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Original Article

Improved pregnancy outcome in gestational diabetes mellitus patients treated with insulin aspart and metformin: a comparative study

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Abstract: Objective: To investigate the impact of combining metformin with insulin aspart on blood glucose control, renal injury, and pregnancy outcome in gestational diabetes mellitus (GDM) patients. Methods: In this retrospective analysis, the clinical data of 140 GDM patients treated at Baoji Maternal and Child Health Hospital between March 2020 and March 2022 were studied. The patients were divided into a control group (insulin aspart alone, n=64) and an observation group (combination of insulin aspart and metformin, n=76) according to their treatment regimen. The blood glucose metabolism, renal injury markers, and pregnancy outcomes between the two groups were assessed and compared. Results: The observation group demonstrated significantly lower levels of blood glucose metabolism markers (fasting plasma glucose [FPG], fasting insulin [FINS], mean amplitude of glycemic excursions [MAGE], and mean of daily differences [MODD]), renal injury indicators (microalbuminuria [mAlb], serum cystatin C [CysC], free fatty acids [FFA], and neutrophil gelatinase-associated lipocalin [NGAL]), and inflammatory markers (interleukin-6 [IL-6], transforming growth factor-β1 [TGF-β1], and lipoprotein-associated phospholipase A2 [Lp-PLA2]) compared to the control group (all $P<0.05$). Additionally, the incidence of adverse pregnancy outcomes in both newborns and mothers was lower in the observation group ($P<0.05$). Logistic regression analysis identified the treatment regimen, patient age, and pre-pregnancy BMI as independent risk factors for adverse pregnancy outcome. Conclusion: The combination of metformin and insulin aspart in treating GDM can effectively reduce blood glucose levels, mitigate renal injury, and improve pregnancy outcome. This treatment approach presents a viable option for optimizing maternal and fetal health in GDM cases.

Keywords: Insulin aspart, metformin, gestational diabetes mellitus, pregnancy outcomes

Introduction

Gestational Diabetes Mellitus (GDM) is a common clinical condition in pregnant women, characterized by abnormal sugar tolerance, leading to hyperglycemia [1]. The global incidence of GDM exceeds 14% and is projected to affect 550 million people by 2030 [2]. In China, with economic advancement, the body mass index (BMI) of pregnant women has also increased [3]. Additionally, the incidence of GDM is rising due to the relaxation of the one-child policy and an increase in older pregnant women [4]. Multiple studies indicate that GDM not only increases the risk of maternal complications, such as gestational hypertension and lipid metabolism disorders, but also impacts fetal intrauterine growth and development. Furthermore, GDM increases the long-term risk of cardiovascular diseases, type 2 diabetic mellitus (T2DM), and lipid metabolism disorders in mothers, as well as the risk of metabolic and cardiovascular disease in infants. However, many pregnant women do not pay enough attention to GDM, leading to inadequate glycemic control and numerous adverse pregnancy outcomes.

The high prevalence of GDM leads to increased healthcare costs, heightened susceptibility to T2DM, and adverse pregnancy outcome, posing a global public health challenge [11]. Clinically,

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there are various treatment options for GDM. Insulin therapy is a primary strategy to control blood sugar levels. Insulin is the traditional standard medication for GDM, but it is expensive and requires patient training since it does not cross the placenta [12]. In contrast, Metformin controls blood sugar without increasing the risk of perinatal adverse outcomes [13]. Metformin lowers blood sugar by inhibiting hepatic gluconeogenesis and increasing insulin sensitivity [14]. Metformin has unique advantages compared to insulin, such as not increasing weight, avoiding hypoglycemia, eliminating the need for injections, and simplifying follow-up [15]. Recent clinical trials [16] have shown that treating with metformin during gestational weeks 12-18 reduces weight gain, effectively controlling disease progression in obese women without affecting newborn birth weight. Additionally, a study [17] has found that metformin treatment is not associated with an increased risk of perinatal complications and has a similar perinatal outcome compared to insulin therapy. Despite this evidence, metformin treatment for GDM is not widely implemented, and guidelines for GDM management lack consistency.

Therefore, this study aimed to provide a more comprehensive treatment plan to enhance the clinical management of GDM patients by comparing the efficacy and impact of insulin aspart alone and its combination with metformin on pregnancy outcomes. The novelty of this study lies in its focus on the effectiveness of glycemic control, pregnancy outcome, and fetal health, thereby offering more comprehensive guidance for clinical practice. Additionally, our study also explored the potential long-term health implications of the combined treatment on pregnant women, providing a scientific basis for future prevention strategies and clinical guidelines.

