Original Article

Comparison of Frequency of Macrosomia among Gravid Females with Gestational Diabetes Treated with Metformin *vs.* Insulin

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ABSTRACT

Background: Foetal macrosomia is a predominant complication of gestational diabetes mellitus (GDM), affecting approximately 14 to 20% of wide range of these pregnancies and significantly increasing perinatal morbidity. Insulin was traditionally used but oral metformin has emerged as a promising alternative that prevents weight promoting side effects with good glycaemic control. Therefore, this study compared the frequency of macrosomia among females with GDM treated with metformin versus insulin to guide evidence-based clinical management.

Methods: This randomized controlled trial was conducted in the outpatient department of Gynaecology and Obstetrics, Government Teaching Hospital Shahdara. A total of 180 gravid females were initially enrolled; 20 were excluded for not meeting criteria, leaving a final analytical sample of 160. The participants were randomized via a lottery method with allocation concealment. Group I received 500 mg of oral metformin daily, while Group II was treated with subcutaneous insulin (0.5 units/kg/day in divided doses). Blood sugar levels were monitored weekly, and neonatal birth weight was recorded within 30 minutes post-delivery. SPSS version 25 was used to analyse data. Results were compared between the two groups.

Results: Amongst initially enrolled 180 participants, 160 were analysed (80 in Group I and 80 in Group II). The mean age was 29.04 ± 5.55 years, mean BMI was 27.41 ± 2.70 kg/m², and mean gestational age at delivery was 37.79 ± 1.54 weeks. Vaginal delivery occurred in 95 (59.4%) participants, while 65 (40.6%) underwent caesarean sections. The frequency of macrosomia was significantly lower in Group I, observed in 11 (13.8%) neonates, compared to 21 (26.3%) neonates in Group II. This represented a statistically significant reduction in the risk of macrosomia for Group I (relative risk = 0.52, 95% CI: 0.27 to 0.99, p = 0.048).

Conclusion: Metformin therapy in women with gestational diabetes mellitus resulted in a significantly lower incidence of macrosomia compared to insulin. These findings suggest that metformin is more effective than insulin specifically for reducing the risk of foetal macrosomia in the management of gestational diabetes.

Keywords: Gestational diabetes mellitus, macrosomia, metformin, insulin, gravid females.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a widespread medical disorder affecting approximately 14 to 20% of pregnancies worldwide, necessitating adequate glycemic control to prevent adverse maternal and fetal complications.[1] While lifestyle modification remains the first-line therapy, pharmacological intervention is required when glycemic targets are not achieved. Insulin has traditionally been the standard treatment; however, it is associated with disadvantages such as multiple daily injections, hypoglycemia risk, and excessive maternal weight gain.[2] Conversely, metformin has emerged as an effective, orally administered alternative that improves insulin sensitivity and reduces hepatic glucose production.[3]

Recent meta-analyses and systematic reviews comparing these therapies report mixed findings on their impact on fetal overgrowth. While some evidence suggests metformin significantly reduces the frequency of macrosomia compared to insulin, other studies report no significant difference.[4] For example, one previous study reported a macrosomia frequency of 5.2% in neonates of insulin-treated mothers compared to 2.8% in the metformin-treated group.[5] Despite these findings, limited local published data exists comparing the effectiveness of these drugs in reducing macrosomia within the regional population.[6] Because macrosomia is linked to severe complications—including prolonged labor, shoulder dystocia, and perinatal asphyxia—determining the optimal pharmacological strategy is crucial.[7, 8] This study will contribute novel, targeted evidence to local literature to help optimize GDM management protocols. The aim of this

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study was to compare the frequency of macrosomia among gravid females with gestational diabetes mellitus treated with metformin versus insulin therapy.

PATIENTS AND METHODS

This randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Government Teaching Hospital Shahdara, Lahore, from 1st March 2023 to 31st August 2023, after approval from the Institutional Review Committee, Ref No: 1032/Gyne/IRB/2023. Amongst 160 enrolled patients, 80 patients were placed each group. The calculated sample size was using 80% power of test and a 5% level of significance, taking the expected frequency of macrosomia among females with gestational diabetes treated with insulin and metformin as 13.4% and 2.8%, respectively.

Study Participants were pregnant women with age of 18–40 years were recruited using a non-probability consecutive sampling technique. Patients were diagnosed with gestational diabetes mellitus (GDM) based on the operational definition of a fasting blood glucose level > 126 mg/dL or an HbA1c > 6.5% at any gestational age.[9] To control for confounding variables by exclusion, patients with multiple pregnancies, known pre-gestational diabetes mellitus, hypertension (systolic blood pressure > 140 mmHg recorded on two occasions 12 hours apart), and renal impairment (serum creatinine > 1.2 mg/dL) were excluded from the study. Written informed consent was obtained from all participants.

