Adverse effects of gestational diabetes-related risk factors on pregnancy outcomes and intervention measures

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Abstract. This study was designed to investigate the risk factors of gestational diabetes mellitus (GDM), analyze its adverse effects on pregnancy outcomes and propose corresponding interventions. From January 2017 to December 2018, 378 GDM patients (GDM group) awaiting delivery in Weifang People's hospital were selected. At the same time, 200 pregnant women with normal blood glucose (NGT) were randomly selected as the control group. According to general and clinical data, the univariate and multivariate logistic regression analyses were used to screen the risk factors for GDM. The pregnancy outcomes of the two groups were calculated and corresponding intervention measures were proposed to provide a basis for the comprehensive prevention and treatment of gestational diabetes. Multivariate logistic regression analysis showed that age, pre-pregnancy body mass index (BMI), family history of diabetes, 2 h postprandial blood glucose (2hPBG), and glycated hemoglobin (HbA1c) were independent risk factors for GDM (P<0.05). The incidence of dystocia and cesarean section, abnormal amniotic fluid, premature rupture of membranes, and pathological pregnancy in the GDM group were significantly higher than those in the normal control group (P<0.01). The probability of fetal distress, macrosomia, small for date infants, and preterm infants in the GDM group was significantly higher than those in the normal control group (P<0.01). The 2hPBG and HbA1c in the GDM group after the intervention were significantly lower than those before intervention (P<0.05). The age of pregnant women and family history of diabetes play important roles in the presence and progression of GDM. Therefore, pregnant women should pay close attention to the relevant risk factors that trigger GDM, in the screening and prevention of GDM during pregnancy, reduce and prevent the presence of GDM to ensure the safety of mothers and infants.

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Abbreviations: GDM, gestational diabetes mellitus; BMI, body mass index; PCOS, polycystic ovary syndrome; FBG, fasting blood glucose; PBG, postprandial blood glucose; HbA1c, glycated hemoglobin; FINS, fasting insulin; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; TC, cholesterol; LDL-C, low density lipoprotein cholesterol

Key words: gestational diabetes, risk factors, pregnancy outcomes, intervention measures

Introduction

Gestational diabetes mellitus (GDM) refers to any degree of blood glucose intolerance that occurs or being discovered for the first time during pregnancy, regardless of whether this condition persists after delivery or whether glucose-control treatment is needed during pregnancy (1). Gestational diabetes does not include diabetes occurred before pregnancy. According to statistics (2), the incidence of GDM is 3-6%, and it usually occurs after 20-24 weeks of pregnancy. It is a common high-risk metabolic complication. Gestational diabetes increases the risk of adverse pregnancy outcomes (3). Studies have found that GDM patients and their infants also have a significantly increased risk of developing chronic diseases such as diabetes, metabolic syndrome, and cardiovascular disease in the future (4,5). In recent years, with the delay of child-bearing age and changes in dietary habits and lifestyles, the incidence of GDM has increased significantly (6). GDM may cause adverse pregnancy outcomes including miscarriage, premature delivery, intrauterine distress, fetal malformation, intrauterine death, intrauterine infection, macrosomia and hypertension during pregnancy, preeclampsia and polyhydramnios (7). Gestational diabetes may increase the risk of type 2 diabetes in the mother. Gestational diabetes patients would meet a peak period to develop diabetes five years after delivery. The vast majority of gestational diabetes patients can resume normal glucose metabolism after delivery, but there are still 40-50% of them who develop type 2 diabetes 5-10 years

after delivery, and long-term treatment is required (8). In view of the short-term and long-term adverse effects of gestational diabetes on mothers and children, it is of great significance to analyze the risk factors of GDM, give early screening and prevention for pregnant women with high-risk factors, provide intervention guidance to actively control blood sugar in the normal range in order to reduce the incidence of GDM and adverse pregnancy outcomes, so as to prevent or delay the presence of long-term adverse prognosis of mother and child. This study analyzed the risk factors of 378 GDM patients admitted to the hospital from January 2017 to December 2018, analyzed the impact on pregnancy outcomes, and proposed corresponding interventions in order to provide a basis for comprehensive prevention and treatment of GDM.