Methods and materials

Ethical statement

Baoji Maternal and Child Health Hospital Medical Ethics Committee approved this study with ethical batch number L (A) 2020084.

Sample size calculation

Based on previous studies, we determined that the incidence of adverse pregnancy outcome in patients with GDM after intervention is approximately 20%. The sample size was calculated using the formula: $n = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{E}\right)^2 \times p \times (1-p)$, with a significance level α=0.05, $Z\alpha$=1.96, a statistical power of 90% ($Z\beta$=1.28), an event rate of 20%, and an effect size of E=0.20. The calculation indicated a requirement for 42 patients. Considering the need for a control group, we aimed to include a total of 84 cases. Accounting for a potential 10% data loss, as least 92 patients needed to be included. The specific number was determined based on the actual clinical cases we were able to enroll.

Case selection

We retrospectively analyzed data of patients with GDM treated in Baoji Maternal and Child Health Hospital from March 2020 to March 2022. Following the inclusion criteria, we initially gathered 204 potential cases. After implementing the exclusion criteria, 64 cases were disqualified, leaving us with 140 eligible cases. These patients were categorized based on their clinical data regarding medication usage, resulting in a control group treated with insulin aspart alone (n=64) and an observation group receiving treatment with insulin aspart in combination with metformin (n=76), as shown in **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria: 1. Patients diagnosed with GDM by lucose tolerance tests; 2. Patients with singleton pregnancy; 3. Patients who had poor response to conventional interventions such as health education and dietary guidance; 4. Patients with complete prenatal records; 5. Patients had received no conflicting medication in the previous two months before admission that might affect the study's outcome.

Exclusion criteria: 1. Patients with known contraindications to the drugs used in this study; 2. Patients with significant dysfunction in important organs; 3. Patients with previous history of diabetes or thyroid dysfunction; 4. Patients with a family history of diabetes or suffering from other endocrine system diseases; 5. Patients with serious disorders of vital organs such as the heart, liver, and kidney; 6. Patients with malignant tumors.

