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Original Article

Insulin plus metformin for gestational diabetes mellitus: impacts on blood glucose, coagulation function, and pregnancy outcomes

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Abstract: Objective: This retrospective study focused on the impacts of insulin plus metformin (MET) on blood glucose (BG), coagulation function, and pregnancy outcomes in patients with gestational diabetes mellitus (GDM). Methods: The subjects were 129 GDM patients visiting The First Affiliated Hospital of Air Force Medical University, including 60 patients receiving insulin aspart (IA; control group) and 69 cases given MET+insulin aspart (observation group). General information and treatment outcomes were compared. Pre- and post-treatment BG (fasting plasma glucose [FPG], 2-hour postprandial plasma glucose [2hPG], glycosylated hemoglobin [HbA1c]), islet function (fasting insulin [FINS], Homeostasis Model Assessment-Insulin Resistance Index (HOMA-IR), HOMA-Beta Cell Function Index [HOMA-β]), coagulation function (activated partial thromboplastin time [APTT], prothrombin time [PT], thrombin time [TT]), adverse drug reactions, pregnancy outcomes, and fetal and neonatal conditions were compared between the two groups. Efficacy determinants were analyzed using univariate and multivariate methods. Results: Compared to controls, MET+IA-treated patients showed superior curative effects, lower post-treatment BG indexes, FINS, and HOMA-IR, higher HOMA-β and various coagulation function parameters, as well as reduced rates of overall adverse pregnancy outcomes, total neonatal adverse events, and macrosomia. The groups were comparable in the adverse drug reaction rate. An abortion history increased the risk of ineffective treatment. Conclusion: Insulin+MET benefits BG control, coagulation function, and pregnancy outcomes in GDM patients.

Keywords: Insulin, metformin, gestational diabetes, blood glucose, coagulation function, pregnancy outcome

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance of varying severity in pregnant women, presents mainly as hyperglycemia without pre-existing diabetes [1]. The disease, a common complication, is diagnosed in the second or third trimester and is associated with an increased risk of adverse pregnancy outcomes such as premature labor (PML), polyhydramnios, and pregnancy-induced hypertension (PIH) [2, 3]. Due to increased maternal age, elevated obesity rates, and changes in diagnostic criteria, GDM has shown a significant upward trend in incidence [4]. Statistically, GDM affects up to 70% of pregnancies, costing an alarmingly $1.6 billion in the United States alone [5]. Besides, the disease may also increase overall mortality and cardiovascular disease-associated death, posing a certain threat to patients' long-term health [6]. If not treated in a timely manner, GDM can exert short- or long-term adverse effects on maternal and infant outcomes [7]. At present, GDM is mainly managed through hyperglycemia control, achieved via lifestyle interventions (e.g., diet adjustment, physical exercise), or hypoglycemic drugs in cases where the above interventions are difficult to adhere to or the effect is unsatisfactory [8]. Insulin is the preferred hypoglycemic agent for GDM, helping effectively control blood glucose (BG) levels and ameliorating maternal and infant outcomes [9].

Despite improving perinatal outcomes, insulin may increase the rates of maternal/neonatal hypoglycemia, cesarean section (CS), and excessive weight gains [10]. Metformin (MET) is a promising first-line alternative that reduces BG and improves insulin sensitivity by promot-

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ing glucose uptake in peripheral tissues and inhibiting hepatic gluconeogenesis [11]. In the report of Bashir et al. [12], MET intervention in GDM was superior to diet control in reducing neonatal hypoglycemia and macrosomia risks; however, it may increase the risk of PML, CS, and neonatal jaundice. Another study reported superiority of MET over insulin in glycemic control and in reducing risks of PML, respiratory distress, and neonatal hypoglycemia [13]. To optimize GDM management, this study evaluated the combination of insulin and MET to comprehensively evaluate the clinical advantages of this therapeutic regimen, thereby providing new insights into the clinical management of such patients.

Materials and methods

General information

This study included 129 GDM patients who visited The First Affiliated Hospital of Air Force Medical University between June 2022 and June 2025. Among them, 60 patients received insulin aspart (IA) alone (control group), while 69 patients received MET in addition to IA (observation group). The cohorts exhibited clinical comparability, evidenced by balanced distributions in general information ($P>0.05$). This study was approved by the Ethics Committee of The First Affiliated Hospital of Air Force Medical University.

