Australia, Asian women are at higher risk of developing GDM the Australian women.[6] South Asian countries reported higher prevalence of GDM as compared to rest of the world. In Pakistan, studies have reported a GDM prevalence ranging from approximately 7% to 14%, reflecting regional and methodological differences. This aligns with the higher prevalence of GDM observed in South Asia[2] However, according to a recent meta-analysis, the prevalence of GDM was reported to be 16.7%, thus posing treat to the rising burden of GDM in this subcontient.[7] The pathophysiology of GDM is complex and involved multiple complex mechanisms of hormonal, metabolic and cellular that leads to impairment of glucose regulation during pregnancy. These factors include insulin resistance, dysfunction in beta cells, and alteration in inflammatory biomarkers, genetic and environmental factors. The diagnosis of GDM is easy and cost effective thereby checking the fasting and random blood sugar during initial consultation. Diagnosis is typically established using a 75-g oral glucose tolerance test (OGTT), with plasma glucose thresholds of =92 mg/dL (5.1 mmol/L) fasting, =180 mg/dL (10.0 mmol/L) at 1 hour, or =153 mg/dL (8.5 mmol/L) at 2 hours.[7,8] The treatment options for the management of GDM are very limited and pharmacotherapy is required alongside diet modifications. The pharmacotherapy includes primarily insulin. However, metformin and glyburide are also considered as an alternative therapy in the management of hyperglycemia. Despite the role of pharmacotherapy, diet modification is as effective as pharmacotherapy in the management of hyperglycemia related to GDM. The ultimate goal of pharmacotherapy and diet modification in GDM is to manage hyperglycemia thereby preventing the mother as well as the fetus from adverse outocomes.[9] Usually metformin is employed in the treatment of GDM and if the hyperglycemia persists, insulin is added. The diverse mechanism of action of metformin beyond its gluco-regulatory and insulin sensitizing properties, makes metformin as a suitable candidate in the management of hyperglycemia associated with GDM. Metformin is also safe and effective in decreasing gestational weight gain, macrosomia and neonatal hypoglycemia.[10] Some randomized control trial reported insulin as more effective in the management of GDM while others found no statistical differences between both drugs while some published reports prefer metformin over insulin in the management of GDM. Studies on the long-term effects of metformin and insulin were also conducted and reports contradicting finding related to both metformin and insulin.[11-13] Thus further studies demanded to evaluate efficacy of both drugs in the management of GDM. Kohat being the fourth most populous city in Khyber Pakhtunkhwa with over 220,000 people, with limited resources and finances, research studies on such population are very impactful to explore these patients. Therefore, this study represents the people of Kohat with GDM and aims to compare the efficacy of metformin and insulin in the management of hyperglycemia related to GDM in Kohat Khyber Pakhtunkhwa.

METHODOLOGY

This quasi-experimental study was conducted in the department of gynecology and obstetrics, Health Ways hospital (HWH) Kohat, Khyber Pakhtunkhwa. The duration of the study was 6 months started from 2nd May 2024 to 30th Dec 2024. Total 160 GDM patients were included in the study which was calculated using openepi () taking power of study 80, 95% confidence interval, 5% margin of error and 11.8% prevalence [2] of GDM in Pakistan. Newly diagnosed GDM patients willing to participate in the study as per World Health Organization (WHO) criteria (FBS>92mg/dl, 1 hour RBS>180mg/dl or 2 hour RBS>153mg/dl) were included using non-probability convenient sampling.[14] The patients were properly enrolled after issuance of ethical approval letter from HWH via letter no. HWH-109 dated 13-05-2024. All the GDM patients were verbally informed in their local language regarding our research project and GDM patients whose showing willingness to participate in the study; proper consent was signed from each patient. Patients not consenting, having metabolic illness, and having pre-gestational diabetes were excluded from the study. After fulfillment of the inclusion criteria, the enrolled patients were thoroughly undergoing a detailed interview process where the demographics including age, parity, trimester, and BMI were initially recorded in a predesigned proforma. The patients were then categorized into two groups (group A and group B). Group A were prescribed metformin while group B was prescribed insulin. There was drop-off of 4 patients in metformin group and 7 patients in insulin group which were compensated by recruiting additional patients to meet the criteria of 80 patients in each group. To metformin group, metformin 500mg thrice daily was prescribed to maximum of 750mg thrice a day while insulin (mixtard70/30) were prescribed to insulin group as per gestational age and body weight. The target FBS was set to be <95mg/dl for which the dose was titrated after 72 hours till the target was achieved. All the patients were followed for 2 months with FBS after 1st week, 2nd week, 14 days and 1 month interval. If the target FBS was not achieved after two weeks in metformin group, the dose was increased to maximum (750mg), small doses of insulin were added to metformin group if the target FBS was not achieved with maximum dose. The criteria were adopted as per previous report published with slight modifications.[15] all the data was analyzed using SPSS version 26.0. The numerical variables were presented in mean ±