Subjects and methods

Clinical data. From January 2017 to December 2018, 378 GDM patients awaiting delivery in Weifang People's Hospital (Shandong, China) were selected as the research subjects. At the same time, 200 pregnant women with normal blood glucose (NGT) during the same period were randomly selected as controls. Inclusion criteria: Patients who meet the GDM diagnostic criteria: Fasting blood glucose (FBG) ≥5.1 mmol/l, 1 h blood glucose ≥10.0 mmol/l, 2 h blood glucose ≥8.5 mmol/l. GDM was diagnosed when blood glucose exceeds the diagnostic criteria at any time point; patients who can independently participate in the study; patients with no history of mental illness; patients with complete pregnancy examination data and postpartum follow-up data. Exclusion criteria: Patients with diabetes combined with pregnancy; patients with severe mental disorders; patients combined with severe heart, liver, kidney and autoimmune diseases before pregnancy.

This study was approved by the Ethics Committee of Weifang People's Hospital (sdlunl:20170116), and all pregnant women signed informed consent and were included in the study on a voluntary basis.

Methods

Laboratory indicators. According to the time requirements, 3 ml of elbow vein blood was drawn from each research subject [self-coagulation was used for blood glucose and blood lipid, EDTA-K2 anticoagulation was used for glycated hemoglobin (HbA1c)]. Centrifugation was performed at 2,264 x g for 20 min to separate the upper serum (or plasma). Lipemia or hemolysis were excluded in all specimen. It is completed within 2 h from specimen collection to testing.

Blood glucose and blood lipids were measured using Hitachi 7170S automatic biochemical analyzer (Hitachi, Ltd.); fasting insulin was detected by electrochemical immunoluminescence (Roche Diagnostics); HbA1c was analyzed by G8 HbA1c analyzer (Japan Tosoh Corporation). Oral glucose tolerance test (OGTT): All pregnant women underwent an OGTT at 24-28 weeks of gestation. Examine were fasted for 8-12 h before the test, then venous blood was taken to measure FBG at around 8 am. Patients were asked to drink 300 ml warm water with 75 g anhydrous glucose powder within 5 min, and blood was taken 1 and 2 h later to measure blood glucose. Blood lipids and HbA1c were tested when FBG was tested.

A self-designed questionnaire was used to investigate the general data of pregnant women and clinical laboratory data, including age, pre-pregnancy body mass index (BMI), weight gain during pregnancy, height, family history of diabetes, women's menstrual period, pregnancy times, history of polycystic ovary syndrome (PCOS), history of adverse pregnancy and delivery, history of gestational diabetes, FBG, 1 h postprandial blood glucose (1hPBG), 2 h postprandial blood glucose (2hPBG), HbA1c, fasting insulin level (FINS), triglyceride (TG), cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and pregnancy outcomes. The questionnaires are distributed and collected by trained investigators. The questionnaire's recovery rate and efficiency are both 100%. Pre-pregnancy overweight is defined as pre-pregnancy BMI ≥25 kg/m^2, for giant baby is defined as body mass ≥4 kg.

Intervention measures. Promote health education: Promote community pre-pregnancy health education and publicity, pre-pregnancy counseling and training for women of appropriate age; spread GDM-related knowledge, including the occurrence, progression and harmfulness of GDM; enhance pregnant women's self-care awareness; improve community medical services, including general surveys of blood sugar and weight; improve the health files of pregnant women in the community, and do regular follow-up during pregnancy. Diet intervention: Diet intervention is the primary method of weight control, vigorously advocate a healthy lifestyle, guide rational diet before and during pregnancy to actively control weight. GDM patients are instructed to develop a personalized diet plan. The diet includes carbohydrates 40%, protein 20%, fat 40%, with more whole grains, replacing fruits with vegetables like cucumbers and tomatoes. Foods with a high sugar production index were excluded in the balanced diet. Exercise intervention: Pregnant women were guided to do appropriate physical exercise according to their own situation. Exercise can reduce body weight, reduce insulin resistance, and reasonable exercise can effectively control weight gain during pregnancy. Diet intervention and exercise intervention were implemented in the GDM group, and the levels of blood glucose 2 h after meal (2hPBG) and HbA1c before and after intervention were compared.

Statistical analysis. Data were statistically processed using SPSS 25.0 (IBM Corp). Measurement data were expressed as mean ± standard deviation (SD), Student's t-test was used for comparison between groups; enumeration data were expressed by percentage, and χ^2 test was used for comparison between groups. GDM risk factors were analyzed using logistic regression. Univariate analysis was used for general data and clinical data; multivariate unconditional logistic regression analysis was performed with statistical parameters ($P<0.05$) as independent variables and with GDM as dependent variables. $P<0.05$ was considered statistically significant.

