



## Effect of vitamin D combined with probiotic-assisted insulin pump on glucose-lipid metabolism, intestinal flora and pregnancy outcome in gestational diabetes mellitus

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Abstract:	<p><b>Objective:</b> This study aimed to observe the effect of vitamin D combined with probiotic-assisted insulin pump on glucose-lipid metabolism, intestinal flora and pregnancy outcome in gestational diabetes mellitus (GDM).</p> <p><b>Methods:</b> The study group and the control group were established (75 cases each). Both groups were treated until the delivery of the baby. The glycemic metabolic indices, lipid metabolic indices, improvement of gut microbiota indicators, blood glucose compliance rate, delivery method, and adverse pregnancy outcomes were compared in both groups.</p> <p><b>Results:</b> After treatment, HDL-C, Bifidobacterium and Lactobacillus were increased in both groups (<math>P &lt; 0.05</math>), and FINS, FPG, 2hPG, HbA1c, LDL-C, TC, TG, Coccidioides, Enterobacteriaceae, and Saccharomycetes were all reduced (<math>P &lt; 0.05</math>); and all of them were improved in the study group versus the control group (<math>P &lt; 0.05</math>). The study group exhibited higher blood glucose compliance rate, lower cesarean section rate, and lower overall incidence of adverse pregnancy outcomes versus the control group.</p> <p><b>Conclusion:</b> Vitamin D combined with probiotics assisted insulin pump therapy for GDM can significantly improve the patient's glucose and lipid metabolism levels, maintain intestinal microbiota balance, and reduce adverse pregnancy outcomes.</p>

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**Effect of vitamin D combined with probiotic-assisted insulin pump on glucose-lipid metabolism, intestinal flora and pregnancy outcome in gestational diabetes mellitus**

**Running title:** Combined treatment on GDM

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## Abstract

**Objective:** This study aimed to observe the effect of vitamin D combined with probiotic-assisted insulin pump on glucose-lipid metabolism, intestinal flora and pregnancy outcome in gestational diabetes mellitus (GDM).

**Methods:** The study group and the control group were established (75 cases each). Both groups were treated until the delivery of the baby. The glycemic metabolic indices, lipid metabolic indices, improvement of gut microbiota indicators, blood glucose compliance rate, delivery method, and adverse pregnancy outcomes were compared in both groups.

**Results:** After treatment, HDL-C, Bifidobacterium and Lactobacillus were increased in both groups ( $P < 0.05$ ), and FINS, FPG, 2hPG, HbA1c, LDL-C, TC, TG, Coccidioides, Enterobacteriaceae, and Saccharomycetes were all reduced ( $P < 0.05$ ); and all of them were improved in the study group versus the control group ( $P < 0.05$ ). The study group exhibited higher blood glucose compliance rate, lower cesarean section rate, and lower overall incidence of adverse pregnancy outcomes versus the control group.

**Conclusion:** Vitamin D combined with probiotics assisted insulin pump therapy for GDM can significantly improve the patient's glucose and lipid metabolism levels, maintain intestinal microbiota balance, and reduce adverse pregnancy outcomes.

**Keywords:** Gestational diabetes mellitus; Vitamin D; Probiotics; Insulin pump; Glycolipid metabolism; Intestinal microbiota; Pregnancy outcome

**Clinical trial:** Not applicable

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**Introduction**

Gestational diabetes mellitus (GDM) refers to glucose intolerance that first occurs or is found during pregnancy [1]. GDM is characterized as a transitory form of diabetes mellitus induced by insulin resistance and pancreatic beta-cell dysfunction during pregnancy, and it has been identified as one of the major barriers to improving the health of mothers and infants [2]. GDM imposes a heavy load on patients and is linked with a higher incidence of adverse pregnancy outcomes, such as preeclampsia, prenatal depression, preterm birth, instrumental or surgical delivery, as well as birth trauma [3]. With the global obesity incidence rate reaching epidemic levels, the case of pregnant women diagnosed with GDM is increasing [4]. At present, there is a lack of international consensus on the GDM diagnosis, which reflects its complicated historical evolution and pragmatic considerations of prenatal resources [5].