standard deviation (SD) while categorical variables were shown in frequency and percentages. To determine the possible association between categorical variables, chi-square test was used. For numerical variables, mean differences in both groups were observed using independent sample t-test. The considered test values were two-tailed and p-value <0.05 was considered significant. The graphs were constructed using MS-excel version 2013.

RESULTS

The clinical presentation of the patients is summarized in table 1. In metformin group primigravidas were present in 47.5% GDM patients while 52.5% were in insulin group. Similarly, multigravidas were prevalent in 52.5% and 47.5% in metformin and insulin group respectively. There were no statistically significant differences observed between both groups with p-value 0.31 reflecting a balanced enrollment of patients in both groups. In metformin group, 32.5% patients were in 1st trimester, 41.25% were in 2nd trimester while 41.25% were in 3rd trimester while in insulin group the frequency of 1st, 2nd and 3rd trimester was 33.75%, 52.5% and 13.75% respectively. Chi-square test reveals no statistical differences between both groups with p-value 0.12. The overall frequencies of trimester presentation are graphically shown in figure 1.

Table 1: Presentation of GDM patients and its association between groups

Variables	Groups	Metformin group (n=80)	Insulin group (n=80)	p-value
Obs. status	Primigravida	38 (47.5%)	42 (52.5%)	0.31
	Multigravida	42 (52.5%)	38 (47.5%)	
Trimester	1st trimester	26 (32.5%)	27 (33.75%)	0.12
	2nd trimester	33 (41.25%)	42 (52.5%)	
	3rd trimester	21 (26.25%)	11 (13.75%)	

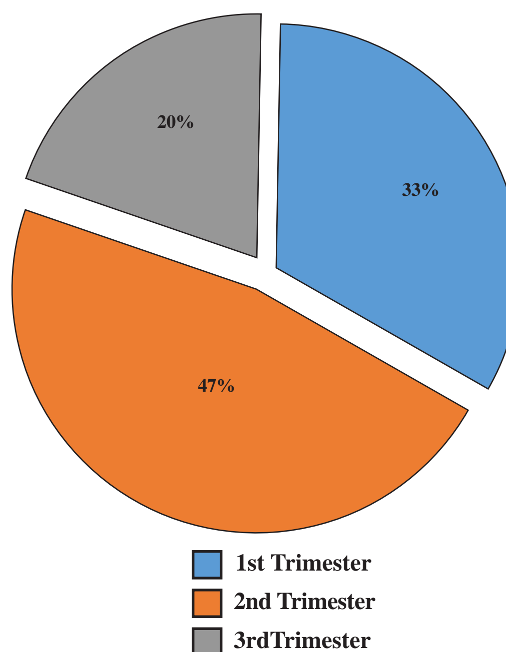
Table 2: determination of mean differences between both groups (n=160)

Variables	Groups	Mean±SD	p-value	95%CI
Age (years)	Metformin	26.74±3.5	0.96	-1.18-1.13
	Insulin	26.76±3.1		
BMI (kg/m^2)	Metformin	24.18±2.2	0.73	-0.83-0.58
	Insulin	24.30±2.3		
FBS (mg/dl)	Metformin	135.16±9.7	0.87	-3.12-2.65
	Insulin	135.46±8.7		
FBS after 1 week	Metformin	91.28±10.4	0.73	-2.76-3.91
	Insulin	91.70±10.9		
FBS after 2nd week	Metformin	87.98±8.8	0.12	-4.9-0.59
	Insulin	90.14±8.7		
FBS after one month	Metformin	88.16±8.9	0.16	-0.72-4.1
	Insulin	86.48±6.2		
FBS after two months	Metformin	86.94±8.0	0.04	0.02-4.0
	Insulin	84.89±4.4		