Results

Univariate analysis of GDM risk factors. A univariate analysis of the two groups of data showed that there were differences between the two groups in age, family history of diabetes,

Table I. Univariate analysis of risk factors for GDM [n (%), mean ±SD].

Variables	GDM (n=378)	NGT (n=200)	χ^2/t	P-value
Age n (%), ≥35 years	124 (32.80)	32 (16.00)	χ^2=19.378	<0.001
BMI before pregnancy (kg/m^2)	28.16±1.38	22.78±1.04	t=6.416	0.004
Weight gain during pregnancy (kg)	16.82±1.46	14.51±1.41	t=1.247	0.259
Height (cm)	163.57±2.67	164.98±2.41	t=0.174	0.868
Family history of diabetes n (%)	132 (34.92)	22 (13.00)	χ^2=31.641	<0.001
Menstrual period (d)	3.62±0.97	3.84±0.88	t=0.235	0.786
Gravidity	2.11±0.63	1.91±0.52	t=0.224	0.831
PCOS history n (%)	113 (29.89)	40 (20.00)	χ^2=6.579	0.010
History of adverse pregnancy n (%)	60 (15.87)	22 (11.00)	χ^2=2.551	0.110
GDM history n (%)	162 (42.86)	10 (5.00)	χ^2=87.679	<0.001
FBG (mmol/l)	6.89±1.20	4.52±0.48	t=3.003	0.024
1hPBG (mmol/l)	12.32±1.65	8.29±0.92	t=3.274	0.017
2hPBG (mmol/l)	9.33±1.42	5.01±0.86	t=7.851	<0.001
HbA1c (%)	8.98±0.42	5.56±0.22	t=7.232	<0.001
FINS (mmol/l)	18.43±3.78	11.26±1.82	t=2.697	0.035
TG (mmol/l)	3.08±0.79	1.92±0.63	t=2.612	0.042
TC (mmol/l)	4.97±1.02	3.89±0.98	t=1.015	0.349
HDL-C (mmol/l)	0.92±0.12	1.53±0.15	t=2.967	0.028
LDL (mmol/l)	3.38±0.82	3.36±0.77	t=0.765	0.432

BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; FBG, fasting blood glucose; 1hPBG, 1 h postprandial blood glucose; 2hPBG, 2 h postprandial blood glucose; HbA1c, glycated hemoglobin; FINS, fasting insulin level; TG, triglyceride; TC, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

BMI before pregnancy, GDM history, PCOS history, FBG level FBG, 1hPBG, 2hPBG, HbA1c, FINS, TG, and HDL-C (P<0.05) (Table I).

Multivariate non-conditional logistic regression analysis of risk factors for GDM. Multivariate non-conditional logistic regression analysis was performed using statistically significant (P<0.05) parameter in the single factor analysis as the independent variable and the presence or absence of GDM as the dependent variable. The results showed that age, BMI, history of GDM before pregnancy, family history of diabetes, 2hPBG, and HbA1c were independent risk factors for GDM (Table II).

Comparison of pregnancy outcomes between GDM and control group. GDM has adverse effects on both pregnant and perinatal infants. This study showed that the incidence of maternal dystocia, cesarean section, abnormal amniotic fluid, premature rupture of membranes, and pathological pregnancy in the GDM group were significantly higher than those in the normal control group, and the differences were statistically significant (P<0.01); the probability of fetal distress, macrosomia, small for date children and premature children in the perinatal infants in the GDM group were significantly higher than those in the normal control group, and the difference was statistically significant (P<0.01) (Table III).

Comparison of 2hPBG and HbA1c levels in the GDM group before and after the intervention. The 2hPBG and HbA1c levels in the GDM group after intervention were significantly lower than those before intervention (t=2.842, 2.986, P=0.029, 0.020). The comparison of 2hPBG post-intervention and pre-intervention is shown in Fig. 1. The comparison of HbA1c post- and pre-intervention is shown in Fig. 2.

