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Original Article

Effects of metformin combined with insulin aspart on gestational weight gain, lipid metabolism, immune function, and delivery outcomes in pregnant women with gestational diabetes

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Abstract: Objective: To evaluate the effects of metformin combined with insulin aspart on gestational weight gain, lipid metabolism, immune function, and delivery outcomes in women with gestational diabetes mellitus (GDM). Methods: Clinical data from 95 GDM patients were retrospectively analyzed. Patients were divided into two groups: the control group (45 cases) received only insulin aspart, and the study group (50 cases) received a combination of metformin and insulin aspart. Clinical efficacy, blood glucose levels, body weight, lipid metabolism levels [total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low - density lipoprotein cholesterol (LDL-C)], immune function, insulin resistance [fasting insulin (FINS), homeostasis model assessment of β-cell function (HOMA-β), homeostasis model assessment of insulin resistance (HOMA-IR)], inflammatory markers, delivery outcomes, and drug safety were compared between the two groups. Results: The study group had a significantly higher total effective rate (96.00%) compared to the control group (80.00%) ($P < 0.05$). Post-treatment, blood glucose levels decreased significantly in both groups, with lower levels observed in the study group (all $P < 0.05$). Both groups showed weight gain, but the increase was less in the study group ($P < 0.05$). Levels of TC, TG, LDL-C, FINS, HOMA-IR, and inflammatory markers decreased significantly in both groups, with greater reductions in the study group (all $P < 0.05$). HDL-C, immune function markers, and HOMA-β increased, with more significant increases in the study group (all $P < 0.05$). The incidence of adverse delivery outcomes was significantly lower in the study group (26.00% vs. 62.22%) ($P < 0.05$), with no significant difference in adverse reaction rates (10.00% vs. 8.89%) ($P > 0.05$). Conclusion: Metformin combined with insulin aspart demonstrates significant therapeutic benefits in treating GDM. It effectively regulates blood glucose and lipid metabolism, controls weight gain, enhances immune function, reduces insulin resistance, suppresses inflammation, and lowers the incidence of adverse delivery outcomes, with good drug safety.

Keywords: Gestational diabetes mellitus, lipid metabolism, weight, metformin, immune function, insulin aspart, delivery outcomes

Introduction

Gestational diabetes mellitus (GDM) is a common pregnancy-related complication with a relatively high incidence, primarily caused by decreased glucose uptake and utilization, alongside insufficient insulin secretion. Lifestyle factors, such as changes in sleep patterns, dietary habits, rapid weight gain, and low physical activity, further increase the risk of developing GDM [1]. GDM not only raises the risk of hypertension and oligohydramnios but also leads to fetal developmental abnormalities and neonatal hypoglycemia, significantly affecting delivery outcomes [2, 3].

Currently, the clinical management of GDM typically involves exercise and dietary interventions to lower blood glucose levels. However, some patients still face inadequate glycemic control

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and require antidiabetic medications [4]. The main treatments for GDM include oral hypoglycemic agents such as glyburide and metformin, as well as insulin preparations like insulin lispro and insulin aspart. However, the efficacy of these medications can vary, and no standardized treatment protocol has yet been established [5, 6].

Insulin aspart is commonly used for GDM treatment, effectively supplementing basal insulin levels and improving pancreatic β-cell function. However, in some patients, insulin aspart monotherapy may not provide ideal blood glucose control, and its subcutaneous injection method can affect therapeutic outcomes if not administered properly [7]. As a result, combined treatment with other medications is often necessary. Metformin, a widely used oral hypoglycemic agent, enhances glucose utilization, reduces intestinal glucose absorption, and improves insulin resistance, offering reliable glycemic control [8, 9]. This study retrospectively analyzed the clinical data of 95 GDM patients to explore the therapeutic efficacy of combining these two medications.