In order to determine the mean differences between both groups, independent sample t-test was used. The mean age, BMI and FBS in metformin group were 26.74±3.5 years, 24.18±2.21 and 135.16±9.74 mg/dl respectively. Similarly, in insulin group, the mean age was 26.76±3.1 years, mean BMI was 24.30±2.3 kg/m^2, and mean FBS was 135.46±8.7mg/dl. After 1st week of follow-up, the mean FBS in metformin and insulin group was 91.28±10.4mg/dl and 91.70±10.9mg/dl respectively. In 2nd follow-up after 2 weeks, the mean FBS in metformin group was 87.98±8.8mg/dl and in insulin group it was 90.14±8.7mg/dl. After 3rd follow-up (one month), both mean FBS levels were comparable (88.16±8.9mg/metformin group vs. 86.48 ± 6.2mg/dl in insulin group). There were no statistical differences observed between mean values of both group with p-values 0.96, 0.73 and 0.87 respectively. This proves that both drugs are helpful in controlling the blood glucose in GDM patients. However, after two months of follow-up the mean FBS levels in metformin and insulin group were 86.94±8.0mg/dl and 84.89±4.4mg/dl respectively, showing that insulin group provides statistically significant reduction in controlling the FBS after two months as compared to metformin with p-value 0.04. Further details of the demographic and biochemical variables are summarized in table 2.

The insulin group achieved the targeted FBS after two months follow up while only 5% patients in metformin group does not achieve targeted FBS levels and insulin were added to their regimen.

Figure 1: Trimester presentation of GDM patients



DISCUSSION

The prevalence of DM in our country is up surging at alarming rate creating financial burden on developing country like Pakistan. Though the exact prevalence of GDM in our country is yet to known but city based small studies reports high prevalence of GDM in Pakistan. This condition poses high risk to both mother and child leading to high rate of morbidity and mortality. To limit the adverse outcomes, proper screening is necessary to diagnose GDM early in pregnancy and provide effective treatment to properly control the hyperglycemia related to GDM. In general, the studies focusing on the use of metformin in GDM are very limited as compared to insulin. This study compared the efficacy of metformin and insulin in controlling FBS levels in non-obese GDM patients. Such studies are not conducted particularly in Kohat Khyber Pakhtunkhwa and we are the 1st to report such studies from the peripheries.

In this experimental study, we enrolled 160 GDM patients who were equally divided into two groups (group A and group B) and were followed for 2 months at four follow-up intervals. Group A were prescribed metformin 500mg thrice daily to maximum of 750mg thrice a day while insulin (mixtard70/30) were prescribed to insulin group as per gestational age and body weight. The target FBS was set to be <95mg/dl in both groups. The demographics of our study participants in both groups including age, BMI, gestational age and clinical presentation were similar and does not differ significantly (p-value >0.05), suggesting that patients in both groups were enrolled with extreme cautions and the differences observed in FBS control were more likely due to different treatment modalities rather than underlying patient factors.