Discussion

GDM is a hyperglycemia in pregnant women. In recent years, the incidence of GDM has been increasing year by year. The early clinical symptoms of GDM are not typical. Without being promptly screened and early intervention, it will affect not only the health of the mother, but also the health of the infant for a long period of time. Exploring the risk factors of GDM, analyzing the adverse effects on pregnancy outcomes, and proposing corresponding preventive measures are of great significance for reducing the presence and progression of GDM and ensuring the safety of mothers and infants.

Previous studies have shown (9,10) that pre-pregnancy obesity and advanced age are closely related to GDM. The higher the BMI before pregnancy and the older the age of pregnancy, the higher the incidence of GDM. As pregnancy progresses, hormones such as prolactin (HPL) and prolactin (PRL) secreted by the placenta gradually increase, resulting in insulin resistance; in addition, obesity is prone to insulin resistance, and insulin resistance produces and exacerbates obesity, so overweight and obese pregnant women are more likely to develop GDM. Riskin-Mashiah *et al* (11) conducted a statistical analysis of BMI in early pregnancy and found

Table II. Multivariate non-conditional logistic regression analysis of risk factors for GDM.

Items	B	S.E	Wald	P-value	OR	95% CI
Age ≥35 years	0.637	0.179	12.078	<0.001	1.891	1.332-2.686
BMI before pregnancy	1.117	0.307	13.261	<0.001	3.045	1.657-5.571
Family history of diabetes	0.738	0.178	16.927	<0.001	2.093	1.472-2.978
PCOS history	0.363	0.655	3.718	0.054	3.536	0.783-6.928
GDM history	1.005	0.728	14.002	<0.001	5.326	2.315-6.489
FBG	0.491	0.405	1.474	0.225	1.634	0.739-3.613
1hPBG	0.553	0.574	0.861	0.354	0.587	0.190-1.809
2hPBG	0.452	0.188	5.801	0.016	1.572	1.008-2.271
HbA1c	0.678	0.312	12.309	<0.001	2.989	1.621-5.509
FINS	0.179	0.153	1.378	0.241	1.196	0.887-1.614
TG	0.238	0.296	0.649	0.420	1.259	0.711-2.266
HDL	0.104	0.329	0.101	0.751	1.110	0.583-2.115

CI, confidence intervals; BMI, body mass index; PCOS, polycystic ovary syndrome; GDM, gestational diabetes mellitus; FBG, fasting blood glucose; 1hPBG, 1 h postprandial blood glucose; 2hPBG, 2 h postprandial blood glucose; HbA1c, glycated hemoglobin; FINS, fasting insulin level; TG, triglyceride; HDL, high-density lipoprotein.

Table III. Comparison of adverse pregnancy outcomes between the GDM and the control group, n (%).

Groups	Dystocia and cesarean section	Abnormal amniotic fluid	Premature rupture of membranes	Pathological pregnancy	Fetal distress	Macrosomia	Small for date children	Preterm children
GDM (n=378)	170 (44.97)[a]	51 (13.49)[a]	65 (17.20)[a]	105 (27.78)[a]	55 (14.55)[a]	78 (20.63)[a]	34 (8.99)[a]	64 (16.93)[a]
Control (n=200)	58 (29.00)	9 (4.50)	11 (5.50)	12 (6.00)	6 (3.00)	8 (4.00)	5 (2.50)	8 (4.00)
χ^2	13.972	11.368	15.667	38.423	18.485	28.578	8.763	20.056
P-value	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	0.003	<0.001

GDM, gestational diabetes mellitus. [a]P<0.01.

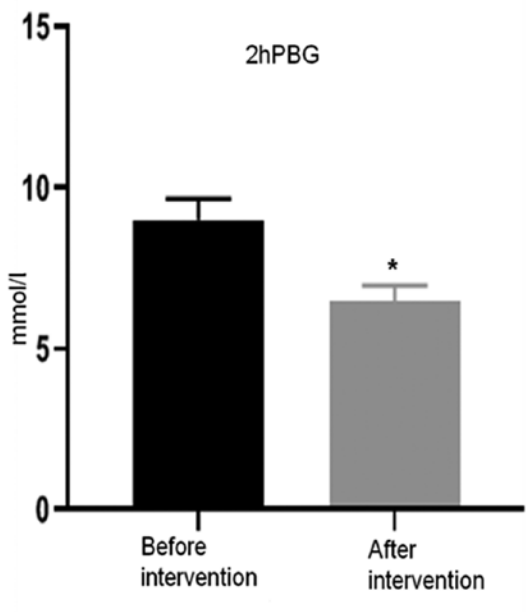

Figure 1. Comparison of 2hPBG before and after the intervention. 2hPBG, 2 h postprandial blood glucose. *P<0.05.