Materials and methods

General data

This study retrospectively collected clinical data from 95 GDM patients treated at Xi'an International Medical Center Hospital between October 2021 and August 2023. The cohort consisted of 55 primiparous and 40 multiparous women, with a mean age of 28.59 ± 3.25 years. Gestational age ranged from 24 to 36 weeks, with an average of 32.05 ± 2.58 weeks. The number of pregnancies per patient ranged from 1 to 4, with a mean of 1.52 ± 0.31. The patients were divided into two groups based on their treatment regimens: the control group (45 cases) received only insulin aspart, while the study group (50 cases) received a combination of insulin aspart and metformin. Ethical approval for this study was obtained from the ethics committee of Xi'an International Medical Center Hospital.

Sample size calculation

Since this was a retrospective analysis, the sample size was calculated based on existing data, effect sizes from key references and similar studies, and the required statistical power. Based on literature and clinical experience, it was anticipated that metformin combined with insulin aspart would have a medium effect (effect size of 0.5) on pregnancy weight gain, lipid metabolism, immune function, and delivery outcomes in GDM patients. To ensure sufficient statistical power, the significance level was set at 0.05, and the statistical power was set at 80% ($1 - \beta = 0.80$). Using sample size calculation software (such as G*Power), under the assumption of an independent-samples t-test, with an effect size of 0.5, a significance level of $\alpha = 0.05$, and statistical power of 0.80, at least 45 patients were required in each group. Considering the data availability and the retrospective nature of the study, the final sample sizes were determined to be 45 in the control group and 50 in the study group, ensuring sufficient statistical power and accounting for potential missing data or other uncontrollable factors.

Inclusion and exclusion criteria

(1) Inclusion criteria: Patients were diagnosed with GDM, aged between 20 and 40 years, had complete clinical data, were carrying singletons with normal fetal positions, required medication due to inadequate blood glucose control through exercise and dietary modifications, and demonstrated good treatment compliance [10].

(2) Exclusion criteria: Patients with other pregnancy-related complications or acute diabetes complications, a history of allergies to metformin, insulin aspart, or similar medications, pre-existing diabetes before pregnancy, use of hypoglycemic agents within three months prior to enrollment, or severe organic diseases were excluded.

Methods

All patients received dietary and exercise interventions [11]. The control group was treated with insulin aspart (Tonghua Dongbao Pharmaceutical Co., Ltd., National Drug Approval No. S20210041), administered subcutaneously at a dose of 0.5-1.0 U/(kg·d). The study group received combined treatment with metformin (Shandong Priman Pharmaceutical Co., Ltd., National Drug Approval No. H20174087). The initial oral dose was 0.5 g once daily, which was increased by 0.5 g daily after one week. Both groups continued treatment until delivery.

Observational indicators

(1) Clinical efficacy: Clinical efficacy was assessed according to the Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 edition), with outcomes classified as follows [12].

Markedly effective: Symptoms nearly disappeared or were significantly alleviated, and blood glucose levels returned to the normal range.

Effective: Symptoms were somewhat alleviated, and blood glucose levels decreased significantly, with 2-hour postprandial glucose (2 hPG) < 8.3 mmol/L.

Ineffective: Symptoms were not alleviated or worsened, and blood glucose levels did not decrease or increase. The total efficacy rate was calculated as the sum of the effective and markedly effective rates.

(2) Blood glucose levels: Before and after treatment, 5 ml of morning fasting venous blood was collected from each group. Serum was obtained by centrifugation, and fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and 2 hPG levels were measured using a blood glucose analyzer.

(3) Body weight: The body weight of both groups was measured before and after treatment. Each measurement was taken three times, and the average value was recorded.

(4) Lipid metabolism levels: Before and after treatment, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels in both groups were measured using an automated biochemical analyzer.

(5) Immune function: Before and after treatment, immunoglobulin levels (IgA, IgG, IgM) in both groups were assessed using the immunoturbidimetric method.

