

Original Article

# Frequency of Metformin-Poor Response And Factors Associated With The Need For Insulin As A Complementary Treatment Among The Patients of Gestational Diabetes Mellitus

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## Abstract

**Objective:** To determine the incidence of patients transitioning from metformin monotherapy to a combined regimen of insulin and metformin during the second or third trimesters of pregnancy for managing gestational diabetes.

**Methods:** This descriptive cross-sectional study was conducted in the Department of Obstetrics and Gynecology at DHQ Hospital, Rawalpindi, from May 11, 2021, to May 10, 2022.

This analysis involved 246 pregnant women aged between 20 and 35 years, diagnosed with GDM during the first or second trimester of pregnancy, who were taking metformin monotherapy. These women were followed up, and a poor response to metformin was defined as the need for supplemental insulin during the 2<sup>nd</sup> or 3<sup>rd</sup> trimester.

**Results:** The mean age of the women was 26.6±4.6 years. The mean BMI of these women was 26.8±4.5 Kg/m<sup>2</sup> and 43.5% of women were obese. family history of diabetes was noted in 46.7% of women, while 28.0% of women had a history of GDM in a previous pregnancy. Poor response to metformin therapy was noted in 45 (18.3 %) women with GDM. Upon comparison, it was observed that the incidence of advanced maternal age (≥30 years) (53.3% vs. 23.4%; p-value<0.001), early onset of gestational diabetes mellitus (GDM) (gestational age ≤15 weeks) (77.8% vs. 46.8%; p-value<0.001), and obesity (62.2% vs. 39.3%; p-value=0.005) exhibited a statistically significant elevation among individuals with an inadequate response to metformin therapy, necessitating the inclusion of supplemental insulin.

**Conclusion:** In the current study, we observed that a considerable proportion of pregnant women with GDM showed poor response to metformin, and the frequency of older maternal age, early onset of GDM, and obesity was significantly higher among such cases. This suggests that such women should be considered at a higher risk of failure of metformin monotherapy.

**Keywords:** Gestational Diabetes, Metformin, Insulin, Treatment Outcome, Blood Glucose

## Introduction

The global prevalence of gestational diabetes mellitus (GDM) has experienced a discernible increased in recent decades, primarily due to the elevated maternal age and insulin resistance induced by obesity.<sup>1</sup> Current estimates suggest that GDM affects more than 10% of pregnancies, contingent upon the diagnostic criteria employed and the demographic under investigation.<sup>2</sup> Notably, the HAPO research revealed a significant association between heightened maternal glucose levels and an elevated risk of macrosomia, shoulder dystocia or birth injury, and neonatal hypoglycaemia.<sup>3</sup>

Maintaining optimal glycaemic control plays a pivotal role in mitigating the risk of obstetrical complications.<sup>4</sup> When lifestyle interventions, encompassing nutritional adjustments and physical activity, prove inadequate in achieving desired glucose levels, pharmacological intervention becomes necessary. Historically, insulin has been the primary therapeutic option due to its established safety and efficacy. Nevertheless, oral hypoglycaemic agents, notably metformin, have emerged as reliable alternatives for blood glucose management, offering a safe and cost-effective option.<sup>1</sup> Insulin remains the conventional choice for treating gestational diabetes mellitus (GDM), particularly if maternal glucose levels persistently remain elevated despite adherence to medical nutrition therapy.<sup>5,6</sup>

Notwithstanding the myriad advantages, up to 46% of women do not attain adequate glycemic control solely through metformin, necessitating the adjunctive use of insulin. In the cohort utilizing metformin, a notable proportion (23.4%) required supplemental insulin. Furthermore, this subgroup exhibited a statistically significant lower weight gain in comparison to those undergoing insulin mono-therapy (p<0.001).<sup>7</sup>

The rationale of this study is that partial local data are accessible regarding the frequency of pregnant women who shifted from metformin monotherapy to insulin plus metformin mixture therapy for the treatment of gestational diabetes and the factors predisposing to metformin poor response; therefore, we designed this study. Determining the exact burden of this group will allow us to emphasise its importance, which should not be

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SI SN FF SB - Conception, Design  
SS SM - Acquisition, Analysis,  
Interpretation  
SI FF SB - Drafting  
SN SS SM - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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### Institutional Review Board

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ignored, and risk factors should be determined for our local population. With an early diagnosis of metformin-poor response in patients, their significant maternal and foetal morbidity can be controlled.