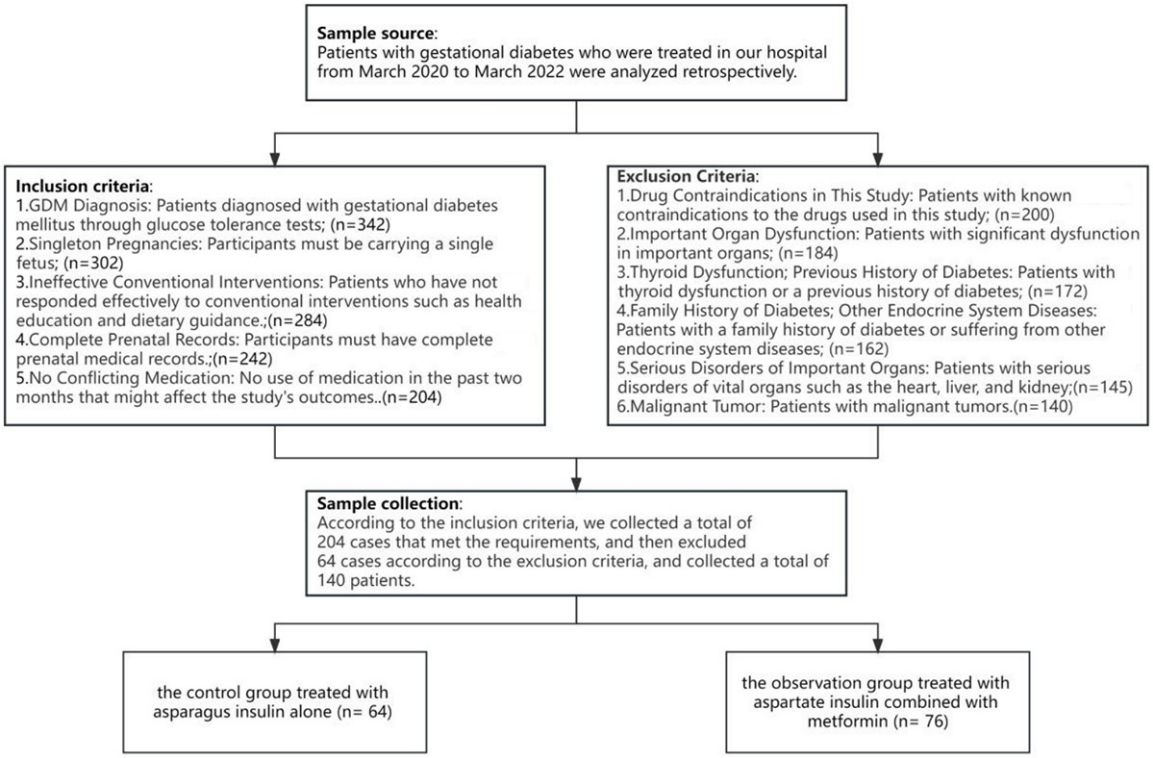

Figure 1. Flow chart of patient sample screening and grouping.

Treatment protocol

Both groups received standard treatments. Daily dietary intake was calculated based on gestational week, blood sugar level, and weight to ensure a balanced diet that met the nutritional needs of both the patient and the fetus. Tailored exercise plans were made for individual patients, with appropriate types, durations, and intensities specified. Blood sugar level was regularly monitored, and adjustments to diet and exercise plans were made as necessary. In the control group, insulin aspart injections were administered (Novo Nordisk (China) Pharmaceutical Co., Ltd.; S20153001) 30 minutes before meals, beginning at a dosage of 0.2-0.3 U/(kg·d), with further adjustments based on specific blood sugar levels, continuing until the onset of labor. In the observation group, in addition to the standard treatment, Metformin Hydrochloride tablets were taken (Sino-American Shanghai Squibb Pharmaceuticals Ltd.; H20023370) at a dosage of 0.5 g per dose, twice a day with meals. The dosage was adjusted based on specific blood sugar levels, with a maximum daily dose of 2 g, and treatment was discontinued upon the onset of labor.

Clinical data collection

Clinical and laboratory data were extracted from patients' electronic medical records. Clinical data encompassed information such as age, gestational week, parity, pre-pregnancy BMI, educational level, and miscarriage history. Laboratory data included measurements of FPG (fasting plasma glucose) levels before treatment and one month after treatment, FINS (fasting insulin) level, MAGE (mean amplitude of glycemic excursions), MODD (mean of daily differences), mAlb (microalbumin), CysC (cystatin C), FFA (free fatty acids), NGAL (neutrophil gelatinase-associated lipocalin), IL-6 (interleukin 6), TGF-β1 (transforming growth factor beta 1), and Lp-PLA2 (lipoprotein-associated phospholipase A2) level.

Laboratory testing methods

Fasting elbow venous blood samples were obtained from patients before and after treatment for the measurement of blood glucose metabolism indicators. Blood samples were subjected to centrifugation to separate the supernatant, and FPG levels were determined using a Hitachi 7600 automatic biochemical

Table 1. Comparison of patients' baseline data

Consideration	Control group (n=64)	Observation group (n=76)	χ^2-value	*P*-value
Age				
≥30 years old	39	48	0.073	0.787
<30 years old	25	28		
Gestation period				
≥28 weeks	48	61	0.558	0.455
<28 weeks	16	15		
Number of pregnancies				
Primiparous woman	42	46	0.387	0.534
Menstruation	22	30		
Pre-pregnancy BMI				
≥25 kg/m^2	16	15	0.558	0.455
<25 kg/m^2	48	61		
Educational attainment				
≥ University	38	40	0.64	0.424
< University	26	36		
History of abortion				
Yes	14	10	1.859	0.173
No	50	66		

Note: BMI, Body Mass Index.

Table 2. Clinical efficacy assessment

Group	Effective Treatment	Improvement	Ineffective Treatment	Total efficiency
Control group (n=64)	28	21	15	49 (76.56%)
Observation group (n=76)	46	24	6	70 (92.10%)
$\chi^{Z/2}$ values		2.431		6.583
P-value		0.015		0.010

analyzer with the glucose oxidase method. Fasting FINS levels were measured through enzyme-linked immunosorbent assay (ELISA), while MAGE and MODD were monitored in real-time. For the assessment of renal injury indicators, 24-hour urine samples collected before and after treatment were analyzed. mAlb levels were quantified using immunoturbidimetry, while CysC, FFA, and NGAL levels were determined using ELISA. The reagent kits utilized were sourced from BoYan Biotechnology Co., Ltd. In addition, the level of inflammatory markers (IL-6, TGF-β1 and Lp-PLA2) in serum were measured by ELISA, with the ELISA kits being provided by Shanghai Enzyme Research Biotechnology Co., Ltd.