(6) Insulin resistance: Fasting insulin (FINS) levels in both groups were measured using radioimmunoassay. The homeostasis model assessment of β-cell function (HOMA-β) and insulin resistance index (HOMA-IR) were calculated.

(7) Inflammatory response: Before and after treatment, C-reactive protein (CRP) levels in both groups were measured using the immunoturbidimetric method. Tumor necrosis factor-α (TNF-α) and interleukin (IL-1β, IL-8) levels were measured using ELISA.

(8) Delivery outcomes: The incidences of adverse delivery outcomes were compared between the two groups, including cesarean section, premature birth, premature rupture of membranes, amniotic fluid conditions, and occurrences of hypoglycemia and hyperglycemia in parturients.

(9) Fetal and neonatal conditions: The incidences of macrosomia, neonatal hypoglycemia, neonatal jaundice, and neonatal respiratory distress were compared between the two groups.

(10) Medication safety: Adverse reactions were compared between the two groups.

Statistical methods

SPSS 23.0 software was used for statistical analysis. Count data, such as efficacy, adverse pregnancy outcomes, and drug safety, were presented as n (%) and analyzed using χ^2 tests. Measurement data, such as blood glucose, body weight, lipid levels, immune function, insulin resistance, and inflammatory response, were presented as mean ± standard deviation ($\bar{x} \pm s$) and analyzed using the t-test. A significance level of $P < 0.05$ was considered statistically significant.

Results

Comparison of general data

The demographic variables, including age, gestational weeks, number of pregnancies, and type of delivery, were similarly distributed between the two groups of GDM patients. The lack of statistically significant differences indicates that the general characteristics of the two groups were comparable (all $P > 0.05$). See **Table 1**.

Comparison of clinical efficacy

The overall clinical efficacy rate in the control group was 80.00% (36/45), which was significantly lower than the 96.00% (48/50) observed in the study group ($P < 0.05$). See **Table 2**.

Table 1. Comparison of general information between the two groups [n/($\bar{x}$±s)]

Group	Age (years)	Gestational age (weeks)	Number of pregnancies	Primipara/Multipara	BMI (kg/m^2)
Control group (n = 45)	28.23 ± 4.03	32.31 ± 2.41	1.60 ± 0.43	24/21	27.51 ± 2.27
Study Group (n = 50)	28.84 ± 3.87	31.87 ± 2.67	1.47 ± 0.38	31/19	26.95 ± 2.75
t/χ^2	0.759	0.840	1.564	0.730	1.075
P	0.550	0.403	0.121	0.393	0.285

Table 2. Comparison of clinical efficacy between the two groups n (%)

Group	Markedly effective	Effective	Ineffective	Total efficacy
Control group (n = 45)	24 (53.33)	12 (26.67)	9 (20.00)	36 (80.00)
Study Group (n = 50)	32 (64.00)	16 (32.00)	2 (4.00)	48 (96.00)
χ^2				5.922
P				0.015

