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COMPARISON OF EFFICACY OF METFORMIN ALONE AND METFORMIN+ GLIBENCLAMIDE IN GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is associated with significant maternal and neonatal complications if inadequately treated. While insulin remains the gold standard for pharmacological management, hypoglycemic agents such as metformin and glibenclamide are increasingly considered due to promising results.

Objective: To compare the frequency of treatment failure between metformin monotherapy and a combination of metformin plus glibenclamide in the management of GDM.

Methods: This randomized controlled trial included 160 pregnant women with GDM at ≥28 weeks gestation. Participants were randomized into two groups: Group A received metformin alone, while Group B received metformin combined with glibenclamide. Glycemic control was evaluated after two weeks. Treatment failure was defined as persistently elevated glucose levels requiring insulin.

Results: Combination therapy significantly reduced treatment failure (12.5%) compared to metformin alone (41.3%) ($p = 0.00004$). Glycemic control was shown in 88% patients of the combination group versus 59% in the metformin group. The efficacy of combination therapy was consistent across all BMI categories.

Conclusion: The addition of glibenclamide to metformin significantly improves glycemic control and reduces treatment failure in GDM patients, offering a viable alternative in resource-constrained settings.

INTRODUCTION

Gestational diabetes mellitus (GDM) complicates 2-10% of pregnancies[1]. Its prevalence is increasing with increase in both obesity and advanced maternal age[2]. It is usually diagnosed in late 2nd trimester (24-28 weeks) of pregnancy. Uncontrolled gestational diabetes mellitus can lead to adverse pregnancy outcomes for both mother and fetus [3]. Fetal complications include macrosomia, pre-term birth, neonatal hypoglycaemia and hyperbillirubenemia[4].

Treatment of gestational diabetes mellitus can prevent neonatal and maternal complications. Initial treatment of gestational diabetes mellitus includes dietary modification and physical activity[5]. Lack of diet and lifestyle modifications results in requirement of pharmacological therapy for the treatment of gestational diabetes mellitus; insulin has been used for such patients[6.] Insulin lowers maternal blood glucose levels by stimulating peripheral glucose uptake and glucose production by liver [7].However it requires multiple daily injections, risk of hypoglycaemia, and increase in appetite and weight gain[8]. Treatment compliance, cost of treatment, need for refrigeration and skilled handling is always an issue in under developing countries like Pakistan[9].

Over the years various studies have compared efficacy of Glibenclamide to Insulin, oral agents have been increasingly viewed as potential alternatives. Their ease of administration, lower cost, and easy availability makes them a better acceptable option[10, 11]. Metformin, belongs to the biguanide group, and it plays major role in reducing fasting and post-prandial glucose levels. It inhibits hepatic and renal gluconeogenesis and it stimulates the glucose uptake and glycolysis in peripheral tissues[12.] Also, it slows glucose absorption from GIT and reduces plasma glucagon level. As a result, metformin is being increasingly used in the management of gestational diabetes mellitus [13]. Glyburide is 2nd generation sulfonylurea drug and it controls post-prandial glucose levels in human body.[14]

Oral hypoglycaemic agents are considered better alternative than insulin for the ease of administration, affordability and better compliance of patients [15]. Nachum and colleagues conducted a study on comparison of outcomes of metformin with glibenclamide and their combination for treatment of GDM, the authors reported primary drug failure in 34% patients in glibenclamide group and 29% in metformin group. After adding glibenclamide with metformin, the failure rate reduced to 13%. This combination reduced the need of insulin from 32% to 10% (P=0.00021). The authors reported that combination of metformin plus glibenclamide is more effective than metformin alone[16.]

There are some potential gaps in the literature regarding the comparison of the efficacy of metformin alone versus metformin combined with glibenclamide in the treatment of gestational diabetes mellitus (GDM). Many studies have focused on short-term outcomes during pregnancy or immediately postpartum [17]. While efficacy is crucial, ensuring maternal and fetal safety is paramount in GDM treatment. There exists a gap in literature about comparative safety profiles of metformin alone versus metformin combined with glibenclamide, including risks of hypoglycaemia, teratogenicity, and other adverse effects [18].

Addressing these gaps could enhance our understanding of the relative efficacy, safety, and cost-effectiveness of metformin alone versus metformin combined with glibenclamide in the treatment of GDM, ultimately improving clinical decision-making and patient outcomes. This study aims to compare the frequency of treatment failure with administration of metformin alone versus metformin plus glibenclamide for management of gestational diabetes mellitus.