Adverse pregnancy outcome assessment

Adverse pregnancy outcomes in mothers, including postpartum hemorrhage, hypertension, infection, and uterine prolapse, were recorded and compared between the two groups.

Efficacy evaluation criteria

Effective: blood glucose levels reached the target range during pregnancy and remained stable throughout the pregnancy; Improved: blood glucose levels reached the target range with continued medication for maintenance due to relapse, indicating that despite the success of the initial treatment, the patient's blood glucose levels remained unstable that require additional medication; Ineffective: failure to meet the "effective treatment" or "improvement" criteria above. In this case, the patient's blood glucose levels were neither in the target range nor improved after treatment. Total effective rate = (effective cases + improved cases)/ total number * 100%.

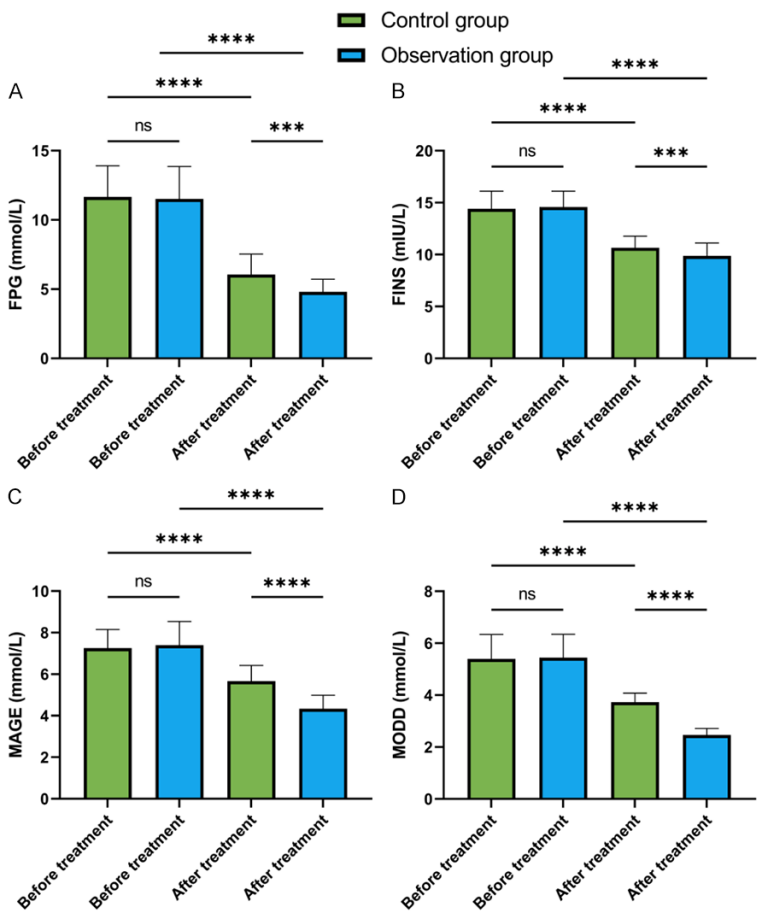

Figure 2. Comparison of changes in blood glucose metabolic indexes before and after treatment of patients. A: Variation in FPG levels in both groups. B: Changes in FINS levels across the two groups. C: Alterations in MAGE in both groups. D: Modification in MODD levels in each group. Note: nsP>0.05, ***P<0.01, ****P<0.0001. FPG, Fasting Plasma Glucose; FINS, Fasting Insulin; MAGE, Mean Amplitude of Glycemic Excursions; MODD, Mean of Daily Differences.

Outcome measurement

Primary indicators: 1. The comparison of treatment effects between the two groups. 2. The identification of independent risk factors for adverse pregnancy outcomes in mothers by logistic regression analysis.

Secondary indicators: 1. The comparison of clinical baseline data between the two groups. 2. The comparison of changes in blood glucose metabolism, renal injury, and inflammatory response indicators before and after treatment.