The objectives of this study were to assess the frequency of patients transitioning from metformin monotherapy to a combined regimen of insulin and metformin during the second or third trimesters of pregnancy for the management of gestational diabetes and to investigate the factors contributing to a suboptimal response to metformin in the treatment of gestational diabetes mellitus.

## Materials And Methods

The sample size for this study was determined using the WHO sample size calculator with the following parameters: an anticipated prevalence of metformin-poor response in gestational diabetes patients (P) set at 22.95% (as reported in reference 8), a confidence level of 95%, and an absolute precision of 5%. Utilising the formula  $n = z^2 \cdot p(1-p) / d^2$ , the calculated sample size was 246. Patients were selected through non-probability consecutive sampling.

All women aged 20–35 years who received metformin monotherapy for the treatment of gestational diabetes in the second or third trimesters of pregnancy were included in this report.

Patients with insulin-dependent diabetes before pregnancy, renal disease (indicated by elevated serum creatinine), rheumatic disease (on history), history of thromboembolic disease, abnormal placenta, eclampsia, multiple pregnancies, miscarriage, and IUGR (on history and clinical examination) were excluded.

Following approval from the Ethical Review Board to conduct this study, individuals meeting the operational definitions and inclusion criteria were recruited after obtaining informed consent. The study included all pregnant women diagnosed with gestational diabetes mellitus (GDM) who were undergoing metformin as the primary pharmacologic therapy. The participants were stratified into two distinct groups: individuals who were exclusively undergoing metformin treatment and those who necessitated supplemental insulin in combination with metformin. A detailed analysis was conducted on the latter subgroup to determine factors contributing to an insufficient response to metformin. The primary investigator undertook the data collection process. Subsequently, all datasets were anonymised with respect to patient and hospital identification, ensuring the confidentiality of the acquired data.

Tailored nutritional advice was provided to all participants based on guidelines documented during the consultation. Additionally, as an adjunctive strategy, patients were encouraged to engage in low- or moderate-intensity physical activity for 30–45 min, three times per week.

The maternal variables analysed were age, parity, pre-gestational BMI, diagnostic gestational age (GA), preeclampsia, and pregnancy-induced hypertension. Patients were followed from the diagnosis/enrollment until delivery in the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. Any patient who met the operational definition of a metformin-poor responder was noted.

Data were analysed using SPSS version 23.0. Numerical variables, including age, gestational age at the diagnosis of gestational diabetes mellitus (GDM), fasting glucose level on the initial oral glucose tolerance test (1st OGTT), and body mass index (BMI), were summarised and presented as the mean  $\pm$  standard deviation.

Parity was assessed by calculating the frequency. Categorical variables, including educational status, socioeconomic status, family history of diabetes, gestational diabetes mellitus (GDM) in a previous pregnancy, hypertensive disorders of pregnancy (pregnancy-induced hypertension, preeclampsia, and eclampsia), poor response to metformin, and factors predisposing to poor metformin response (older age  $\geq 30$  years, early onset of GDM with gestational age  $\leq 15$  weeks, and obesity), were depicted using frequency and percentage. The frequency of predisposing factors of poor metformin response (older age  $\geq 30$  years, early onset of GDM; gestational age  $\leq 15$  weeks, and obesity) was compared between women with and without poor metformin response, and the chi-square test or Fisher's exact test was applied, with a p-value  $\leq 0.05$  considered significant. The data were stratified based on fasting glucose levels during the initial oral glucose tolerance test (OGTT), parity, family history of diabetes, gestational diabetes mellitus (GDM) in previous pregnancies, socioeconomic status, educational attainment, and hypertensive disorders of pregnancy, to account for potential confounding factors. Post-stratification was followed by the application of either the chi-square test or Fisher's exact test, and statistical significance was set at a p-value of  $\leq 0.05$ .