Case selection criteria

Inclusion criteria: meeting GDM diagnostic criteria [14]; singleton pregnancy; failure to achieve glycemic control with diet and exercise; good maternal compliance, stable condition, and regular check-ups; and complete clinical data.

Exclusion criteria: vaginal bleeding or severe abdominal pain; pre-existing diabetes or overt diabetes diagnosed during pregnancy; severe cardiac, pulmonary, renal, or endocrine diseases; drug allergies; hereditary diseases; acute infections or abnormal newborn screening; history of medication affecting insulin secretion or sensitivity; or maternal smoking, alcohol consumption, or drug abuse history.

Specific GDM diagnostic criteria: An oral glucose tolerance test (OGTT) was conducted on all patients at 24-28 weeks of pregnancy. 75 g of glucose was administered orally on an empty stomach, with BG during a fasting status and at 1 h and 2 h post-administration monitored. GDM was diagnosed if fasting glucose was ≥5.1 mmol/L, 1-hour glucose ≥10.0 mmol/L, or 2-hour glucose ≥8.5 mmol/L.

Treatment methods

The control group received insulin aspart 50 injection subcutaneously at 0.2-0.3 U/kg before dinner once daily, with dose adjustments based on blood glucose monitoring, continued until delivery.

Beyond the above-mentioned IA therapy, MET (0.5 g, per os, twice daily) was further used in the observation group. The drug was not discontinued until delivery.

Detection indicators

Efficacy. Evaluation criteria: The treatment is deemed markedly effective if the patient's BG level returns to the normal range; Effective treatment means the approximation of BG to the normal range. If the patient's BG level changes non-significantly or worsens, it is judged as ineffective. Total effective rate = (number of markedly effective + number of effective)/total cases × 100%.

BG metabolism. Fasting venous blood draws (5 mL per sample) were collected from all participants before and after treatment. Following serum separation via centrifugation, fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (2hPG), and glycosylated hemoglobin (HbA1c) were measured with a BG monitor.

Islet function. With an automatic biochemical analyzer, we measured patients' fasting insulin (FINS) levels before and after treatment. Additionally, Homeostasis Model Assessment-Insulin Resistance Index (HOMA-IR) and Beta-Cell Function Index (HOMA-β) were evaluated.

Coagulation function. Using an automatic coagulometer, we recorded pre- and post-treatment activated partial thromboplastin time (APTT), prothrombin time (PT), and thrombin time (TT).

Adverse drug reactions (ADRs). We counted the number of cases of maternal hypoglycemia and

Table 1. Comparison of general information between the two groups

Data	Control group (n=60)	Observation group (n=69)	χ^2/t/Z	P
Age (years)	32.43±3.92	32.67±5.08	0.297	0.767
Gestational age (weeks)	39.00 (38.00, 39.00)	39.00 (38.00, 39.00)	-0.922	0.357
Prenatal BMI	27.41±3.37	27.40±3.01	0.018	0.986
Parity			0.616	0.433
Primipara	43 (71.67)	45 (65.22)		
Multipara	17 (28.33)	24 (34.78)		
Educational level			0.908	0.341
Senior high school or above	28 (46.67)	38 (55.07)		
Below senior high school	32 (53.33)	31 (44.93)		
History of abortion			0.264	0.607
No	40 (66.67)	43 (62.32)		
Yes	20 (33.33)	26 (37.68)		
Polycystic ovary syndrome			0.278	0.598
No	57 (95.00)	64 (92.75)		
Yes	3 (5.00)	5 (7.25)		

Note: BMI, body mass index.

Table 2. Comparison of curative effects between the two groups

Categories	Control group (n=60)	Observation group (n=69)	χ^2	P
Marked effectiveness	21 (35.00)	30 (43.48)		
Effectiveness	24 (40.00)	33 (47.83)		
Ineffectiveness	15 (25.00)	6 (8.70)		
Overall effectiveness	45 (75.00)	63 (91.30)	6.260	0.012

gastrointestinal reactions, as well as neonatal hypoglycemia, in the two groups, and computed the corresponding percentage for comparative analysis.

Pregnancy outcomes. The perinatal complications, such as PML, polyhydramnios, PIH, and CS, were observed and recorded in all patients.

Fetal and neonatal conditions. We observed and recorded the number of adverse reactions (e.g., macrosomia, hypoglycemia, respiratory distress, jaundice) in all newborns and calculated the corresponding percentage for evaluation.