Statistical analysis

Data were processed using SPSS 20.0 software. The Kolmogorov-Smirnov test was used to analyze data distribution. Quantitative data were expressed as mean ± standard deviation (Mean ± SD). Independent sample t-tests were used to compare normally distributed data between groups and paired t-tests for within-group comparisons, represented by t. Non-parametric tests were used for non-normally distributed data, represented by Z. Counted data were expressed as rate and related comparisons were performed using the chi-square test. Multifactor logistic regression analysis was used to identify independent risk factors affecting adverse pregnancy outcomes in patients. A *P*-value <0.05 was considered significant.

Results

Baseline data

Comparison of baseline data between the two groups revealed no significant differences in age, gestational week, number of births, pre-pregnancy BMI, educational level, and history of miscarriage (all P>0.05, **Table 1**).

Clinical efficacy assessment

A comparison of clinical efficacy after treatment between the two groups showed that the total effective rate in the control group was significantly lower than that in the observation group (P=0.010, **Table 2**).

Comparison of blood glucose metabolism indicators

Before treatment, there were no differences in FPG, FINS, MAGE, or MODD levels between the two groups (all P>0.05). However, after the treatment, the FPG, FINS, MAGE, and MODD levels significantly decreased in both groups compared to before treatment (all P<0.001); and further comparison revealed that post-treatment FPG, FINS, MAGE, and MODD levels in the observation group were significantly lower than those in the control group (all P<0.01), as shown in **Figure 2**.

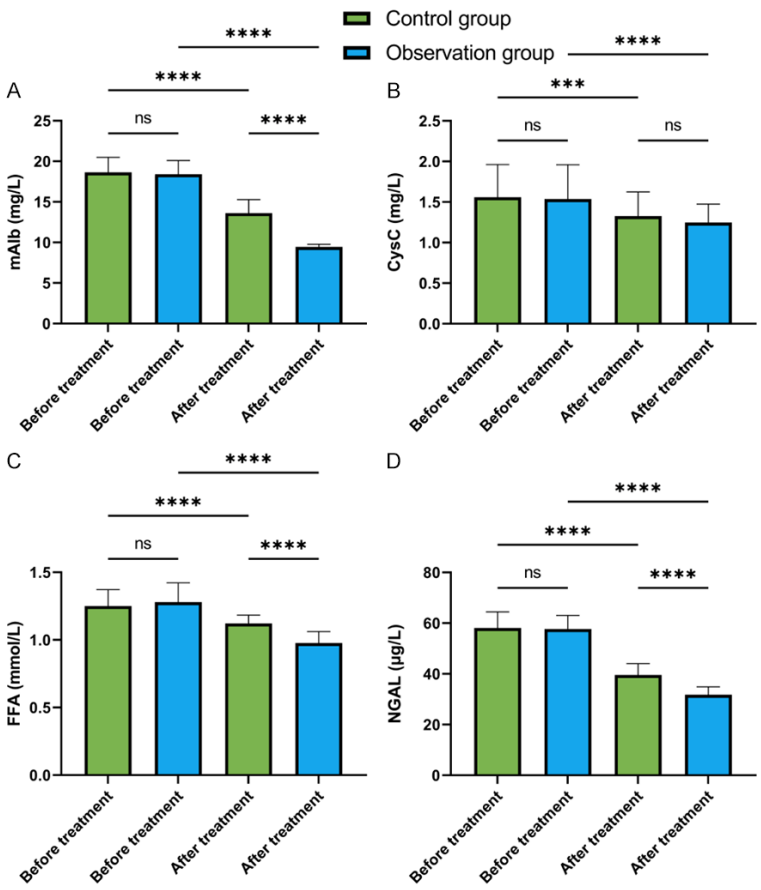

Figure 3. Comparison of renal injury indexes before and after treatment. A: Shifts in mAlb levels in control and observation groups. B: Variations in CysC levels pre- and post-treatment. C: Changes in FFA levels between groups. D: Differences in NGAL levels in both groups. Note: nsP>0.05, ***P<0.01, ****P<0.0001. mAlb, Microalbumin; CysC, Cystatin C; FFA, Free Fatty Acids; NGAL, Neutrophil Gelatinase-Associated Lipocalin.

Comparison of renal injury indicators

Before treatment, there were no significant differences in mAlb, CysC, FFA, or NGAL levels between the two groups (all P>0.05). However, after the treatment, the levels of mAlb, CysC, FFA, and NGAL significantly decreased in both groups compared to before treatment (all P<0.001); and further comparison revealed that post-treatment levels of mAlb, FFA, and NGAL in the observation group were significantly lower than those in the control group (all P<0.01), as shown in **Figure 3**. Notably, the two groups did not differ obviously in post-treatment CysC level (P>0.05, **Figure 3**).