## Results

The women enrolled in the study were aged 20–35 years, with a mean age of  $26.6 \pm 4.6$  years. The majority ( $n=175$ , 71.1%) of the women were aged  $< 30$  years. The parity of the women ranged from 1 to 4, with a mean of  $2.4 \pm 1.0$ . There were 64 (26.0%) primiparas and 182 (74.0%) multiparas. Fasting blood sugar levels at the 1<sup>st</sup> OGTT ranged from 92 to 125 mg/dL with a mean of  $107.8 \pm 9.7$  mg/dL. The BMI of these women ranged from  $20.2 \text{ Kg/m}^2$  to  $33.9 \text{ Kg/m}^2$  with a mean of  $26.8 \pm 4.5 \text{ Kg/m}^2$ . 107 (43.5%) women were obese ( $\text{BMI} \geq 30.0 \text{ Kg/m}^2$ ). family history of diabetes was positive in 115 (46.7%) women, whereas 69 (28.0%) women had a history of GDM in a previous pregnancy. Hypertensive disorders of pregnancy were diagnosed in 47 (19.1%) women. 128 (52.0%) women belonged to lower socioeconomic classes, whereas 95 (38.6%) women had primary or below education, as shown in Table-1.

A sub-optimal response to metformin therapy was observed in 45 (18.3%) women diagnosed with gestational diabetes mellitus (GDM), as detailed in Table-2. Upon comparison, no statistically significant difference was identified in the frequency of poor metformin response across diverse subgroups of women with GDM, stratified based on fasting glucose levels during the first oral glucose tolerance test (1st OGTT) ( $p=0.968$ ), parity ( $p=0.912$ ), family history of diabetes ( $p=0.990$ ), GDM in previous pregnancy ( $p=0.890$ ), socioeconomic status ( $p=0.891$ ), educational status ( $p=0.833$ ), and hypertensive disorders of pregnancy ( $p=0.866$ ), as shown in Table 3.

When Compared, the frequency of older ( $\geq 30$  years) maternal age (53.3% vs. 23.4%;  $p\text{-value} < 0.001$ ), early onset (gestational age  $\leq 15$  weeks) of GDM (77.8% vs. 46.8%;  $p\text{-value} < 0.001$ ), and obesity (62.2% vs. 39.3%;  $p\text{-value} = 0.005$ ) was substantially greater among women with poor response to metformin therapy requiring supplemental insulin, as shown in Table-4.

**Table-1: Demographic Features of Study Cohort**

Characteristics	Participants (n=246)
<b>Age (years)</b>	26.6±4.6
• <30 years	175 (71.1%)
• ≥30 years	71 (28.9%)
<b>Parity</b>	2.4±1.0
• Primiparas	64 (26.0%)
• Multiparas	182 (74.0%)
<b>Gestational Age (weeks)</b>	14.8±3.8
• ≤15 weeks	129 (52.4%)
• >15 weeks	117 (47.6%)
<b>FBG on 1st OGTT (mg/dl)</b>	107.8±9.7
• <110 mg/dl	136 (55.3%)
• ≥110 mg/dl	110 (44.7%)
<b>BMI (Kg/m<sup>2</sup>)</b>	26.8±4.5
• Non-Obese (<30.0 Kg/m <sup>2</sup> )	139 (56.5%)
• Obese (≥30.0 Kg/m <sup>2</sup> )	107 (43.5%)
<b>Family History of DM</b>	
• Yes	115 (46.7%)
• No	131 (53.3%)
<b>GDM in Previous Pregnancy</b>	
• Yes	69 (28.0%)
• No	177 (72.0%)
<b>Hypertensive Disorder of Pregnancy</b>	
• Yes	47 (19.1%)
• No	199 (80.9%)
<b>Socioeconomic Status</b>	
• Lower Class	128 (52.0%)
• Middle Class	118 (48.0%)
<b>Educational Status</b>	
• Primary or Below	95 (38.6%)
• Matric or Inter	79 (32.1%)
• Bachelor's or Above	72 (29.3%)

**Table 1: Frequency of Poor Metformin Response among GDM Patients**

Poor Metformin Response	Frequency (n)	Percent (%)
Yes	45	18.3 %
No	201	81.7 %
<b>Total</b>	<b>246</b>	<b>100.0 %</b>