Randomization and Allocation of patients was done into two equal groups. To adhere to CONSORT guidelines and minimize selection bias.[10] The generation of random sequence was done by using a simple lottery method by an independent researcher who was not involved in clinical care. To make sure of allocation concealment the use of sequentially numbered, opaque, sealed envelopes, and the allocation was implemented independently**.** Interventions and compliance baseline confounding factors—such as maternal BMI, parity, severity of GDM, and gestational age at diagnosis—were recorded at enrollment. All patients received standard counseling on dietary and lifestyle modifications.

Group I (Metformin) Patients received an initial dose of 500 mg of metformin once daily. Random blood glucose levels were monitored daily for one week. If blood glucose levels remained uncontrolled, the dose was increased to 500 mg twice daily, and subsequently to a maximum of 1000 mg twice daily if required, with follow-ups scheduled every two weeks until delivery. Group II (Insulin): Insulin therapy was initiated by the attending obstetrician in the outpatient department when blood glucose levels exceeded target cutoffs despite lifestyle interventions. Following standard established guidelines insulin was initiated at a dose of 0.5 units/kg of body weight per day in divided doses. The morning dose comprised of NPH insulin two thirds and one-third of regular insulin, whereas the evening dose consisted of half NPH insulin and half regular insulin with an additional one-third regular insulin dose. Doses were adjusted weekly to maintain fasting blood glucose levels (FBS) strictly less than 110 mg/dL.

Other recorded study parameters and neonatal outcomes included maternal age, BMI, parity, gestational age at delivery, mode of delivery, and neonatal gender while neonatal weight was the main outcome. All data were recorded on a predesigned proforma.

Statistical Analysis was done using SPSS version 26. Quantitative variables, including patient age, gestational age, and neonatal birth weight, were presented as mean ± SD. Qualitative variables, including macrosomia, mode of delivery, and neonatal gender, were presented as frequencies and percentages. The Chi-square test was applied to compare the frequency of macrosomia between both groups. To strengthen the statistical analysis, effect estimates were calculated as Relative Risk (RR) with 95% Confidence Intervals (CI). To address residual confounding, the data were stratified for gestational age at delivery, neonatal gender, parity, mode of delivery, and maternal BMI, followed by post-stratification Chi-square tests. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Participants of the study were total 160 patients. Baseline demographic and clinical characteristics were statistically comparable amongst the metformin (Group I) & insulin (Group II) groups ($p > 0.05$ for all variables). Maternal BMI was operationally categorized according to standard criteria as normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥ 30.0 kg/m²). A comprehensive breakdown of these basic characteristics is provided in Table 1.

The primary outcome showed a significantly lower frequency of macrosomia in metformin group compared to the insulin group (13.8% vs. 26.3%, $p = 0.048$; Relative Risk [RR] 0.52, 95% CI 0.28–0.98). To address important confounding variables, a multivariable logistic regression analysis was performed controlling for maternal BMI, parity, and gestational age. In this adjusted analysis, metformin therapy remained significantly associated with a reduced risk of macrosomia (adjusted Odds Ratio [aOR] 0.45, 95% CI 0.22–0.94, $p = 0.034$).

Subgroup analyses across age, body mass index (BMI) categories, parity, gestational age at delivery, mode of delivery, neonatal gender, as well as GDM severity and duration consistently demonstrated lower macrosomia

rates in the metformin group. While the differences within individual subgroups did not reach independent statistical significance (p > 0.05), the overall trend favored metformin (Table 2). Multivariable logistic regression controlling for maternal BMI, parity, and gestational age yielded an adjusted Odds Ratio (aOR) of 0.45 (95% CI 0.22–0.94, p = 0.034) for overall macrosomia.

Table 1: Demographic characteristics of study groups

Characteristics	Group I (Metformin arm)	Group II (Insulin arm)	p-value*
Age ([mean ± SD] years)	28.83 ± 4.82	29.26 ± 6.23	0.620
BMI (mean ± SD)	27.36 ± 2.98	27.46 ± 2.40	0.814
Parity (mean ± SD)	2.71 ± 1.08	2.81 ± 1.16	0.607
Gestational age at Delivery (weeks)	37.86 ± 1.62	37.71 ± 1.47	0.874
Mode of delivery			
Vaginal	72.5%	67.5%	0.490
Cesarean	27.5%	32.5%	
Neonatal gender			
Boy	60%	45%	0.057
Girl	40%	55%	

*The p-values calculated using Independent samples t-test for continuous variables and Chi-square test for categorical variables.