Comparison of inflammatory markers

Before treatment, there were no significant differences in IL-6, TGF-β1, and Lp-PLA2 levels between the two groups (all P>0.05). However, after the treatment, IL-6, TGF-β1, and Lp-PLA2 levels significantly decreased in both groups compared to before treatment (all P<0.001); and further comparison revealed that post-treatment levels of IL-6, TGF-β1, and Lp-PLA2 in the observation group were significantly lower than those in the control group (all P<0.01), as shown in **Figure 4**.

Comparison of adverse pregnancy outcomes

Statistical results of adverse pregnancy outcome showed that the total number of adverse pregnancy outcomes in the control group was significantly higher than that of the observation group (P=0.005, **Table 3**).

Analysis of risk factors affecting adverse pregnancy outcome

Patients were sub-grouped according to the presence or absence of adverse pregnancy outcome for the analysis of risk factors. Univariate analysis revealed that age, pre-pregnancy BMI, treatment plan, pre-treatment FPG, and pre-treatment FINS were associated with adverse pregnancy outcome (all P<0.01, **Table 4**). Subsequently, the data were assigned values (**Table 5**), with measured data categorized into two groups using cut-off values. Multivariate logistic regression analysis identified the treatment plan, age, and pre-pregnancy BMI as independent risk factors affecting adverse pregnancy outcome (all P<0.01, **Table 6**).

Discussion

Gestational Diabetes Mellitus (GDM) is typically diagnosed between the 24th and 28th weeks of pregnancy. If hyperglycemia during pregnancy remains uncontrolled, it can lead to severe adverse outcomes for the mother, fetus, and newborn [18]. GDM is associated with neonatal

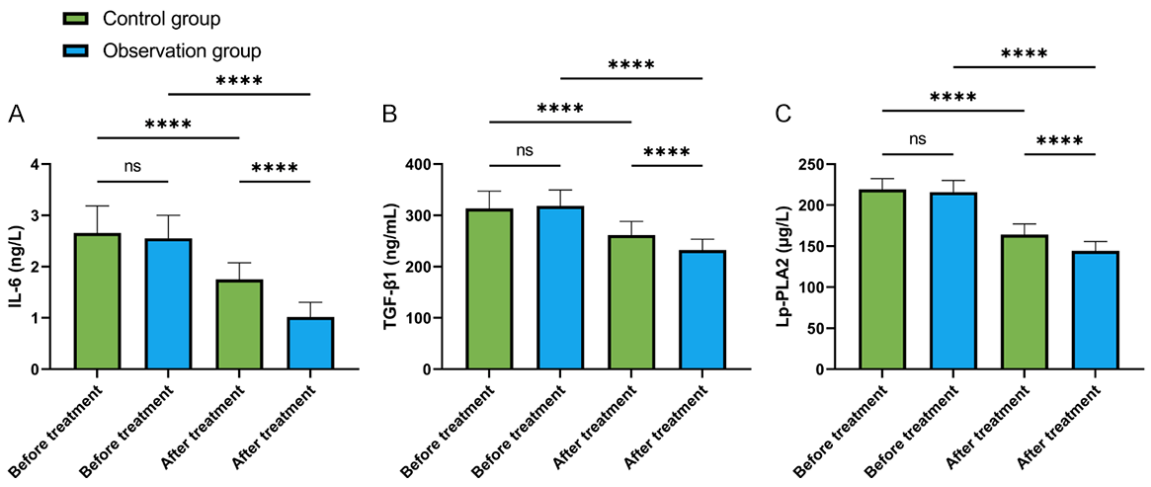

Figure 4. Comparison of renal injury indicators before and after treatment. A: Comparison of IL-6 levels in both groups. B: Comparison of TGF-β1 levels in both groups. C: Comparison of Lp-PLA2 levels in both groups. Note: ns P>0.05, ****P<0.0001. IL-6, Interleukin 6; TGF-β1, Transforming Growth Factor Beta 1; Lp-PLA2, Lipoprotein-Associated Phospholipase A2.