**Table-3: Social stratification of Poor Metformin Response across Various Subgroups of Women with GDM**

Subgroups	n	Poor Metformin Response n (%)	P-value
<b>Parity</b>			
• Primiparas	64	12 (18.8%)	0.912
• Multiparas	182	33 (18.1%)	
<b>FBG on 1<sup>st</sup> OGTT</b>			
• <110 mg/dl	136	25 (18.4%)	0.968
• ≥110 mg/dl	110	20 (18.2%)	
<b>Family History of DM</b>			
• Yes	115	21 (18.3%)	0.990
• No	131	24 (18.3%)	
<b>GDM in Previous Pregnancy</b>			
• Yes	69	13 (18.8%)	0.890
• No	177	32 (18.1%)	
<b>Hypertensive Pregnancy</b>			
• Yes	47	9 (19.1%)	0.866
• No	199	36 (18.1%)	
<b>Socioeconomic Status</b>			
• Lower Class	128	23 (18.0%)	0.891
• Middle Class	118	22 (18.6%)	
<b>Educational Status</b>			
• Primary or Below	95	19 (20.0%)	0.833
• Matric or Inter	79	13 (16.5%)	
• Bachelor's or Above	72	13 (18.1%)	

**Table 2: Contrast of Predisposing Factors involving Women with versus without Poor Response to Metformin**

Predisposing Factors	n	Poor Metformin Response		P-value
		Yes (n=45)	No (n=201)	
<b>Age</b>				
• <30 years	175	21 (46.7%)	154 (76.6%)	<0.001*
• ≥30 years	71	24 (53.3%)	47 (23.4%)	
<b>Gestational Age at Onset</b>				
• ≤15 weeks	129	35 (77.8%)	94 (46.8%)	<0.001*
• >15 weeks	117	10 (22.2%)	107 (53.2%)	
<b>BMI</b>				
• Non-Obese (<30.0Kg/m <sup>2</sup> )	139	17 (37.8%)	122 (60.7%)	0.005*
• Obese (≥30.0Kg/m <sup>2</sup> )	107	28 (62.2%)	79 (39.3%)	

Chi-square test, \* noticed deviation was statistically significant.

## Discussion

Gestational diabetes mellitus (GDM) has historically been linked to adverse obstetric and neonatal outcomes, particularly foetal macrosomia.<sup>8,9</sup> Moreover, it is progressively acknowledged as a threat to the development of subsequent maternal and offspring cardiorespiratory diseases.<sup>10</sup> The global prevalence of GDM is increasing, attributed to the increasing prevalence of obesity among women of reproductive age and the advancing maternal age demographic.

Insulin has traditionally been the primary pharmaceutical intervention in the management of women with gestational diabetes mellitus (GDM) due to its efficacy and non-transplacental properties.<sup>11</sup> However, alternative therapeutic approaches involving oral antidiabetic drugs (OADs), including metformin or glyburide, have gained attention in recent years. This shift is motivated by the inherent drawbacks associated with insulin therapy in GDM.<sup>2</sup> Over the past decade, metformin has witnessed increased utilisation as a superior treatment option compared to insulin or glyburide, particularly in terms of mitigating foetal and maternal side effects.<sup>7</sup>

However, there are cases in which metformin shows poor response, and supplemental insulin is required. The timely identification of women at a higher risk of failure of metformin monotherapy can help in appropriate management planning.<sup>12</sup> A few existing studies have reported that older maternal age, early gestational age at onset of GDM, and obesity are associated with poor metformin response and can be used for risk stratification of such cases.<sup>1</sup>

In this study, the mean age of the women with gestational diabetes mellitus was 26.6±4.6 years, and it was observed that 26.0% of women with GDM were primiparous. In a similar study conducted in Gujrat, Pakistan, Kousar et al. reported a mean age of 26.8±3.4 years among pregnant women with GDM and reported a proportion of 28.0% primiparous women among those diagnosed with GDM in Gujrat.<sup>13</sup> Our findings are also in line with those of Riaz et al. (2019), who evaluated pregnant women with GDM presenting at Baqai Institute of Diabetology and Endocrinology Karachi and reported a mean age of 27.0±5.8 years, and 26.0% of women in this study with GDM were primiparous.<sup>14</sup> Wali et al. conducted a parallel investigation at Sheikh Saeed Memorial Hospital in Karachi, reported a mean age of 26.1±4.7 years in women diagnosed with gestational diabetes mellitus.<sup>15</sup> In an analysis involving Indian women with GDM, Chebroolu et al. (2020) reported a comparable mean age of 26.2±4.5 years, aligning with the findings of the current study.<sup>16</sup>