Statistical analyses

Non-normally distributed data were expressed as median (interquartile range) [M (Q1, Q3)], and between-group differences were evaluated using the Mann-Whitney U test. Normally distributed continuous variables were expressed as mean ± standard deviation (SD); and inter-group comparisons were performed using the independent-samples t-test, while intra-group pre- and post-treatment comparisons were conducted using the paired t-test. Categorical data, expressed as count and percentage (n/%), were compared between groups using χ^2 tests. Data analyses were executed in SPSS version 20.0. Statistical significance was present at a *P*-value below 0.05.

Results

Comparative general data analysis

The observation and control groups showed balanced distributions in age, gestational age, prenatal body mass index (BMI), parity, education level, abortion history, and PCOS (P>0.05; **Table 1**).

Comparative efficacy evaluation

The total number of effective cases was 45 in the control group and 63 in the observation group, indicating superior overall effectiveness in the observation group (P<0.05; **Table 2**).

BG comparison

By detecting BG levels, we found equivalence in baseline FPG, 2hPG, and HbA1c across the

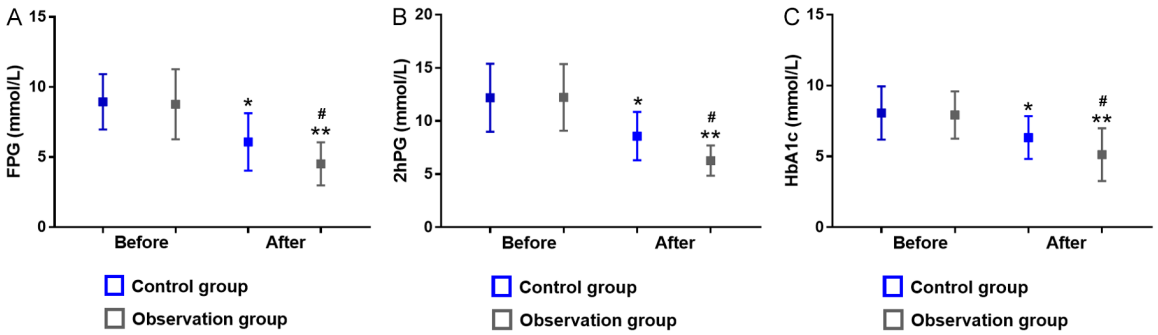

Figure 1. Comparative blood glucose evaluation. A. Pre- and post-treatment FPG assessments. B. Pre- and post-treatment 2hPG measurements. C. Pre- and post-treatment HbA1c assessments. Note: *P<0.05 and **P<0.01 vs. before treatment; #P<0.05 vs. Control. FPG, fasting plasma glucose; 2hPG, 2-hour postprandial plasma glucose; HbA1c, glycosylated hemoglobin.

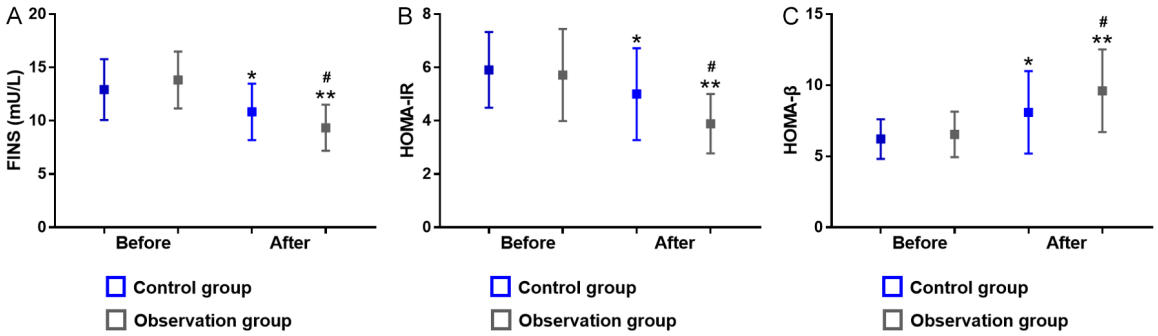

Figure 2. Comparative evaluation of islet function. A. Pre- and post-treatment FINS measurements. B. Pre- and post-treatment HOMA-IR assessments. C. Pre- and post-treatment HOMA-β assessments. Note: *P<0.05, **P<0.01 vs. before treatment; #P<0.05 vs. Control. FINS, fasting insulin; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance Index; HOMA-β, HOMA-Beta Cell Function Index.

groups (P>0.05). The treatment resulted in a significant downward trend in all BG indexes of varying extents in both cohorts (P<0.05), with even lower levels in the observation group (P<0.05; **Figure 1**).

