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ORIGINAL ARTICLE

Potential Biomarkers in Early Pregnancy for Predicting Gestational Diabetes Mellitus and Adverse Pregnancy Outcomes

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SUMMARY

Background: **Gestational diabetes mellitus (GDM) is typically diagnosed based on a 75-g oral glucose tolerance test conducted at 24 - 28 weeks of pregnancy. A method for earlier diagnosis is needed. The present study aimed to identify one or more blood biomarkers detected within the first trimester that can predict the occurrence of GDM and pregnancy outcome.**
Methods: **This retrospective study included 2,116 pregnant women who underwent examination and delivery in our hospital between January 2018 and December 2019. The predictive value of various clinical measurements in early pregnancy for predicting GDM and pregnancy outcome was analyzed.**
Results: **The fasting plasma glucose (FPG), vitamin A, vitamin E, glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), uric acid, free thyroxine (FT3), anti-peroxidase antibody (TPOAb), and ferritin levels differed significantly between the GDM and non-GDM groups (all $p < 0.05$). The area under the receiver operating characteristic curve for FPG in GDM diagnosis was 0.766 (95% confidence interval [CI] 0.717 - 0.814, $p < 0.001$). The odds ratios (ORs) for FPG and TG for GDM prediction were 1.318 (95% CI 1.228 - 1.416) and 2.050 (95% CI 1.203 - 3.493), respectively. The ORs for FPG, vitamin A, and vitamin E for pregnancy outcome prediction were 1.214 (95% CI 1.123 - 1.268), 0.717 (95% CI 0.601 - 0.886), and 0.852 (95% CI 0.761 - 0.954), respectively.**
Conclusions: **Screening of blood biomarkers in early pregnancy may be useful for predicting, and thus preventing, GDM and adverse pregnancy outcomes. Immediate intervention is recommended if an elevated FPG (> 4.7 mmol/L) or TG (> 1.83 mmol/L) level is detected in early pregnancy, and vitamin A, vitamin E, and FT3 levels need to be maintained within normal ranges throughout pregnancy.**
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INTRODUCTION

Gestational diabetes mellitus (GDM) encompasses varying degrees of abnormal glucose metabolism occurring or first discovered during pregnancy [1,2]. While some cases convert to type 2 diabetes mellitus after pregnancy, for most patients GDM is a pregnancy-specific disease that disappears with the end of pregnan-

cy. GDM is a very serious condition for both pregnant women and their offspring and increases the risks of complications such as large-for-gestational-age infants, stillbirth, pre-term birth, neonatal shoulder dystocia, need for caesarean section, and neonatal hypoglycemia [3]. Studies have shown that adverse maternal and infant outcomes are directly and linearly correlated with maternal hyperglycemia [4]. With long-term hyperglycemia, higher levels of glucose pass through the placenta into the fetal circulation, which causes the blood glucose level of the fetus to be higher than normal. The abnormal glucose elevation stimulates the fetal pancreas to release more insulin, resulting in overgrowth of the fetus, one of the most common complications of GDM [5,6].

The best method for screening and diagnosis of GDM remains controversial [7]. GDM screening includes one-step and two-step methods. With the two-step method, pregnant women receive a 50 g 1-hour glucose challenge test (GCT) at 24 - 28 weeks gestation. If the patient's glucose level is greater than 7.8 mmol/L on this test, then a 75-g oral glucose tolerance test (OGTT) is administered. The one-step method is relatively simpler and more convenient, with pregnant women receiving only the OGTT at 24 - 28 weeks gestation. Both methods have distinct advantages, and at present, there is no consensus on which method is best.

The National Institute for Health and Care Excellence (NICE) guidelines state that GDM can be diagnosed if the fasting blood glucose level is > 5.6 mmol/L or the 2-hour post-OGTT glucose level is > 7.8 mmol/L. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel recommended a lower fasting glucose level of > 5.1 mmol/L, a 1-hour post-OGTT glucose level of > 10.0 mmol/L, or a 2-hours value of 8.5 mmol/L for the diagnosis of GDM. These IADPSG diagnostic criteria have now been adopted by the World Health Organization (WHO), the American Diabetes Association (ADA), the International Diabetes Federation (IDF), and the International Federation of Gynecology and Obstetrics (FIGO).

Since the change in China's second-child policy in 2015, tens of thousands of families have chosen to have a second child. Inevitably, the overall age of women during their second pregnancy is higher than that during their first pregnancy, and thus, the incidence of GDM has increased. GDM is a complex disease related to many factors. The known risk factors for the development of GDM include maternal age > 25 years, maternal body mass index (BMI) > 30 kg/m^2, a history of GDM or large-for-gestational-age/macrosomic infant in previous pregnancy, a history of impaired glucose tolerance, multiple pregnancy, ethnicity with a high diabetes prevalence, a family history of type 2 diabetes (particularly 1st degree relative), polycystic ovary syndrome (PCOS), subfertility or conception using assisted reproductive technologies, prolonged glucocorticoid exposure, etc. [8].