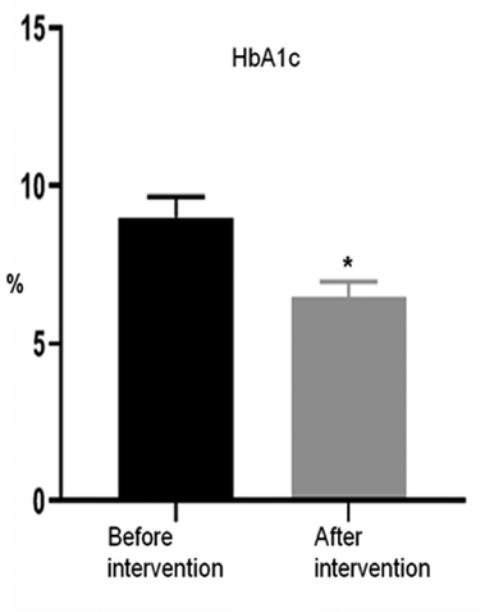

Figure 2. Comparison of HbA1c levels before and after the intervention. HbA1c, glycated hemoglobin. *P<0.05.

that for every 3.5 kg/m^2 increase in BMI in early pregnancy, the risk of GDM increased by 1.5 times. Kim *et al* (12) analyzed the association between BMI and GDM and found that the incidence of GDM in normal body weight pregnant women, overweight pregnant women, obese pregnant women, and severely obese pregnant women increased 2.3, 4.8, 5.5, and 11.5%, respectively, suggesting the association between BMI and GDM before pregnancy. Ogonowski *et al* (13) found through case-control studies that the risk of GDM increases with the increase in BMI before pregnancy. In addition, advanced pregnancy is currently recognized as one of the major risk factors for gestational diabetes. Lao *et al* (14) retrospectively analyzed 15,827 pregnant women from 1998 to 2001 in Hong Kong, China, and concluded that the incidence risk of GDM significantly increases with the age of pregnant women. The results of this study showed that pregnant women aged ≥35 years and being overweight before pregnancy are independent risk factors for the progression of GDM, which is consistent with the above-mentioned report, and their OR values for GDM were 1.891 and 3.045, respectively.

Family history of diabetes plays a very important role in the presence of gestational diabetes. Genetics may be related to susceptibility genes and intrauterine high glucose environment. The incidence of type 2 diabetes in maternal lines of women with gestational diabetes is high. It can be speculated that their mothers have also suffered from gestational diabetes, and their children were in intrauterine high glucose environment when they were embryo. In addition, fetal pancreatic islet β cells and adipocytes are stimulated by hyperglycemia and abnormally proliferate, so it is prone to produce large infant. Those infants are prone to obesity and insulin resistance in adulthood, and prone to GDM after pregnancy (15). Retnakaran *et al* (16) has shown that 38.1% of GDM have a family history of diabetes, which is a 2.9-fold increase in the risk of GDM compared with those without a family history of diabetes. According to a previous study (17), the risk of GDM in people with a previous history of GDM during multiple pregnancies is 13.2 times that of those without a history of GDM, and the risk of GDM in those who have twice previous histories of GDM is 25.9 times that of those without a history of GDM. In addition, the risk of GDM is closely related to the postprandial hyperglycemia and high HbAIc of pregnant women (18). The 2hPBG does not meet the standard, indicating impaired glucose tolerance. HbAIc reflects the level of blood glucose control in the past 2-3 months, and can better reflect the situation of blood glucose control than FBG. There might be insulin resistance in the indirect reaction of long-term OGTT 2 h blood glucose and HbAIc control failure. The results of this study showed that family history of diabetes, GDM, 2hPBG, and HbA1c were independent risk factors for gestational diabetes. The OR values of multi-factor unconditional logistic regression analysis were 2.903, 5.326, 1.527, and 2.989, respectively, indicating that family history of diabetes, GDM, 2hPBG, HbA1c are risk factors for GDM.