Comparative islet function evaluation

Patients' islet function was evaluated through FINS, HOMA-IR, and HOMA-β measurements (**Figure 2**). The groups were similar in baseline levels (P>0.05). A reduction in FINS and HOMA-IR, along with a rise in HOMA-β, were noted across the groups post-intervention (P<0.05), with the corresponding changing amplitude being more pronounced in the observation group relative to the control group (P<0.05).

Coagulation function comparison

The evaluation of APTT, PT, and TT, indicators reflecting coagulation function, revealed no evident inter-group differences at baseline (P>0.05); all indices of both groups were up-regulated to varying degrees, with higher levels in the observation group when compared to the control group (P<0.05; **Table 3**).

Comparative evaluation of ADRs

This study determined 10 cases of maternal hypoglycemia, 3 of maternal gastrointestinal reactions, and 7 of neonatal hypoglycemia in control patients, with the corresponding case numbers in the observation group being 4, 12, and 5. The study cohorts did not differ significantly in various ADRs (P>0.05; **Table 4**).

Comparative assessment of pregnancy outcomes

Among control patients, 2 experienced PML, 3 had polyhydramnios, 4 developed PIH, and 6 underwent CS, with the corresponding cases in the observation group being 0, 2, 2, and 3 respectively. The between-group comparison

Table 3. Comparison of coagulation function between the two groups

Categories	Control group (n=60)	Observation group (n=69)	t	P
APTT (s)				
Pre-treatment	28.32±2.19	28.41±2.53	0.214	0.831
Post-treatment	29.74±2.75	31.86±2.61	4.488	<0.001
PT (s)				
Pre-treatment	7.78±0.36	7.83±0.43	0.710	0.479
Post-treatment	9.82±1.44	11.31±2.15	4.552	<0.001
TT (s)				
Pre-treatment	15.97±0.51	15.91±0.80	0.499	0.619
Post-treatment	16.14±1.02	17.07±1.48	4.094	<0.001

Note: APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

indicated a lower total incidence of adverse pregnancy outcomes in the observation group (P<0.05). However, each single adverse pregnancy outcome showed no marked inter-group difference (P>0.05; **Table 5**).

Inter-group comparison of fetal and neonatal conditions

We further recorded fetal and neonatal conditions across the groups, noting macrosomia, neonatal hypoglycemia, neonatal respiratory distress, and neonatal jaundice in 5, 4, 5, and 3 cases in the control group, and 0, 2, 3, and 2 cases in the observation group, respectively. The data indicated a lower overall incidence of the above events in the observation group (P<0.05). In addition, a lower macrosomia incidence was found in the observation group compared to the control group (P=0.020); the other individual adverse neonatal outcomes differed insignificantly when compared between the groups (P>0.05; **Table 6**).

Identification of efficacy determinants

Through univariate screening, we identified prenatal BMI, education level, abortion history, PCOS, FINS, HOMA-IR, and therapeutic regimen as significant determinants of curative effects (P<0.05). These significant indexes were subsequently incorporated into the binary Logistic regression model, confirming that an abortion history was an independent factor influencing efficacy (P<0.05), with those having an abortion history facing a 4.306-fold elevated risk of ineffective treatment compared to those without. See **Tables 7**, **8** for details.

Discussion

Like ordinary diabetes, GDM is mainly clinically present with excessive water intake, increased food consumption, and increased urine output [15]. Without prompt and adequate BG control, it may cause ketoacidosis and hypertension. Meanwhile, the resultant uterine metabolic environment abnormalities can adversely affect neonatal outcomes, leading to macrosomia, stillbirth, fetal intellectual abnormality, and abnormal physical development [16]. To improve the maternal and infant outcomes in GDM pregnancies, it is necessary to explore more effective therapies.