Several studies show that metabolism of lipid during gestation might play a significant role in the etiology and development of GDM [9], and it is established that changes in blood lipids can occur throughout the entire pregnancy. Similarly, other biomarkers such as liver function markers, kidney function markers, vitamin A, vitamin D, vitamin E, and hemoglobin may also be altered during pregnancy, to varying degrees during different stages of pregnancy [10-13].

The existing guidelines (e.g., IADPSG diagnostic criteria for GDM) provide recommendations for the diagnosis of GDM during the second and third trimesters of pregnancy. However, many pregnant women may experience GDM before this time, and controversy persists regarding the stage of pregnancy at which stage GDM is best diagnosed [1,14]. To provide a potential means of predicting or diagnosing GDM earlier in pregnancy, we investigated whether one or more blood biomarkers measured during the first trimester correlated significantly with the development of GDM and pregnancy outcomes.

MATERIALS AND METHODS

Patients and methods

This observational retrospective cohort study included pregnant women who attended routine antenatal visits and delivered in Tsinghua University First Hospital, an 800-bed tertiary care hospital in Beijing, between January 2018 and December 2019. All women underwent a complete blood biomarker test in the first trimester and an OGTT between 24 and 28 weeks of pregnancy. The study group included 326 women diagnosed with GDM and was compared to a control group of 1,790 women who delivered during the same gestational age period but without known GDM. By consulting the examination records of the early obstetrics clinical examinations and the case records from the time of delivery, we obtained each patient's age, previous medical history, BMI, gestational age at delivery, birth weight of the newborn, Apgar score of the newborn, and admission to the neonatal intensive care unit (NICU) after birth, and other details. We recorded the specific values of the studied biomarkers from the laboratory information system. This study was approved by the institutional review board (IRB) of Beijng Huaxin Hospital First Hospital of Tsinghua University, and the requirement of informed consent was waived for this retrospective study by the IRB.

Inclusion and exclusion criteria

The pregnant women were included in this retrospective study according to the following inclusion criteria: available records for routine blood tests for liver function, kidney function, thyroid function, ferritin, vitamin A, vitamin D, vitamin E, fasting plasma glucose (FPG), and blood cell analysis before 12 weeks of gestation, available results for an OGTT performed within 24 - 28 weeks of pregnancy, and delivery within our hospital.

The pregnant women were excluded from this retrospective study according to the following exclusion criteria: GDM in a previous pregnancy, obvious type 2 diabetes mellitus (FPG > 7.0 mmol/L), high blood pressure, multiple pregnancy, hypertension, history of alcoholism, hypothyroidism, PCOS, liver or kidney failure (which can affect glucose metabolism), active termination of pregnancy, and pregnancy with a fetus or newborn having confirmed chromosomal and/or structural congenital anomalies.

Diagnostic criteria

We adopted the IADPSG diagnostic criteria for GDM based on a FPG level > 5.6 mmol/L, or a 2-hour post-OGTT glucose level > 7.8 mmol/L. The defined adverse pregnancy outcomes in this study included: diagnosis of intrahepatic cholestasis of pregnancy (IPC), thyroid disease, intrauterine growth restriction, fetal distress, premature delivery, dystocia, stillbirth, and abnormal amniotic fluid (overseas) during delivery (too much, too little, or pollution of degree II and above), macrosomic infant, low birth weight infant, postpartum hemorrhage, placental membrane-related problems, and neonatal admission to NICU after birth.

Blood analysis and blood biomarker measurement in the first trimester

Commercially available reagents were used for analysis of blood biomarkers, including detection of glucose by the hexokinase method; measurement of total cholesterol (TC), triglycerides (TG), creatinine (Cre), urea, uric acid (UA), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) by enzymatic methods; measurement of vitamin A, vitamin D, vitamin E, thyroid-stimulating hormone (TSH), free thyroxine (FT4), ferritin, free thyroxine (FT3), and anti-peroxidase antibody (TPOAb) by electrochemiluminescence (ECL) assay; and detection of glycosylated hemoglobin (HbA1c) by high-performance liquid chromatography (HPLC). The HbA1c reagent was purchased from Bio-Rad, and the other reagents were purchased from Roche Diagnostics.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences (SPSS), Version 19.0 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA). Continuous and normally distributed variables were described as mean and standard deviation (SD) values and analyzed by independent samples *t*-test. Categorical variables were described as proportions and examined with the chi-squared test. Multiple logistic regression models were used to explore the association of biomarkers in early pregnancy and the risk of GDM and adverse pregnancy outcomes. If inclusion of a factors led to a change of more than 10%, the final model retained the potential confounding factor. Adjusted odds ratios (ORs) and 95% confidence interval (CIs) were reported together. Statistical significance was defined by a p-value < 0.05, and all tests were two-tailed.