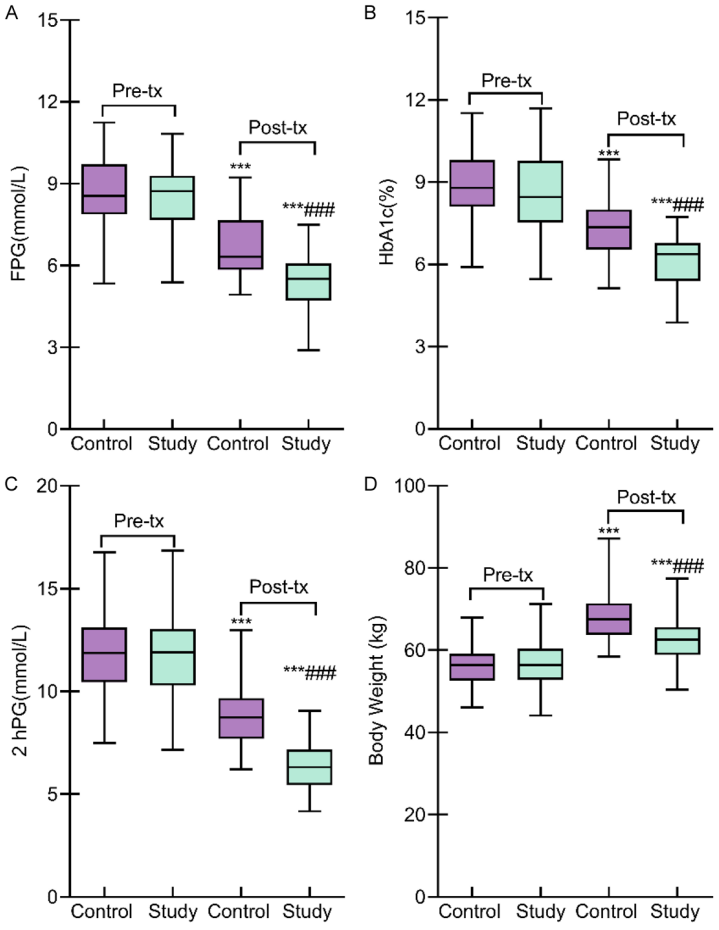

Figure 1. Comparison of blood glucose indicators and body weight between the two groups. A: FPG; B: HbA1c; C: 2 hPG; D: Body weight. Note: Compared with the group Pre-tx, ***P < 0.01; Compared with the control group, ###P < 0.01. FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; 2 hPG, 2-hour post-meal plasma glucose; Pre-tx, pre-treatment.

Comparison of blood glucose and body weight

Before treatment, the blood glucose indicators (FPG, HbA1c, 2 hPG) and body weight were comparable between the two groups (all P > 0.05). After treatment, significant reductions in FPG, HbA1c, and 2 hPG, along with an increase in body weight, were observed in both groups (all P < 0.05). However, the study group demonstrated significantly lower levels of FPG, HbA1c, 2 hPG, and body weight compared to the control group (all P < 0.05). See **Figure 1**.

Comparison of lipid metabolism

Before treatment, the levels of TC, TG, LDL-C, and HDL-C were comparable between the two groups (all P > 0.05). After treatment, significant reductions were observed in TC, TG, and LDL-C levels, while HDL-C was significantly higher compared to baseline. Notably, the improvements in the study group were more remarkable (all P < 0.05). See **Figure 2**.

Comparison of immune function

Before treatment, no significant differences were found in the immune function indicators (IgA, IgG,