Vitamin D deficiency is an emerging risk factor for GDM and increases the risk of developing GDM, and the current prevalence of vitamin D-deficient pregnant women not only elevates the risk of developing other pregnancy disorders, but may also enhance the risk of adverse health outcomes for mother and child [6]. Recent vitamin D intervention studies and a meta-analysis of a large number of studies display that vitamin D supplementation during pregnancy may improve maternal, fetal, immediate and later offspring health [7]. . The relations between vitamin D and GDM have been widely investigated, but the results have not been determined because of selection bias, time and method of vitamin D measurement, as well as diagnostic time and criteria of GDM [8]. The most common pharmacologic interventions for GDM are the administration of metformin, probiotics, and vitamin D. Insulin is the drug of choice for the treatment of hyperglycemia in gestational diabetes [1]. Insulin may be added when glycemic goals cannot be achieved with nutritional modifications [9]. As reported, women who used insulin pumps during pregnancy have lower HbA1c, which does not enhance the risk of severe hypoglycemia or diabetes ketoacidosis, and also does not improve other pregnancy outcomes [10]. Although pump therapy is usually the preferred choice for patients and experts, but it has not been proven to be better than injecting

insulin multiple times a day during pregnancy [11]. Probiotics are a relatively new intervention that can lower blood glucose levels, prevent GDM, decrease the resulting maternal and fetal complications by assessing the mother's metabolism, and may have the ability to prevent or control diabetes during pregnancy, but confirmatory studies are still needed. Clinical evidence supports the hypothesis that modulation of the gut microbiota by probiotics may be effective in preventing gestational diabetes [12]. Yet, there is no consensus on the optimal dosage and bacterial load of probiotics, as well as an adequate duration of treatment [13]. Herein, this study aimed to observe the effect of vitamin D combined with probiotic-assisted insulin pump on glucose-lipid metabolism, intestinal flora and pregnancy outcome in GDM.

## Materials and methods

### Ethics statement

The study was under the approval of the Ethic Committee of Women's Hospital of Nanjing Medical University (approval number: 20200108). Written informed consent was acquired from all subjects.

### Basic information

A total of 150 cases of GDM patients who visited Women's Hospital of Nanjing Medical University from May 2020 to May 2022 were recruited as the study subjects, and they were randomized into the study group and the control group (75 cases each). The difference between the general information of the two groups (Table 1) was not statistically significant ( $P > 0.05$ ), and the groups were balanced and comparable.

### Inclusion criteria

(1) The patient met the diagnostic criteria for GDM, i.e., no previous history of diabetes mellitus, gestational age of 24-28 weeks, fasting plasma glucose (FPG)  $\geq 5.1$  mmol/L or 1-h postprandial glucose (1hPG)  $\geq 10.0$  mmol/L or 2-h postprandial glucose (2hPG)  $\geq 8.5$  mmol/L as indicated by a 75-g oral glucose tolerance test (OGTT) [14]; (2) maternal age  $\geq 20$  years; (3) no

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2 treatment in the past month that would affect blood glucose, blood lipid levels, and intestinal flora;  
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4 (4) normal cognitive function and adherence; (5) the patients gave their informed consent and  
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6 agreed to participate.  
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9 **Exclusion criteria**

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11 (1) Patients with other special diseases, such as hepatic and renal dysfunction, neurological or  
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13 psychiatric disorders, coagulation disorders, tumors, immune system deficiencies, heart disease,  
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15 blood disorders, thyroid disorders, metabolic bone disease, etc.; (2) combined with other pregnancy  
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17 complications, such as gestational hypertension, intrahepatic biliary stasis in pregnancy, acute fatty  
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19 liver disease in pregnancy, placenta previa, premature rupture of membranes, placenta praevia, and  
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21 preterm miscarriage; (3) pre-pregnancy diabetes patients; (4) accompanied by acute complications  
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23 of diabetes mellitus, such as ketoacidosis and infections; (5) allergy to the drugs in this experiment;  
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25 (6) combined with infectious diseases.  
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30 **Methods**