In our study, both metformin and insulin provide effective control in managing targeted FBS (<95mg/dl) in GDM patients. Metformin manages hyperglycemia in GDM patients primarily by reducing hepatic glucose production and improving peripheral insulin sensitivity. It also decreases the production of glucose in the liver, which lowers the amount of glucose released into the bloodstream. Additionally, metformin also facilitates the transport of glucose in the muscle and adipose tissue, thereby increasing glucose utilization and reducing blood glucose levels. Unlike insulin, metformin does not stimulate insulin secretion but improves the body's response to existing insulin, making it effective in managing hyperglycemia in GDM without causing hypoglycemia. On the other hand, insulin controls hyperglycemia in gestational diabetes mellitus (GDM) patients primarily by facilitating glucose uptake and utilization, thereby lowering elevated blood glucose levels. In GDM, insulin resistance increases due to placental hormones, leading to impaired glucose regulation. Administered insulin compensates for this resistance by enhancing cellular glucose uptake, especially in muscle and adipose tissues. Suppress the hepatic glucose production, reducing endogenous glucose release into the bloodstream. Promote glycogen synthesis and storage in the liver and muscles. Inhibit the lipolysis, which reduces free fatty acid levels that can worsen insulin resistance. The advantage of metformin over insulin is that metformin does not cause hypoglycemia while insulin may cause hypoglycemia so patient education is very necessary.[16] Our findings are similar with the studies published previously. According to a randomized control trial (RCT) by Tertti et al reported that both metformin and insulin provides comparable results in treating GDM patients reflecting our initial findings that both metformin and insulin manage the glucose levels effectively in GDM patients.[17] A meta-analysis published by Xin Bao et al also reported potential benefits of metformin for pregnant women and babies with no adverse effects, showing the safety and efficacy of metformin and insulin to both mother and child in a long run.[18] Based on determination of adverse events, a study published by Paavilainen et al reported no differences between metformin and insulin in neuropsychological and cognitive outcome in children whose mother were treated with metformin and/or insulin, showing comparable results of metformin and insulin related to prospective child health.[18] Similarly, another randomized control trials (RCT) published by Sheng et al related to the neonatal adverse outcome in GDM patients on metformin versus insulin found no short term adverse outcome in metformin group suggesting that metformin is safe and effective alternative to inuslin.[20]

Our study demonstrated a statistically significant difference in controlling FBS levels after two months. These findings are in line with Ainuddin et al who showed that insulin therapy was more effective than metformin in achieving glycemic control in GDM patients.[21] The superior glycemic control with insulin as compared to metformin may be attributed to its direct action on glucose metabolism, allowing for more precise control of blood glucose levels. A most recent meta-analysis published by Wu et al also reported that metformin may also reduce adverse outcome related to both mother and child as compared to insulin, however long-term follow-up in necessary.[22] However, contradicting findings related the effects of metformin and insulin was also reported. A study conducted by Cesar et al, reported metformin provides better control of post prandial sugar as well as lower episodes of hypoglycemia and maternal weigh gain as compared to insulin.[23] Similarly, a meta-analysis summarizes fifty RCTs representing Chinese population also reported that metformin provides better picture in controlling maternal hyperglycemia and glycated hemoglobin levels as compared to insulin.[24]

The findings of our study have important implications for clinical practice in the management of GDM patients especially in financially deprived area, Kohat Khyber Pakhtunkhwa. As our findings report comparable results of both metformin and insulin, metformin may be considered

as the first line drug for non-obese GDM patients where insulin therapy may be challenging due to cost or access constraints. Studies related to the cost and effectiveness were also done and according to a study published by Ainuddin et al, reported that metformin is an effective and cheap treatment option for patients with GDM [21] with no potential harm or adverse outcomes to both mother and child.[25]

From the previous published reports, it has been summarized that both insulin and metformin show comparable results in the management of hyperglycemia associate with GDM. Furthermore, studies on long term follow-up to evaluate the efficacy and adverse outcomes also reported comparable results of both metformin and insulin. In a net shell, though most of the studies were in favor of insulin but metformin cannot be subsided because of its cheap price, no hypoglycemia effects as well as no short- and long-term adverse outcome both maternal and fetal. Thus, metformin is safe and effective alternate for insulin in the management of GDM especially in our vicinity.

Limitation of the study: This study was limited to single ethnic group and one center. Enrollment of patients from different ethnic groups, urban and rural as well as involving multiple centers with large sample size would provide a better picture of the current study. Furthermore, a longer maternal follow-up duration as well as studies focusing children born from GDM mothers will present a better picture for both drugs.

CONCLUSION

In our study both metformin and insulin show promising results in the management of FBS in non-obese GDM patients. However, insulin provides a slightly better control but given to its cost effectiveness and comparable efficacy, metformin is a better first line therapy option for non-obese GDM patients. Further research is needed to determine the long-term outcomes and potential benefits of combination therapy in GDM management.

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Authors Contribution:
Naimatullah Khan: Conception, Design and collection of data
Waheed Iqbal: Data analysis, interpretation and writing
Heema: Conception, Design and collection of data
Nizamuddin: Conception, data analysis, Approval of final draft
Syed Hasnain Ali Shah: Interpretation of data and analysis
Noor ul Ain: Revision and finalization of manuscript

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