This study found enhanced efficacy in GDM patients on insulin+MET therapy. This improvement may be attributed to enhanced insulin sensitivity, increased peripheral glucose uptake, and better glucose utilization in non-insulin-dependent tissues [17, 18]. In the study of Li et al. [19], insulin+MET for GDM patients improved the total effective rate from 68.52% (insulin pump alone) to 84.26%, echoing our results. In the glycemic control comparison, we found that insulin+MET resulted greater reductions in FPG, 2hPG, and HbA1c. This may be due to IA, which inhibits hepatic glyconeogenesis through subcutaneous injection and thus effectively regulates BG levels [20]. MET improves insulin resistance by promoting glycogen and fat synthesis and enhancing insulin-mediated glucose uptake in peripheral tissues [21]. Therefore, the hypoglycemic effect is more significant under the combination of the two. Cui et al. [22] reported that insulin combined with MET can achieve a more powerful reduction in BG levels in GDM pregnancies, consistent with our observations. The insulin-MET combination also had significant clinical advantages in improving islet function, evidenced by marked FINS and HOMA-IR reductions as well as HOMA-β elevation. This may be attributed to the fact that MET can improve the insulin sensitivity of peripheral tissues by decreasing hepatic glucose output [23]. In the study of Zhao et

Table 4. Comparison of adverse drug reactions between the two groups

Category	Control group (n=60)	Observation group (n=69)	χ^2	P
Maternal hypoglycemia	10 (16.67)	4 (5.80)		0.086
Maternal gastrointestinal reactions	3 (5.00)	12 (17.39)		0.051
Neonatal hypoglycemia	7 (11.67)	5 (7.25)	0.743	0.389

Table 5. Comparison of pregnancy outcomes between the two groups

Categories	Control group (n=60)	Observation group (n=69)	χ^2	P
Premature labor	2 (3.33)	0 (0.00)		0.214
Hydroamnious	3 (5.00)	2 (2.90)		0.663
Pregnancy-induced hypertension	4 (6.67)	2 (2.90)		0.416
Caesarean section	6 (10.00)	3 (4.35)		0.302
Total	15 (25.00)	7 (10.14)	5.006	0.025

Table 6. Comparison of fetal and neonatal outcomes between the two groups

Events	Control group (n=60)	Observation group (n=69)	χ^2	P
Macrosomia	5 (8.33)	0 (0.00)		0.020
Neonatal hypoglycemia	4 (6.67)	2 (2.90)		0.416
Neonatal respiratory distress	5 (8.33)	3 (4.35)		0.471
Neonatal jaundice	3 (5.00)	2 (2.90)		0.663
Total	17 (28.33)	7 (10.14)	7.011	0.008

Table 7. Univariate analysis of factors associated with therapeutic efficacy

Items	Ineffective group (n=21)	Effective group (n=108)	χ^2	P
Age (years)			0.850	0.357
<32 (n=61)	8 (38.10)	53 (49.07)		
≥32 (n=68)	13 (61.90)	55 (50.93)		
Gestational age (weeks)			1.895	0.169
<39 (n=39)	9 (42.86)	30 (27.78)		
≥39 (n=90)	12 (57.14)	78 (72.22)		
Prenatal BMI			4.442	0.035
<27.58 (n=64)	6 (28.57)	58 (53.70)		
≥27.58 (n=65)	15 (71.43)	50 (46.30)		
Parity			2.901	0.089
Primiparas (n=88)	11 (52.38)	77 (71.30)		
Multiparas (n=41)	10 (47.62)	31 (28.70)		
Educational level			5.123	0.024
Senior high school or above (n=66)	6 (28.57)	60 (55.56)		
Below senior high school (n=63)	15 (71.43)	48 (44.44)		
History of abortion			10.512	0.001
No (n=83)	7 (33.33)	76 (70.37)		
Yes (n=46)	14 (66.67)	32 (29.63)		
Polycystic ovary syndrome			7.116	0.008
No (n=121)	17 (80.95)	104 (96.30)		
Yes (n=8)	4 (19.05)	4 (3.70)		
Pre-treatment FPG (mmol/L)			0.458	0.499
<8.92 (n=64)	9 (42.86)	55 (50.93)		
≥8.92 (n=65)	12 (57.14)	53 (49.07)		