METHODOLGY

This randomized controlled trial was conducted in Unit III of the Department of Obstetrics and Gynecology at Sir Ganga Ram Hospital, Lahore, over 6 months from October 2024 to March 2025. The sample size was determined to ensure a statistical power of 80%, a 5% level of significance, and an expected treatment failure rate of 29% in the Metformin group compared to 13% in the Metformin plus Glibenclamide group.[16] After obtaining informed consent, 160 pregnant women aged 18 to 40 years with singleton pregnancies beyond 28 weeks of gestation and newly diagnosed with gestational diabetes mellitus (GDM) based on the IADPSG criteria were enrolled using non-probability consecutive sampling. Women with a history of hypersensitivity to study medications, significant hepatic or renal dysfunction, or comorbidities such as preeclampsia were excluded from the study.

Participants were randomly allocated into two treatment arms via a computer-generated randomization list. Group A received Metformin alone, initiated at 500 mg twice daily and titrated weekly up to a maximum of 2000 mg/day. Group B was treated with a combination regimen consisting of Metformin (up to 2000 mg/day) and Glibenclamide (initiated at 5 mg/day and increased up to 20 mg/day, administered 30 minutes before meals). Glycemic control was evaluated two weeks after therapy initiation using fasting and one-hour postprandial blood glucose measurements. Treatment failure was defined as the presence of two or more elevated glucose readings per meal (fasting >100 mg/dL or postprandial >130 mg/dL) despite the use of maximum tolerated doses, thereby necessitating the initiation of insulin therapy. Participants who maintained adequate glycemic control continued regular antenatal follow-up in the outpatient setting, under the direct care of a consultant obstetrician. Data were recorded using a structured proforma and analyzed using SPSS version 25.0, with a p-value ≤ 0.05 considered statistically significant.

RESULT

A total of 160 pregnant women diagnosed with gestational diabetes mellitus (GDM) were randomly assigned into two equal groups: Group A received Metformin monotherapy (n = 80), while Group B received a combination of Metformin and Glibenclamide (n = 80). Baseline demographic and clinical variables were similar between the two groups. The mean age of participants was 29.80 ± 4.00 years in Group A and 31.88 ± 3.85 years in Group B. The average gestational age at enrollment was 30.28 ± 1.34 weeks in the Metformin group and 30.27 ± 1.46 weeks in the combination group. Mean body mass index (BMI) values were 26.35 ± 3.23 kg/m² in Group A and 26.83 ± 3.10 kg/m² in Group B.

Fasting blood glucose levels averaged 93.50 ± 5.62 mg/dL in the Metformin group and 92.12 ± 5.43 mg/dL in the combination group. Postprandial glucose levels were 127.75 ± 10.44 mg/dL and 123.76 ± 8.21 mg/dL, respectively.

Glycemic targets were achieved in 70 participants (88%) receiving combination therapy, compared to 47 participants (59%) treated with Metformin alone, showing a statistically significant difference ($p = 0.000041$). Treatment failure, defined as inadequate glycemic control requiring escalation to insulin, occurred in 33 patients (41.3%) in the Metformin group and in 10 patients (12.5%) in the combination therapy group ($p = 0.00004$).

Subgroup analysis by BMI category further supported the superior efficacy of combination therapy. Among participants with BMI <25, treatment failure was noted in 6 (40%) in Group A and 1 (10%) in Group B. For those with BMI 25–29.9, failure rates were 40% (n = 16) and 16.7% (n = 5), respectively. In participants with BMI ≥30,

44% (n = 11) in Group A experienced treatment failure, compared to only 3.3% (n = 1) in Group B. These results underscore the enhanced effectiveness of combination therapy across all BMI categories.

Variable	Group A (Metformin)	Group B (Met + Glibenclamide)
Mean Age (years)	29.80 ± 4.00	31.88 ± 3.85
Gestational Age (weeks)	30.28 ± 1.34	30.27 ± 1.46
BMI (kg/m²)	26.35 ± 3.23	26.83 ± 3.10
Fasting Blood Sugar (mg/dL)	93.50 ± 5.62	92.12 ± 5.43
Postprandial Glucose (mg/dL)	127.75 ± 10.44	123.76 ± 8.21