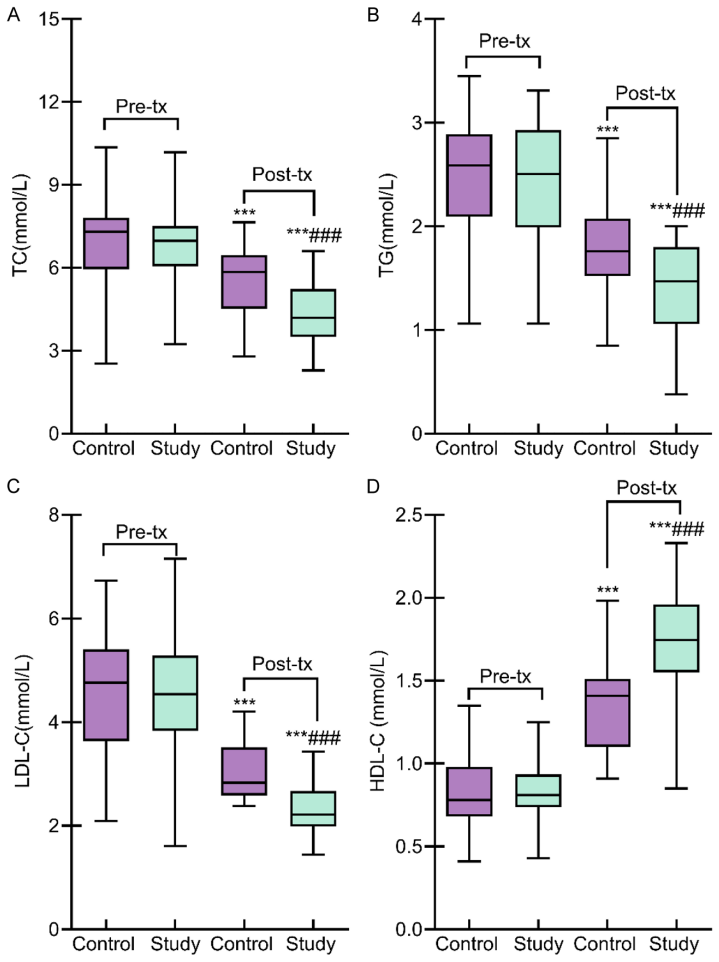

Figure 2. Comparison of lipid metabolism -related indexes between the two groups. A: TC; B: TG; C: LDL-C; D: HDL-C. Note: Compared with the group Pre-tx, ***P < 0.01; Compared with the control group, ###P < 0.01. TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Pre-tx, pre-treatment.

IgM) between the two groups (all P > 0.05). After treatment, immune function indicators increased significantly in both groups, with the study group showing higher levels (all P < 0.05). See **Table 3**.

Comparison of insulin resistance

Before treatment, the levels of FINS, HOMA-β, and HOMA-IR were similar between the two groups, with no significant differences (all P > 0.05). After treatment, FINS and HOMA-IR levels significantly decreased, while HOMA-β levels significantly increased in both groups. Moreover, the improvements in FINS, HOMA-β, and HOMA-IR were significantly greater in the study group compared to the control group (all P < 0.05). See **Figure 3**.

Comparison of the inflammatory response

Before treatment, there were no significant differences in the levels of inflammatory markers (IL-1β, IL-8, TNF-α, CRP) between the two groups (all P > 0.05). After treatment, the levels of all inflammatory markers decreased significantly in both groups, with the study group showing lower levels than the control group (all P < 0.05). See **Figure 4**.

Comparison of maternal complications

The incidences of polyhydramnios, premature birth, and cesarean section in the study group were significantly lower than those in the control group (all P < 0.05). There were no statistically significant differences in the incidences of complications between the two groups (all P > 0.05). Both groups were followed up for six months after delivery. The proportion of patients developing type 2 diabetes after delivery in the control group was slightly higher than in the study group, but there was no statistically significant difference (P > 0.05). See **Table 4**.

Comparison of fetal and neonatal conditions

The incidences of neonatal jaundice and macrosomia in the study group were significantly lower than those in the control group (both P < 0.05). See **Table 5**.

Comparison of placental maturity

There was no statistically significant difference in placental maturity between the two groups (P > 0.05). See **Table 6**.

Table 3. Comparison of immune function related indexes between the two groups

Group		Control group (n = 45)	Study Group (n = 50)	*t*	*P*
IgA	Before treatment	0.58 ± 0.11	0.62 ± 0.13	1.61	0.111
	After treatment	1.32 ± 0.17*	1.87 ± 0.23*	13.132	< 0.001
IgG	Before treatment	7.58 ± 1.22	7.87 ± 1.16	1.187	0.238
	After treatment	10.25 ± 2.28*	12.47 ± 1.98*	5.079	< 0.001
IgM	Before treatment	0.81 ± 0.15	0.84 ± 0.16	0.94	0.350
	After treatment	1.25 ± 0.21*	1.48 ± 0.23*	5.07	< 0.001

Note: Compared within the same group before treatment, *P < 0.05. IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