Pre-treatment 2hPG (mmol/L)			0.126	0.723
<12.15 (n=63)	11 (52.38)	52 (48.15)		
≥12.15 (n=66)	10 (47.62)	56 (51.85)		
Pre-treatment HbA1c (mmol/L)			1.331	0.249
<8.05 (n=64)	8 (38.10)	56 (51.85)		
≥8.05 (n=65)	13 (61.90)	52 (48.15)		
Pre-treatment FINS (mU/L)			4.442	0.035
<13.61 (n=64)	6 (28.57)	58 (53.70)		
≥13.61 (n=65)	15 (71.43)	50 (46.30)		
Pre-treatment HOMA-IR			6.680	0.010
<5.85 (n=64)	5 (23.81)	59 (54.63)		
≥5.85 (n=65)	16 (76.19)	49 (45.37)		
Pre-treatment HOMA-β			1.331	0.249
<6.49 (n=64)	8 (38.10)	56 (51.85)		
≥6.49 (n=65)	13 (61.90)	52 (48.15)		
Pre-treatment APTT (s)			0.569	0.451
<28.10 (n=64)	12 (57.14)	52 (48.15)		
≥28.10 (n=65)	9 (42.86)	56 (51.85)		
Pre-treatment PT (s)			0.077	0.782
<7.81 (n=64)	11 (52.38)	53 (49.07)		
≥7.81 (n=65)	10 (47.62)	55 (50.93)		
Pre-treatment TT (s)			0.569	0.451
<15.99 (n=64)	12 (57.14)	52 (48.15)		
≥15.99 (n=65)	9 (42.86)	56 (51.85)		
Therapeutic regimen			6.260	0.012
Insulin aspart (n=60)	15 (71.43)	45 (41.67)		
Insulin aspart + metformin (n=69)	6 (28.57)	63 (58.33)		

Note: BMI, body mass index; FPG, fasting plasma glucose; 2hPG, 2-hour postprandial plasma glucose; HbA1c, glycosylated hemoglobin; FINS, fasting insulin; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance Index; HOMA-β, HOMA-Beta Cell Function Index; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, prothrombin time.

Table 8. Multivariate analysis of independent factors affecting therapeutic efficacy

Items	B	SE	WALD	P	OR	95% CI
Prenatal BMI	0.851	0.606	1.976	0.160	2.342	0.715-7.676
Educational level	0.971	0.608	2.553	0.110	2.640	0.802-8.686
History of abortion	1.460	0.578	6.378	0.012	4.306	1.387-13.371
Polycystic ovary syndrome	1.803	0.946	3.635	0.057	6.069	0.951-38.731
FINS	0.959	0.627	2.337	0.126	2.609	0.763-8.925
HOMA-IR	1.124	0.642	3.061	0.080	3.076	0.874-10.828
Therapeutic regimen	-0.679	0.610	1.237	0.266	0.507	0.153-1.677

Note: SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval; BMI, body mass index; FINS, fasting insulin; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance Index.

al. [24], MET also positively modulates islet function in PCOS patients. Furthermore, the combination therapy significantly enhanced the coagulation function of GDM patients, manifested in the more significant prolongation of APTT, PT, and TT levels.

We also evaluated the maternal and infant outcomes of GDM pregnancies. Beyond significantly lowering the total incidence of adverse pregnancy outcomes (e.g., PML, polyhydramnios, PIH, CS), insulin+MET application in GDM pregnancies was more effective than insulin in

preventing adverse fetal and neonatal events (macrosomia, neonatal hypoglycemia, neonatal respiratory distress, and neonatal jaundice). This may be due to more effective glycemic control achieved via insulin+MET co-medication, thus helping to avoid a series of adverse events caused by hyperglycemia. In the study of Jiao et al. [25], insulin+MET in GDM pregnant women helped reduce the risk of PIH and PML, lending support to our findings. Wang et al. [26] further noted the ability of insulin+MET to effectively reduce the total incidence of adverse pregnancy outcomes (PML, induced labor, CS) and pregnancy complications (PIH, polyhydramnios, hypoglycemia, ketoacidosis) in GDM-affected mothers, similar to the results of the present research. Univariate and multivariate analyses further revealed that a history of abortion increased the risk of ineffective treatment for GDM pregnancies. The reason is that previous abortions are usually associated with greater risks of oxidative stress, inflammation, and endothelial dysfunction in GDM patients, which may aggravate insulin resistance and heighten treatment difficulty [27].

This study shows room for refinement: (1) Given the absence of analysis on inflammation and oxidative stress, future studies could clarify the effects of the combination therapy on inflammation and oxidative stress in GDM; (2) There are no scale-based assessments of negative emotions and quality of life, and the influence of insulin+MET on these measures can be further understood if relevant measurements can be supplemented later; (3) The patients were not followed up for 3 to 5 years. If relevant data can be supplemented subsequently, the potential long-term prognostic advantages of the combined intervention can be verified.

Conclusion

Insulin combined with MET confers high efficacy for GDM patients, contributing to superior BG control and better islet and coagulation functions, and reduced adverse maternal and infant outcomes. In addition, GDM patients with an abortion history face an increased risk of ineffective treatment.

Disclosure of conflict of interest

None.

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