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32 All patients were admitted to the hospital to receive diet, nutrition and exercise guidance. In  
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34 the control group, the patients were treated with insulin aspart (produced by Novo Nordisk  
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36 Pharmaceuticals Co., Ltd., No. S20153001, specification: 3 ml: 300 U), and the basal and  
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38 preprandial additional amounts were injected subcutaneously through the catheter by selecting the  
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40 placement point of the catheter in the abdomen, through the IP-101-1 insulin pump (produced by  
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42 Royal Fornia Medical Equipment Co., Ltd.). The initial insulin dose was calculated according to the  
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44 ideal body mass index (BMI) of the pregnant patient, 0.5 U/(kg · d), 40%~50% of the initial amount  
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46 was set as the basal amount, and 50%~60% of the initial amount was set as the preprandial  
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48 high-dose; as well as combined with vitamin D drops [produced by Huaxia National Pharmaceutical  
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50 (Heze) Pharmaceutical Co, Ltd., No. H20193298, specification: 400 U/capsule], which was taken  
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52 orally for treatment, 2 times a day, 1 capsule/time. In the study group, Viable Bifidobacterium  
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54 Tablets (Hangzhou Grand Biologic Pharmaceutical Co., Ltd., No S20060010, 0.5 g/tablet) were  
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56 added on the basis of the control group for oral administration, 3 times/day, 2 tablets/times. Both  
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groups continued treatment until delivery.

### Observation indicators

(1) Blood glucose metabolic indices: before and after treatment, patients were instructed to abstain from drinking and fasting after 21:00 on the previous day, and 5 ml of fasting venous blood was drawn early in the morning of the next day, and centrifuged at 3000 r/min for 10 min. The supernatant was retained to determine glycated hemoglobin (HbA1c) by high-performance liquid chromatography with a fully automated biochemistry analyzer (Myriad, BS-180) (kit from Shanghai Huachen Biological Reagent Co., Ltd.); FPG and 2hPG were determined by glucose oxidase method (kit from Shanghai Jining Industrial Co., Ltd.); and fasting insulin (FINS) was examined by radioimmunoassay (kit from the Isotope Research Institute of the China Institute of Atomic Energy).

(2) Lipid metabolism indices: before and after treatment, blood serum was drawn as above, and serum high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG) levels were assessed by ELISA (reagents from Shanghai mlbio Co., Ltd.), using a full-automatic biochemistry analyzer (Myeri, BS-180).

(3) Intestinal flora: before and after treatment, fresh feces ( $\geq 1$  g) were collected from patients early in the morning and sent for examination within 1 h after being placed in a sterile box. The feces were removed and dissolved in 9 ml of saline at a ratio of 1:9, and then repeatedly diluted to  $10^{-6}$ . The highly diluted samples (0.1 ml) were aspirated in turn and evenly spread on the culture medium. Bifidobacterium and Lactobacillus were cultivated using anaerobic medium and incubated at 37°C for 48 h to observe the results; Coccidioides, Enterobacteriaceae, and Saccharomycetes were cultivated using aerobic medium and incubated at 37°C for 24 h to observe the results. The number of colonies = mean number of colonies  $\times$  dilution  $\times$  10, and the results were expressed as the logarithmic value of colony-forming units per gram of feces.

(4) Blood glucose compliance rate: the blood glucose compliance rate of the two groups of patients after treatment was recorded. According to the fluctuation of blood glucose, the patients

were classified into complete compliance, basic compliance and non-compliance. Complete compliance: blood glucose control was completed within 5 d after the administration of the drug (blood glucose control meant that during the maintenance period of the drug, the patient's random blood glucose was < 11.1 mmol/L, and the FPG was < 6.5 mmol/L), and in the subsequent period of the perioperative period, the blood glucose did not exceed the standard or was too low or the number of abnormalities was less than one time/week. Basic compliance: the patients' blood glucose control was completed within 7 d, and in the subsequent perioperative period, the blood glucose still fluctuated to some extent, but the number of abnormalities was less than 3 times/week. Non-compliance: the patients' blood glucose still did not return to the normal range after 7 d of the treatment or the blood glucose fluctuated drastically after the treatment. Standardization rate = (number of fully achieved cases + number of basically achieved cases)/total number of cases × 100%.

(5) Pregnancy outcomes: the mode of delivery (vaginal delivery, cesarean section) was compared between the two groups, and the occurrence of adverse pregnancy outcomes (preterm delivery, excess amniotic fluid, hypoglycemic children, macrosomic children, malformed children, death or miscarriage, and postpartum hemorrhage, etc.) was recorded.