We observed that the mean BMI of women with GDM was 26.8±4.5 Kg/m<sup>2</sup> and 43.5% of women were obese. Our observation is in line with that of Rafiq et al., who observed a similar mean BMI of 26.7±6.2 Kg/m<sup>2</sup> among such women presenting at the Combined Military Hospital, Sialkot.<sup>17</sup> In a similar study conducted in Gujrat, Pakistan, Kousar et al. observed a comparable frequency of obesity among pregnant women with GDM and reported it to be 44.4%.<sup>13</sup> Bahl et al. reported it to be 41.9% among Indian pregnant women with gestational diabetes mellitus.<sup>18</sup> In our study, a family history of diabetes was observed in 46.7% of women with GDM. A comparable frequency of 43.0% has been reported by Khattak et al. at PNS Shifa Hospital, Karachi.<sup>19</sup> Chanda et al. reported rates to be 38.0% and 50.0%, respectively, among Indian pregnant women with gestational diabetes mellitus.<sup>20</sup>

In the present study, 28.0% of women with GDM had a history of GDM in a previous pregnancy. Our observation is in line with that of Wali et al., who conducted a similar study at Sheikh Saeed Memorial Hospital, Karachi, and observed that 27.3% of women with gestational diabetes mellitus had a history of GDM in a previous pregnancy.<sup>15</sup>

We observed that 18.3% of women with GDM had poor responses to metformin therapy and required supplemental insulin therapy. When compared, the frequency of older (≥30 years) maternal age (53.3% vs. 23.4%; p-value<0.001), early onset (gestational age ≤15 weeks) of GDM (77.8% vs. 46.8%; p-value<0.001), and obesity (62.2% vs. 39.3%; p-value=0.005) was significantly higher among women with poor responses to metformin therapy requiring supplemental insulin. Our observation is in line with that of Silva et al. (2022), who conducted a similar study on 2891 Portuguese women with GDM receiving metformin.<sup>21</sup> The author observed poor responses to metformin therapy among 23.7% of women. The author also reported that the frequency of maternal age ≥30 years (49.8% vs. 21.2%; p-value<0.001), early gestational age at onset of GDM (68.1% vs. 46.5%; p-value<0.001), and obesity (51.3% vs. 37.7%; p-value<0.001) was significantly higher among women with failure of metformin monotherapy, in line with the present study.<sup>21</sup>

Souza et al. (2019) conducted a similar study on 475 pregnant women with GDM in Brazil. The failure rate of metformin monotherapy was 22.9% in their series. The authors reported a significantly higher frequency of obesity among women with poor responses to metformin therapy (55.04% vs. 37.97%; p-value=0.02). They also reported a significantly higher mean age (34.4±6.3 vs. 31.5±6.9 years; p =0.020) and a significantly lower gestational age (26.0±5.8 vs. 28.8±5.8 weeks; p <0.001) among such women.<sup>1</sup>

In the present study, we observed that a significant proportion of pregnant women with GDM showed poor responses to metformin. We also observed that the frequency of older maternal age, early onset of GDM, and obesity was significantly higher in women with poor responses to metformin. In light of this evidence, women with such conditions should be considered at a higher risk of failure of metformin monotherapy.

A limitation of our study was that we did not compare perinatal outcomes in women with versus without poor metformin response, which could have helped to develop a management plan for such women.

## Conclusions

In the present study, we observed that a substantial proportion of pregnant women with GDM showed poor responses to metformin. The frequency of older maternal age, early-onset GDM, and obesity was significantly higher among such cases, indicating that such women should be considered at a higher risk of failure of metformin monotherapy. Therefore, timely identification and management through supplemental insulin may enhance the outcomes of such cases in the future.

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