The short-term adverse effects of GDM on pregnant women may mainly cause pregnancy-induced hypertension, pre-eclampsia, postpartum hemorrhage, amniotic fluid pollution, premature rupture of membranes; meanwhile, there would be an increase in dystocia, birth injury and cesarean section (19). The long-term impact is mainly a significant increase in the risk of post-natal diabetes. The short-term impact on the fetus is that the continuous high glucose environment in the uterus stimulates the pancreatic β cells of the fetus to secrete insulin, which brings the fetus persistent hyperinsulinemia. Hyperinsulin promotes the increase of fat and protein synthesis, causing excessive growth of the fetus (20), which in turn leads to increased risk of brachial plexus nerve injury and shoulder dystocia (21). At the same time, the incidence of full-term infants, gestational age and premature infants increased, and the perinatal fetal mortality rate increased; the long-term impact is mainly due to the increased risk of obesity and diabetes in adults (22). Women with a history of childbirth have a 2.25 times incidence of GDM when they become pregnant again (23). Obesity can reduce the sensitivity of insulin target organs to insulin and produce insulin resistance. Therefore, women with larger BMI have a higher risk of GDM than healthy women, and the risk of adverse pregnancy outcomes also increases (24,25). The results of this study showed that the incidence of maternal dystocia, cesarean section, abnormal amniotic fluid, premature rupture of membranes, and pathological pregnancy in the GDM group were significantly higher than those in the control group. The probability of fetal distress, huge infants, full-term infants and premature infants in perinatal infants is significantly higher than that in the normal control group, the difference is statistically significant (all $P<0.01$).

Intervention countermeasures: With the increase of gestational age in pregnant women, the hormones that antagonize insulin in the body continue to increase, and the sensitivity to insulin decreases. In order to maintain normal glucose metabolism levels, more insulin secretion is required, and the characteristic of blood sugar metabolism is that blood sugar is more likely to rise after a meal or after a sugar load stimulation. Therefore, it is more difficult to meet the standard for blood glucose after meals. At the same time, long-term hyperglycemia, HbA1c also increases, and the incidence of adverse pregnancy outcomes increases (26), so it is important to actively control postprandial blood glucose. The results of the present study show that after diet intervention and exercise intervention, the blood glucose and HbA1c levels of pregnant women 2 hours after meal were significantly lower than before intervention, which is consistent with literature reports (27). It is necessary for pregnant women who do not meet the blood glucose standards for diet and exercise intervention to receive adjuvant insulin therapy (28). Planned marriage and childbirth age could avoid pregnancy GDM. The government, society and families should encourage early childbirth to minimize the risk of GDM. Family history of diabetes and previous GDM history are non-interventional factors. Patients with such history should take blood sugar screening as soon as possible. Even if the OGTT screening is negative in the early pregnancy, it cannot completely rule out the risk of GDM in the later stage of pregnancy. It is appropriate to select several important GDM high-risk factors for a comprehensive evaluation of pregnant women to assess whether there is a risk of GDM, and then decide whether to conduct repeated OGTT screening of pregnant women, to reduce missed detection rates of GDM (29). The

OGTT screening for pregnant women with 24-28 weeks of pregnancy should be paid more attention to, because during the 24-28 weeks of pregnancy, the levels of hormones (HPL, PRL) secreted by placenta are significantly increased, which can produce insulin resistance against insulin and increase blood sugar. At this time, screening OGTT is conducive to the detection of GDM (21). The early symptoms of GDM are not obvious, and the principle of prevention and treatment is early screening, early diagnosis, and early treatment to improve the prognosis of mothers and infants and avoid the presence of adverse pregnancy outcomes.

In conclusion, the present study comprehensively analyzed the risk factors of gestational diabetes, which is more comprehensive than previous studies, and proposed corresponding intervention countermeasures. In the study, the impact of BMI or age on GDM was reported, and the effects of the family history of diabetes, GDM history, 2hPBG and HbA1c on GDM were discussed.

In the present study, the risk factors of GDM were analyzed. Early screening, early prevention and early intervention can improve the prognosis and outcome of mother and infant, however, long-term follow-up of postpartum mothers and infants is required.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions

WZ conceived the study and drafted the manuscript. JL collected and analyzed the clinical data. QL and WC were responsible for the laboratory indicators. SZ and XS were responsible for the intervention measures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Weifang People's hospital (Shandong, China) (sdlunl:20170116), and all pregnant women signed informed consent and were included in the study on a voluntary basis.

Patient consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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