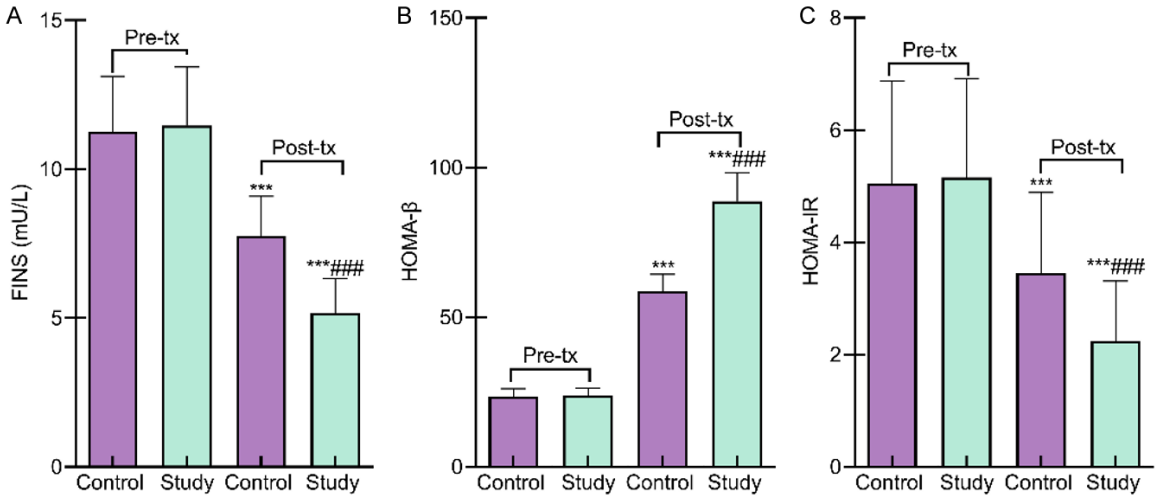

Figure 3. Comparison of insulin resistance-related indexes between the two groups. A: FINS; B: HOMA-β; C: HOMA-IR. Note: Compared with the group Pre-tx, ***P < 0.01; Compared with the control group, ###P < 0.01. FINS, fasting insulin; HOMA-β, homeostasis model assessment of β-cell function HOMA-IR, homeostasis model assessment of insulin resistance; Pre-tx, pre-treatment.

Comparison of medication safety

The incidence of adverse reactions in the control group was 8.89% (4/45), compared to 10.00% (5/50) in the study group. There was no significant difference between the two groups (P > 0.05). See **Table 7**.

Discussion

This study demonstrates that the combination of metformin and insulin aspart effectively improves blood glucose control in GDM patients and reduces the risk of adverse pregnancy outcomes. The results show that the total effective rate in the study group is significantly higher than in the control group, with a marked reduction in the incidence of complications such as macrosomia and preterm delivery. These findings suggest that the combined treatment regimen offers significant clinical value in managing GDM. Additionally, patients in the study group experienced more pronounced improvements in body weight and blood lipid metabolism compared to those in the control group, further supporting the potential role of metformin in addressing metabolic disorders in GDM patients.

Metformin and insulin aspart exert synergistic hypoglycemic effects through distinct mechanisms. Insulin aspart, a rapid-acting insulin analog, lowers blood glucose by promoting glucose uptake in peripheral tissues and inhibiting hepatic glucose production [13]. Notably, the substitution of proline with aspartic acid at position 28 of the human insulin B chain accelerates its onset of action compared to soluble human insulin, leading to a more rapid reduction in blood glucose levels after injection. In