Table 3. Adverse reaction occurrence statistics

Group	Postpartum hemorrhage	High blood pressure	Infections	Uterine prolapse	Total incidence
Control group (n=64)	10	5	3	3	21 (32.81%)
Observation group (n=76)	3	2	3	2	10 (13.15)
χ^2-value					7.785
P-value					0.005

hypoglycemia, respiratory distress syndrome, and macrosomia in newborns, while mothers may experience urinary tract infections, gestational hypertension, and polyhydramnios [19]. A delayed diagnosis and treatment can elevate the risk of adverse maternal and neonatal outcomes. Consequently, investigating effective treatment measures holds significant clinical importance.

Insulin aspart can rapidly lower blood sugar levels, but its long-term effects are limited, and excessive use may lead to hypoglycemia [20]. Conversely, metformin accelerates glycolysis, delays glucose uptake, and enhances insulin sensitivity [21]. In our study, we observed that the combination of insulin aspart and metformin demonstrated superior outcomes in terms of blood glucose metabolism, renal injury markers, and inflammatory markers when compared to insulin aspart alone. This can be attributed to hormonal changes during pregnancy that reduce insulin sensitivity; while the concurrent use of metformin and insulin aspart enhances insulin sensitivity and counteracts the adverse effects of glucose toxicity resulting from hyperglycemia, ultimately enhancing the effectiveness of insulin and reducing blood sugar levels effectively.

Moreover, metformin significantly suppresses cardiovascular inflammation, offering a valuable means of mitigating inflammation and vascular lesions associated with disrupted glucose metabolism. Our study underscores the effectiveness of combining metformin with insulin aspart in GDM treatment, positively impacting blood sugar control and overall health, and optimizing pregnancy outcomes. Previous research has demonstrated that the use of metformin in combination with insulin in GDM treatment is comparable to insulin alone in terms of pregnancy and neonatal complications, weight gain, and insulin dosage [22]. Additionally, studies by Landi et al. have reported that metformin, when compared to insulin, can reduce the risk of planned cesarean sections, which holds significant implications for gestational-age infants

Table 4. One-way analysis of variance

Factor	Normal pregnancy (n=109)	Adverse pregnancies (n=31)	χ^2-value	*P*-value
Age				
≥30 years old	61	26	7.990	0.005
<30 years old	48	5		
Gestation period				
≥28 weeks	86	23	0.310	0.578
<28 weeks	23	8		
Number of pregnancies				
Primiparous woman	68	20	0.047	0.828
Menstruation	41	11		
Pre-pregnancy BMI				
≥25 kg/m^2	11	20	41.468	<0.001
<25 kg/m^2	98	11		
Educational attainment				
≥ University	61	17	0.012	0.911
< University	48	14		
History of abortion				
Yes	17	7	0.829	0.363
No	92	24		
Treatment plan				
Control group	43	21	7.785	0.005
Observation group	66	10		
FPG (mmol/L)	13.01±1.97	11.17±2.22	4.444	<0.001
FINS (mIU/L)	15.55 (14.20, 16.40)	14.32 (13.40, 15.29)	3.089	0.002
MAGE (mmol/L)	7.54±0.88	7.27±1.08	1.426	0.159
MODD (mmol/L)	5.58±1.11	5.37±0.85	0.973	0.336
mAlb (mg/L)	18.22±1.86	18.59±1.75	-0.998	0.323
CysC (mg/L)	1.64±0.39	1.52±0.42	1.500	0.140
FFA (mmol/L)	1.27±0.11	1.26±0.14	0.376	0.709
NGAL (μg/L)	57.71±4.97	57.90±6.04	-0.179	0.859
IL-6 (ng/L)	2.62±0.55	2.59±0.47	0.240	0.812
TGF-β1 (ng/mL)	315.11±32.79	316.42±32.21	-0.196	0.845
Lp-PLA2 (μg/L)	216.87±13.56	217.59±13.90	-0.258	0.798

Note: BMI, Body Mass Index; FPG, Fasting Plasma Glucose; FINS, Fasting Insulin; MAGE, Mean Amplitude of Glycemic Excursions; MODD, Mean of Daily Differences; mAlb, Microalbumin; CysC, Cystatin C; FFA, Free Fatty Acids; NGAL, Neutrophil Gelatinase-Associated Lipocalin; IL-6, Interleukin 6; TGF-β1, Transforming Growth Factor Beta 1; Lp-PLA2, Lipoprotein-Associated Phospholipase A2.