Table 1: Baseline Demographic of Participants

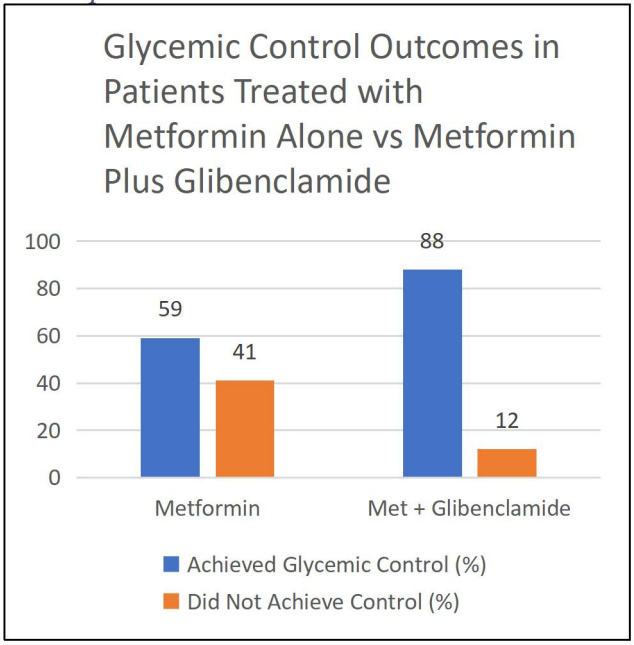

Figure 1: Glycemic Control Outcomes in Patients Treated with Metformin Alone vs Metformin Plus Glibenclamide

Treatment Failure	Metformin (n = 80)	Met + Glibenclamide (n = 80)	P value
Yes	33	10	0.00004
No	47	70	

Table 2: Frequency of Treatment Failure Among Patients Receiving Metformin Alone vs Combination Therapy

BMI Category	Treatment Failure – Metformin Group (n, %)	Treatment Failure – Combination Therapy Group (n, %)
<25	6 (40.0%)	1 (10.0%)
25–29.9	16 (40.0%)	5 (16.7%)
≥30	11 (44.0%)	0 (0.0%)

Table 3: Comparison of Treatment Failure Across BMI Categories Between Metformin Alone and Combination Therapy (Metformin + Glibenclamide)

DISCUSSION

This randomized controlled trial focused on comparing the frequency of treatment failure between metformin monotherapy and metformin combined with glibenclamide in the management of gestational diabetes mellitus (GDM). Our findings show that the combination therapy significantly improved glycemic control, with 88% of women achieving target glucose levels versus 59% under metformin alone (p = 0.000041). Treatment failure was notably lower in the combination group (12.5%) compared to metformin monotherapy (41.3%) (p = 0.00004). Stratified by BMI, these results remained consistent across all weight categories, indicating sustained efficacy of combination therapy even in patients with higher insulin resistance. Recent literature corroborates these outcomes. A meta-analysis including over 4,500 participants across randomized trials found that while metformin is generally effective for glycemic control, its failure rate can reach up to 50%, necessitating additional interventions such as glibenclamide or insulin to achieve target glucose levels.[19] Another study has suggested that metformin monotherapy, although effective for many, has substantial failure rates necessitating supplementary treatment while metformin

demonstrates favourable short-term glycaemic control, a significant proportion (~30–50%) still require insulin or additional agents to achieve target glucose levels.[20] However, the addition of a sulfonylurea like glibenclamide can bridge the efficacy gap by providing more robust glucose lowering, as highlighted in a prospective comparative study which found significantly improved glycaemic outcomes with glibenclamide compared to metformin monotherapy. [21] Another study comparing glibenclamide to insulin in GDM showed comparable glycaemic control between these therapies, supporting the potency of glibenclamide in controlling maternal glucose levels.[22] These findings reinforce the current study's results, demonstrating that metformin plus glibenclamide yields a high rate of glycaemic target attainment and low treatment failure. However, a recent systematic review evaluating 45 studies reported that metformin is generally effective and safer than glibenclamide regarding neonatal and maternal outcomes—yet highlighted that sulfonylureas may lead to higher failure rates and increased risk of neonatal hypoglycaemia or macrosomia.[23] Additionally, another comparative prospective study concluded that although glibenclamide delivers superior glycaemic control compared to metformin, it is associated with more adverse effect.[24] It aligns with our findings that suggesting combination therapy enhances glycaemic success, while careful monitoring for side effects is warranted. This study provides critical insights into the comparative effectiveness of metformin monotherapy versus combination therapy with glibenclamide in managing gestational diabetes mellitus. By evaluating treatment failure rates and stratifying outcomes by BMI, it supports rational decision-making in resource-limited settings where insulin may not be practical.[25] The findings contribute to optimizing glycemic control in pregnancy and reducing the risk of adverse maternal and neonatal outcomes. The study is limited by its single-center design and modest sample size. It did not assess long-term neonatal outcomes or maternal adherence, nor did it include insulin as a comparator. Larger multicenter trials are needed to validate and expand upon these findings.

CONCLUSION

This randomized controlled trial found that combination therapy with metformin and glibenclamide significantly reduced treatment failure rates compared to metformin monotherapy in women with gestational diabetes mellitus. The superiority of the combination regimen was evident across all BMI categories, indicating greater efficacy even in populations with increased insulin resistance. In resource-limited settings, oral combination therapy may serve as a viable alternative to insulin. Nonetheless, due to the potential for adverse effects, careful patient monitoring is essential. Further large-scale, multicentre trials are warranted to confirm these results and evaluate maternal and neonatal safety profiles.

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