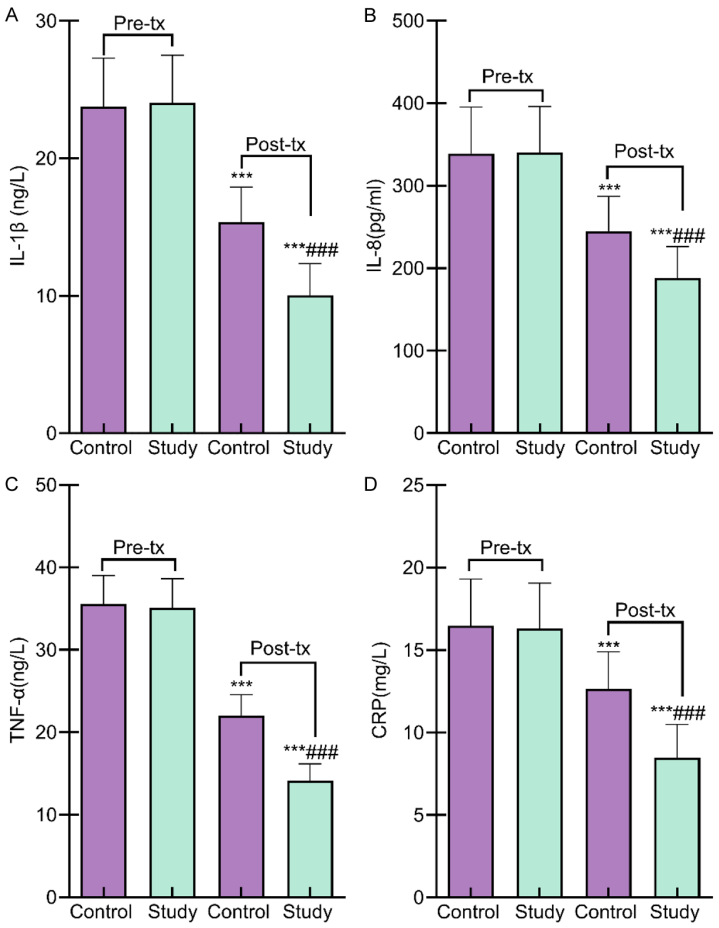

Figure 4. Comparison of insulin resistance-related indexes between the two groups. A: IL-1β; B: IL-8; C: TNF-α; D: CRP. Note: Compared with the group Pre-tx, ***P < 0.01; Compared with the control group, ###P < 0.01. IL-1β, interleukin-1β; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α; CRP, C-reactive protein; Pre-tx, pre-treatment.

contrast, metformin improves insulin sensitivity, suppresses hepatic gluconeogenesis, and regulates inflammatory responses [14]. Additionally, it promotes glycolysis, facilitates glucose uptake and utilization, and enhances pancreatic β-cell function [15]. This study found that, compared with insulin aspart alone, the combination of metformin further reduced fasting and postprandial blood glucose levels and improved insulin resistance, highlighting their synergistic effect on blood glucose control. A prospective study by Zhu et al. supports this finding, reporting a total efficacy rate of 86.49% for metformin combined with insulin aspart in the treatment of GDM, significantly higher than that of insulin aspart alone (64.52%) [16]. These results further confirm the superior hypoglycemic efficacy with combination therapy.

Insulin resistance is closely linked to dyslipidemia, and metformin has been shown to enhance insulin sensitivity and optimize lipid metabolism [17]. Mechanistically, metformin increases AMP-activated protein kinase (AMPK) activity in muscle and adipose tissue, promoting fatty acid oxidation and reducing fatty acid synthesis. Additionally, metformin suppresses AMPK activity in the brain, leading to appetite inhibition, which contributes to reductions in blood lipid levels and overall body weight. Previous studies have indicated that blood lipid levels in GDM patients, such as TC, TG, and lLDL-C, are generally elevated compared to those in healthy pregnant women, with insulin resistance exacerbating lipid metabolism disorders [18-20]. In this study, both groups showed improvements in lipid metabolism indices post-treatment, with the study group exhibiting more substantial improvements. This suggests that metformin may provide an additional metabolic regulatory effect within the combined treatment regimen, potentially mitigating the risk of lipid metabolism disorders during pregnancy.