Table 5. Assignment table

Factor	Assigned value to factor
Age	≥30 years =1, <30 years =0
Pre-pregnancy BMI	≥25 kg/m^2 =1, <25 kg/m^2 =0
Treatment plan	Control group =1, observation group =0
Pre-treatment FPG (mmol/L)	≥12.565 =1, <12.565 =0
Pre-treatment FINS (mIU/L)	≥15.2 =1, <15.2 =0
Adverse pregnancy outcome	Bad ending =1, normal ending =0

Note: BMI, Body Mass Index; FPG, Fasting Plasma Glucose; FINS, Fasting Insulin.

and neonatal hypoglycemia [23]. Notably, combined treatment with metformin and insulin pumps has been shown to significantly reduce blood sugar levels and improve maternal and neonatal outcomes [24]. Further research indicates that metformin treatment is associated with better

Table 6. Independent risk factors for adverse pregnancy outcome

Factor	β	Standard error	Vardø (city in Finnmark, Norway)	Significance	Exp(B)	95% CI
Treatment plan	1.641	0.586	7.843	0.005	5.159	1.636-16.266
Age	1.821	0.685	7.072	0.008	6.181	1.615-23.661
Pre-pregnancy BMI	2.859	0.627	20.756	<0.001	17.441	5.099-59.662
Pre-treatment FPG (mmol/L)	0.215	0.133	2.610	0.106	1.240	0.955-1.609
Pre-treatment FINS (mIU/L)	0.223	0.132	2.845	0.092	1.250	0.964-1.620

Note: BMI, Body Mass Index; FPG, Fasting Plasma Glucose; FINS, Fasting Insulin.

postprandial glucose control, a lower risk of hypoglycemia, reduced maternal weight gain, and lower rates of induced labor and cesarean section [15]. Finally, a systematic review and meta-analysis have found that metformin significantly reduces the risk of gestational hypertension, as well as the occurrence of gestational-age infants, macrosomia, neonatal hypoglycemia, and neonatal ICU admissions [25]. These findings are in alignment with our study, reinforcing the benefit of combined treatment with metformin and insulin aspart in GDM management. However, our study provides a more comprehensive assessment, particularly regarding blood glucose metabolism, renal injury, and the inflammatory response, incorporating markers such as mAlb, CysC, FFA, and NGAL. This comprehensive evaluation contributes to a deeper understanding of GDM treatment.

Adverse pregnancies pose multiple health risks to both mothers and fetuses [26]. They can result in severe complications for pregnant women, jeopardizing their health and even their lives, while also impacting fetal development and the health of newborns [27]. Additionally, adverse pregnancies frequently require cesarean sections, which elevate surgical risk and impose economic and psychological burdens. Hence, the prevention and management of adverse pregnancies are critical for ensuring the well-being of both mothers and infants. Our study has revealed that single-drug treatment, advanced maternal age, and pre-pregnancy obesity are independent risk factors for adverse pregnancy outcomes. This is primarily because the combined treatment group exhibited better outcomes in terms of blood glucose metabolism, renal injury markers, and inflammatory markers when compared to the control group receiving insulin aspart alone. These findings suggest that combined treatment can more effectively manage GDM and its associated complications, reducing the risk of adverse pregnancy outcome [28]. Advanced maternal age and pre-pregnancy obesity are risk factors that independently influence pregnancy outcome. Older pregnant women are more likely to encounter issues such as endometrial ectopia and reduced ovarian function, whereas obese women are at an increased risk of developing metabolic syndrome and experiencing endometrial ectopia [29]. These conditions raise the likelihood of miscarriage, congenital disabilities, and preeclampsia. Furthermore, advanced age and obesity often interact, compounding the adverse effects on pregnancy outcome [30].

However, it is important to acknowledge the limitations of this study. It is a single-center study with relatively small sample size and short observation period. To enhance the credibility of our conclusions, future research should encompass larger sample sizes, longer follow-up duration, and multi-center randomized controlled trials. Furthermore, this study did not record detailed information regarding patients' dietary habits, exercise regimens, and other lifestyle factors, which have the potential to influence the study's outcomes. Subsequent investigations should prioritize the meticulous recording and control of these confounding factors. The long-term safety and effectiveness of the treatment protocol proposed in this study require further verification through prospective cohort studies. By refining the study design, expanding sample sizes, rigorously controlling for confounding variables, and conducting extensive long-term follow-ups, we can enhance the reliability of our conclusions and provide robust guidance for clinical practice.

In summary, metformin combined with insulin aspart in the treatment of GDM can lower blood sugar level, reduce renal injury, and optimize pregnancy outcome.

Disclosure of conflict of interest

None.

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