**Statistical analysis**

Statistical analysis was performed using SPSS 26.0 software. Qualitative data were described by [n (%)], and the  $\chi^2$  test was performed. Normal distribution quantitative data were described by  $\bar{x} \pm s$  and t-test was performed, and skewed distribution quantitative data were described by M (P25, P75) and the Mann-Whitney U test was performed.  $P < 0.05$  was considered a statistically significant difference.

**Results**

**Blood glucose metabolism indicators**

Before treatment, the differences in serum FINS, FPG, 2hPG, and HbA1c between the two

groups were not significant ( $P > 0.05$ ); after treatment, reduced serum FINS, FPG, 2hPG, and HbA1c levels were noted in both groups ( $P < 0.05$ ), and they were all lower in the study group versus the control group ( $P < 0.05$ ; Table 2).

### Lipid metabolism indicators

Before treatment, there exhibited no difference in serum HDL-C, LDL-C, TC, and TG between the two groups ( $P > 0.05$ ); after treatment, increased serum HDL-C and decreased serum LDL-C, TC, and TG were observed in both groups ( $P < 0.05$ ), and the study group showed significant improvement compared to the control group ( $P < 0.05$ ; Table 3).

### Gut microbiota

Before treatment, there presented no difference in various indicators of gut microbiota between the two groups ( $P > 0.05$ ); after treatment, both groups showed an increase in Bifidobacterium and Lactobacillus, and a reduction in Coccidioides, Enterobacteriaceae, and Saccharomycetes ( $P < 0.05$ ). Moreover, the study group showed significant improvement in contrast to the control group ( $P < 0.05$ ; Table 4).

### Blood glucose compliance rates

The blood glucose compliance rate after treatment in the study group (96.00%) was higher than that in the control group (84.00%) ( $P < 0.05$ ; Table 5).

### Pregnancy outcomes

The post-treatment cesarean section rate in the study group (6.67%) was lower versus the control group (18.67%) ( $P < 0.05$ ). There was lower total incidence of adverse pregnancy outcomes after treatment in the study group (14.67%) in comparison to the control group (33.33%) ( $P < 0.05$ ) (Table 6).

## Discussion

GDM has been defined as one of the main obstacles to improving maternal and child health [2]. Lifestyle intervention is an effective frontline prevention strategy for GDM prevention, and it

can also diminish the development of high-risk individuals into GDM. Maintaining good eating and lifestyle habits in the process of pregnancy are of great importance [15]. Herein, this study aimed to observe the effect of vitamin D combined with probiotic-assisted insulin pump on glucose-lipid metabolism, intestinal flora and pregnancy outcome in GDM.

Genetic, environmental and pregnancy-related factors (excessive fat storage, increased secretion of adipokines and cytokines) perform an available role in the pathogenesis of GDM [16]. Vitamin D insufficiency in women during early pregnancy is obviously associated with an increased risk of GDM [17]. Insulin is the first line of treatment for GDM [9], and insulin pump therapy can obtain effective hypoglycemic effects, enhance maternal and infant outcomes, as well as have high safety [18]. Increasing scientific data indicate that vitamin D stimulates insulin secretion and acts an important part in glucose tolerance [19]. Consequently, in the study, we established the control group given vitamin D drops in combination with an insulin pump. Dysbiosis of gut microbiota performs an available part in the development of glucose intolerance in pregnancy [16]. Considering the potential of probiotics in modulating the gut microbiota, naturalization increases intestinal permeability, and probiotics may have the ability to prevent or control diabetes during pregnancy [12], we set up the study group in which added Viable Bifidobacterium Tablets orally on the basis of the control group. The findings demonstrated that reduced serum FINS, FPG, 2hPG, and HbA1c levels, increased serum HDL-C and decreased serum LDL-C, TC, and TG were observed in the study group. Eating probiotics in pregnant women with GDM can markedly control blood sugar and glucose metabolism (and lead to a significant decrease in HOMA-IR), which can also decrease the levels of TC, TG, and even inflammatory markers [16, 20, 21]. Probiotics control local and systemic inflammation by modulating the secretion of pro-inflammatory mediators, thereby diminishing intestinal permeability and enhancing the immune system [12]. Probiotics are a promising tool to diminish the incidence of GDM, as relevant data disclose that they have a positive impact on glycemic control [16]. Some data display that GDM patients have higher bacterial populations of the genera Ruminococcus and Eubacterium, and lower