Moreover, GDM is not only associated with insulin resistance but also with chronic inflammatory responses [21]. Hyperglycemia induces the increased production of inflammatory factors such as IL-6 and TNF-α, which, in turn, exacerbate insulin resistance, creating a vicious cycle [22, 23]. Wei et al. reported that serum levels of inflammatory markers, including CRP, IL-6, and TNF-α, were significantly elevated in GDM patients compared to healthy individuals, indicating varying degrees of systemic inflammation [24]. This study found that inflammatory markers decreased more significantly in the study group after treatment, suggesting that metformin may reduce the production of these inflammatory factors by inhibiting pathways such as NF-κB, thereby improving the inflammatory state in GDM patients [25-28]. The use of insulin aspart may also indirectly

Table 4. Comparison of delivery outcomes between the two groups [n (%)]

Group	Control group (n = 45)	Study Group (n = 50)	χ^2	*P*
Cesarean section	14 (31.11)	6 (12.00)	5.205	0.023
Preterm birth	6 (13.33)	2 (4.00)	1.602	0.206
Premature rupture of membranes	4 (8.88)	1 (2.00)	1.084	0.298
Neonatal asphyxia	6 (13.33)	2 (4.00)	1.602	0.206
Polyhydramnios	15 (33.33)	7 (14.00)	4.975	0.026
Hypoglycemia	6 (13.33)	4 (8.00)	0.261	0.609
Postpartum type 2 diabetes	5 (11.11)	2 (4.00)	0.868	0.352

Table 5. Comparison of fetal and neonatal conditions between the two groups [n (%)]

Group	Macrosomia	Neonatal hypoglycemia	Neonatal jaundice	Neonatal respiratory distress
Control group (n = 45)	11 (24.44)	7 (15.56)	15 (33.33)	8 (17.78)
Study Group (n = 50)	3 (6.00)	4 (8.00)	6 (12.00)	4 (8.00)
χ^2	6.413	1.321	6.26	2.052
P	0.011	0.251	0.012	0.152

Table 6. Comparison of placental maturity between the two groups [n (%)]

Group	Grade 0	Grade 1	Grade 2	Grade 3
Control group (n = 45)	0 (0.00)	2 (4.45)	6 (13.33)	37 (82.22)
Study Group (n = 50)	0 (0.00)	1 (2.00)	4 (8.00)	45 (90.00)
χ^2			5.306	
P			0.152	

Table 7. Comparison of medication safety between the two groups n (%)

Group	Diarrhea	Nausea and vomiting	Glycopenia	Total
Control group (n = 45)	1 (2.22)	2 (4.44)	1 (2.22)	4 (8.89)
Study Group (n = 50)	2 (4.00)	1 (2.00)	2 (4.00)	5 (10.00)
χ^2				0.028
P				0.868

attenuate inflammation, and its combination with metformin could positively impact inflammation regulation in addition to improving blood glucose control [29-31].

Drug safety is a critical concern in the management of GDM. The results of this study show no significant difference in the incidence of adverse reactions between the two groups, suggesting that the combination of metformin and insulin aspart is safe for short-term use. However, given that metformin may affect placental function, potentially influencing fetal growth and development, further longitudinal studies are necessary to assess its long-term safety.

Despite confirming the clinical benefits of metformin combined with insulin aspart for treating GDM, this study has several limitations. First, the long-term growth and development of the fetus were not followed, and the potential impact of this treatment on the metabolic health of newborns and children remains unassessed. Second, as a single-center retrospective study with a relatively small sample size and short follow-up period, the statistical power may be limited. Future multi-center, large-scale prospective studies with extended follow-up are needed to comprehensively evaluate both the short-term and long-term efficacy of metformin combined with insulin aspart. Such research will provide more robust evidence to support the precise treatment of GDM.

In conclusion, the combination of metformin and insulin aspart demonstrates significant

therapeutic efficacy in managing GDM. This regimen effectively regulates blood glucose and lipid metabolism, mitigates excessive weight gain, enhances immune function, alleviates insulin resistance, and suppresses inflammatory responses. Moreover, it reduces the incidence of adverse pregnancy outcomes while maintaining a favorable safety profile.

Disclosure of conflict of interest

None.

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