Table 2: Summary of macrosomia comparison across subgroups

Characteristics	Group I (Metformin arm)	Group II (Insulin arm) (N=80)	Unadjusted RR (95% CI)	p-value
Overall Macrosomia	11/80 (13.8%)	21/80 (26.3%)	0.52 (0.28–0.98)*	0.048
Age (years)				
18–29 years	7/48 (14.6%)	10/43 (23.3%)	0.63 (0.26–1.49)	0.289
30–40 years	4/32 (12.5%)	11/37 (29.7%)	0.42 (0.15–1.18)	0.084
BMI				
Normal Weight	3/11 (27.3%)	5/8 (62.5%)	0.44 (0.15–1.28)	0.125
Overweight	4/49 (8.2%)	9/57 (15.8%)	0.52 (0.17–1.57)	0.233
Obese	4/20 (20.0%)	7/15 (46.7%)	0.43 (0.15–1.20)	0.144
Parity				
≤ 3	8/58 (13.8%)	12/54 (22.2%)	0.62 (0.28–1.39)	0.244
> 3	3/22 (13.6%)	9/26 (34.6%)	0.39 (0.12–1.26)	0.094
Gestational Age at Delivery				
≤ 37 weeks	6/41 (14.6%)	11/40 (27.5%)	0.53 (0.22–1.28)	0.155
> 37 weeks	5/39 (12.8%)	10/40 (25.0%)	0.51 (0.19–1.36)	0.168
Mode of Delivery				
Vaginal Delivery	6/44 (13.6%)	12/51 (23.5%)	0.58 (0.24–1.40)	0.220
Cesarean Section	5/36 (13.9%)	9/29 (31.0%)	0.45 (0.17–1.18)	0.095
Neonatal Gender				
Boy	5/48 (10.4%)	9/36 (25.0%)	0.42 (0.15–1.14)	0.076
Girl	6/32 (18.8%)	12/44 (27.3%)	0.69 (0.29–1.63)	0.388
Severity of GDM				
Baseline Fasting Glucose ≥ 110	6/40 (15.0%)	12/40 (30.0%)	0.50 (0.21–1.19)	0.108
Duration of GDM				
Diagnosed < 24 weeks	5/35 (14.3%)	10/35 (28.6%)	0.50 (0.19–1.31)	0.138

Abbreviations: RR = Relative Risk; CI = Confidence Interval;
*The p-values for unadjusted comparisons were calculated using the Chi-square test (or Fisher's Exact test where expected cell counts were < 5).

DISCUSSION

Gestational diabetes mellitus (GDM) is a prevalent condition associated with significant maternal and neonatal complications. Traditionally, insulin has been the primary treatment; however, metformin is gaining popularity as a viable, less invasive alternative therapy.[11] Aim of this study is to compare the frequency of macrosomia between patients getting metformin (Group I) and those receiving insulin (Group II) to determine which approach is more effective specifically in minimizing the risk of fetal macrosomia.

The primary outcome of this study demonstrated a significantly lower frequency of macrosomia in the metformin group (13.8%) compared with the insulin group (26.3%) (p = 0.048). These findings go in line with recent systematic reviews and meta-analyses demonstrating metformin's effectiveness in reducing the frequency of macrosomia compared to insulin.[12] Biologically, metformin's protective role against macrosomia can be attributed to its insulin-sensitizing properties; it reduces hepatic gluconeogenesis and enhances peripheral glucose uptake. Because metformin improves maternal insulin resistance without promoting the excessive maternal

weight gain often associated with exogenous insulin therapy, it may limit the transplacental transfer of excess glucose and free fatty acids, thereby attenuating fetal hyperinsulinemia and subsequent overgrowth.

While our findings support the efficacy of metformin, some previous studies did not report significant differences between treatment groups.[13,14] Rather than broad regional variations, these discrepancies are likely driven by critical differences in study design, sample size, variations in baseline maternal BMI, differing glycemic control targets, and heterogeneous treatment protocols (such as varying thresholds for initiating insulin or combination therapies). Subgroup analysis in the present study also demonstrated a consistently higher frequency of macrosomia in the insulin-treated group across all categories, although these differences did not achieve independent statistical significance.

From a clinical perspective, these findings have significant practical implications. Because macrosomia directly contributes to complications like shoulder dystocia, birth trauma, and prolonged labor, demonstrating that metformin safely mitigates this specific risk supports its utility as an effective, oral first-line pharmacological therapy in routine clinical practice when lifestyle interventions fail.

The randomized controlled design is the main strength of this study and its targeted assessment of macrosomia. However, the study's strengths must not be overstated. While the sample size was adequate to find differences in the primary outcome, it was likely underpowered for subgroup analyses, warranting cautious interpretation of those specific trends. Several methodological limitations must also be acknowledged. The absence of blinding and potential residual confounding from variables such as baseline glycemic control and variations in maternal BMI may affect the internal validity of the findings. Furthermore, the single-center design restricts the external validity and applicability of the results. Finally, the study was narrow in scope, limiting its ability to evaluate other clinically important maternal and neonatal outcomes.

Future studies should focus on multicenter randomized controlled trials with sufficient power and long-term maternal and neonatal follow-up to definitively validate these findings and establish comprehensive guidelines regarding the use of metformin in GDM management.

CONCLUSION

In this study, metformin was associated with a lower incidence of macrosomia compared with insulin in women with gestational diabetes mellitus. Further large-scale, multicentre trials are needed to confirm these findings and to comprehensively evaluate overall safety and broader neonatal outcomes.

Author Contributions

UA: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, and final approval.
TR: Conception and design, analysis and interpretation of data.
IA: Analysis and interpretation of data, drafting the article.
BM: Acquisition of data, conception and design, analysis and interpretation.
NK: Conception and design, analysis and interpretation of data.
AWK: Conception and design, analysis and interpretation of data.

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