1 bacterial populations of genera *Bacteroides* and *Parabacteroides*. [16]. In this paper, we observed  
2 that vitamin D combined with probiotic-assisted insulin pumps obviously improved the gut flora  
3 environment in GDM. It has been demonstrated that probiotics prevent GDM by evaluating the  
4 mother's metabolism and may reduce the resulting maternal and fetal complications [12]. In our  
5 study, we found that there was lower total incidence of adverse pregnancy outcomes after treatment  
6 in the study group. Interventions based on probiotics/symbiosis can improve glucose and lipid  
7 metabolism, along with anti-inflammatory and antioxidant abilities in GDM patients, and have  
8 beneficial effects on fetal macrosomia, hyperbilirubinemia, as well as neonatal weight [22].

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11 In summary, we find that vitamin D combined with probiotics assisted insulin pump therapy  
12 for GDM can significantly improve the patient's glucose and lipid metabolism levels, maintain  
13 intestinal microbiota balance, and reduce adverse pregnancy outcomes. The innovation of our  
14 article is the combination of vitamin D, probiotics, and insulin pump therapy, which compensates  
15 for the shortcomings of single drug therapy. We did not calculate the sample size in this study,  
16 which is our shortcoming. In addition, the duration of the intervention may not have been sufficient  
17 to identify any changes resulting from supplementation with multiple nutrients. Consequently,  
18 future studies with longer intervention durations are needed to confirm our findings.  
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**Declaration**

**Conflict of interest**

The authors declare no conflicts of interest directly related to the contents of this article.

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For Peer Review

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**Table 1** Comparison of general information between two groups

Variables	Study group (n = 75)	Control group (n = 75)	<i>P</i>
Age (years)			0.542
20~25	7 (9.33%)	11 (14.67%)	-
26~30	42 (56.00%)	37 (49.33%)	-
31~35	26 (34.67%)	27 (36.00%)	-
Body mass index (kg/m <sup>2</sup> )			0.250
<18.50	2 (2.67%)	6 (8.00%)	-
18.50~24.00	42 (56.00%)	35 (46.67%)	-
>24.00	31 (41.33%)	34 (45.33%)	-
Gravidity (times)			0.623
1	43 (57.33%)	40 (53.33%)	-
2	26 (34.67%)	31 (41.33%)	-
≥ 3	6 (8.00%)	4 (5.33%)	-
Parity			0.739
Primiparous	46 (61.33%)	44 (58.67%)	-
Multiparous	29 (38.67%)	31 (41.33%)	-
Gestational week (week)			0.972
24	30 (40.00%)	33 (44.00%)	-
25	17 (22.67%)	18 (24.00%)	-
26	15 (20.00%)	13 (17.33%)	-
27	9 (12.00%)	8 (10.67%)	-
28	4 (5.33%)	3 (4.00%)	-

**Table 2** Comparison of two groups of blood glucose metabolism indicators

Indicator	Time	Study group (n = 75)	Control group (n = 75)	<i>P</i>
FINS (mU/L)	Before treatment	22.42 ± 5.84	23.03 ± 5.65	0.517
	After treatment	17.19 ± 3.22 <sup>a</sup>	18.66 ± 4.02 <sup>a</sup>	0.014
FPG (mmol/L)	Before treatment	7.68 (6.34, 9.11)	7.54 (6.23, 8.93)	0.566
	After treatment	5.14 (4.31, 6.10) <sup>a</sup>	5.65 (4.71, 6.97) <sup>a</sup>	0.007
2hPG (mmol/L)	Before treatment	11.67 (10.03, 13.42)	11.74 (10.06, 13.52)	0.752
	After treatment	6.21 (5.17, 7.32) <sup>a</sup>	7.32 (6.18, 8.53) <sup>a</sup>	<0.001
HbA1c (%)	Before treatment	6.55 ± 0.74	6.51 ± 0.77	0.44
	After treatment	5.16 ± 0.54 <sup>a</sup>	5.52 ± 0.63 <sup>a</sup>	<0.001

Note: <sup>a</sup>*P* < 0.05 vs. Before treatment.

**Table 3** Comparison of two groups of lipid metabolism indicators

Indicator	Time	Study group (n = 75)	Control group (n = 75)	<i>P</i>
HDL-C (mmol/L)	Before treatment	2.37 ± 0.58	2.30 ± 0.62	0.477
	After treatment	4.49 ± 0.83 <sup>a</sup>	3.67 ± 0.68 <sup>a</sup>	<0.001
LDL-C (mmol/L)	Before treatment	4.54 ± 1.10	4.36 ± 1.15	0.327
	After treatment	3.11 ± 0.89 <sup>a</sup>	3.69 ± 0.93 <sup>a</sup>	<0.001
TC (mmol/L)	Before treatment	5.37 ± 1.21	5.41 ± 1.18	0.838
	After treatment	3.13 ± 1.01 <sup>a</sup>	3.87 ± 1.10 <sup>a</sup>	<0.001
TG (mmol/L)	Before treatment	5.01 ± 1.16	5.12 ± 1.09	0.547
	After treatment	2.95 ± 0.92 <sup>a</sup>	3.75 ± 1.10 <sup>a</sup>	<0.001

Note: <sup>a</sup>*P* < 0.05 vs. Before treatment.

**Table 4** Comparison of two groups of gut microbiota

Indicator	Time	Study group (n = 75)	Control group (n = 75)	<i>P</i>
Bifidobacterium (lgN/g)	Before treatment	7.83 ± 0.65	7.79 ± 0.69	0.718
	After treatment	9.54 ± 0.72 <sup>a</sup>	8.77 ± 0.75 <sup>a</sup>	<0.001
Lactobacillus (lgN/g)	Before treatment	7.28 ± 1.05	7.32 ± 1.01	0.814
	After treatment	8.96 ± 1.22 <sup>a</sup>	8.24 ± 1.17 <sup>a</sup>	<0.001
Coccidioides (lgN/g)	Before treatment	7.20 ± 0.54	7.18 ± 0.51	0.816
	After treatment	6.44 ± 0.46 <sup>a</sup>	6.91 ± 0.55 <sup>a</sup>	<0.001
Enterobacteriaceae (lgN/g)	Before treatment	8.67 ± 0.84	8.70 ± 0.80	0.823
	After treatment	7.01 ± 0.33 <sup>a</sup>	7.79 ± 0.52 <sup>a</sup>	<0.001
Saccharomycetes (lgN/g)	Before treatment	6.27 ± 0.82	6.35 ± 0.78	0.541
	After treatment	4.96 ± 0.60 <sup>a</sup>	5.54 ± 0.66 <sup>a</sup>	<0.001

Note: <sup>a</sup>*P* < 0.05 vs. Before treatment.

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**Table 5** Comparison of blood glucose compliance rates between two groups

Indicator	Study group (n = 75)	Control group (n = 75)	<i>P</i>
Complete compliance	64 (85.33%)	49 (65.33%)	-
Basic compliance	8 (10.67%)	14 (18.67%)	-
Non-compliance	3 (4.00%)	12 (16.00%)	-
Compliance rate	72 (96.00%)	63 (84.00%)	0.014

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**Table 6** Comparison of pregnancy outcomes between two groups

Indicator	Study group (n = 75)	Control group (n = 75)	<i>P</i>
Mode of delivery			0.027
Vaginal delivery	70 (93.33%)	61 (81.33%)	-
Cesarean section	5 (6.67%)	14 (18.67%)	-
Adverse pregnancy outcomes	11 (14.67%)	25 (33.33%)	0.007
Preterm delivery	1 (1.33%)	3 (4.00%)	-
Excess amniotic fluid	3 (4.00%)	7 (9.33%)	-
Postpartum hemorrhage	2 (2.67%)	4 (5.33%)	-
Hypoglycemic children	0 (0.00%)	2 (2.67%)	-
Macrosomic children	2 (2.67%)	3 (4.00%)	-
Malformed children	0 (0.00%)	1 (1.33%)	-
Death or miscarriage	3 (4.00%)	5 (6.67%)	-

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