RESULTS

Baseline characteristics and pregnancy outcomes among the study cohort

From January 1, 2018 to December 31, 2019, a total of 3,542 women underwent early pregnancy related examinations in the obstetric clinic. Of these, 1,426 women were excluded from the study, including 651 women with incomplete data, 651 women did not give birth in our hospital, 329 women with thyroid disease, 58 women with obvious type 2 diabetes mellitus, and 34 women with multiple pregnancy. The other 2,116 women underwent routine examinations during pregnancy and delivered without complication in our hospital. Among them, 326 cases formed the GDM group and 1,790 cases formed the control non-GDM group (Figure 1). The baseline data and pregnancy outcomes for the patients in each group are presented in Tables 1 and 2.

Comparison of biomarker levels in the first trimester of pregnancy between the GDM and non-GDM groups

Analysis of the levels of biomarkers in the first trimester of pregnancy showed no significant differences in the levels of vitamin D, Cre, urea, ALT, AST, TSH, and FT4 between the GDM and non-GDM group (all $p > 0.05$). However, the levels of FPG, vitamin A, vitamin E, HbA1c, TC, TG, UA, FT3, TPOAb, and ferritin were significantly different between the GDM and non-GDM groups (all $p < 0.05$, Figure 2). We selected FPG and TG for further receiver operating characteristic (ROC) curve analysis of their predictive value for GDM (Figure 2k). The mean concentrations of FPG and TG in the GDM group were 4.7 ± 0.32 mmol/L and 1.83 ± 0.41 mmol/L, respectively. The area under the ROC curve (AUC) values for GDM prediction based on FPG and TG were 0.766 (95% CI 0.717 - 0.814, $p < 0.001$) and 0.622 (95% CI 0.570 - 0.675, $p < 0.001$), respectively. The cutoff value for FPG was 4.7 mmol/L based on the Youden index, with sensitivity and specificity values of 75.9% and 69.2%, respectively. The cutoff value for TG was 1.83 mmol/L based on the Youden index, with sensitivity and specificity values of 69.8% and 76.5%, respectively.

FPG (mmol/dL) and TG were found to be the better indicators among the tested biomarkers, and elevated FPG and TG levels were also identified as independent risk factors for GDM (Table 3).

Biomarkers in early pregnancy with the potential to predict pregnancy outcomes

With adjustment for potential confounding factors, we investigated which early pregnancy biomarkers correlated significantly with adverse pregnancy outcomes. FPG, vitamin A, vitamin E, and UA showed significant correlations with adverse pregnancy outcomes (Table 4).

Table 1. Baseline characteristics of pregnant women with or without GDM.

Parameter	GDM (n = 324)	Non-GDM (n = 1,790)
Baseline characteristics		
Maternal age, years *	31.2 ± 4.3	31.0 ± 4.0
Weight before delivery, kg	69.7 ± 11.8	66.8 ± 13.2
Weight gain during pregnancy, kg *	13.3 ± 5.0	13.6 ± 4.4
Gravidity	2.27 ± 1.26	2.15 ± 1.06
Gestational age at delivery, weeks	38.8 ± 1.3	39.5 ± 1.5
Family history of diabetes *	4 (1.3)	18 (1.0)
Diabetes history, %	5 (1.5)	14 (0.8)
Systolic blood pressure, mmHg *	117 ± 13	117 ± 12
Diastolic blood pressure, mmHg *	74 ± 10	74 ± 9
Smoking status yes, % *	5 (1.5)	24 (1.3)
75-g OGTT, mmol/L		
Fasting	5.01 ± 0.45	4.47 ± 0.36
1 hour	9.73 ± 1.67	7.67 ± 1.43
2 hours	8.23 ± 1.50	6.52 ± 1.13
Mode of delivery		
Spontaneous vaginal delivery	131 (40.3)	831 (46.4)
Operative vaginal delivery	34 (10.4)	145 (8.2)
Cesarean delivery	161 (49.3)	814 (45.4)
Indication for cesarean delivery		
Previous cesarean delivery *	55 (34.2)	287 (35.3)
Breech *	19 (11.8)	92 (11.3)
Fetal distress *	17 (10.6)	57 (7.0)
Scar uterus *	51 (31.6)	264 (32.4)
Abortion failure	10 (6.2)	69 (8.5)
Others *	9 (5.6)	45 (5.5)
Postpartum hemorrhage *	61 (18.7)	345 (19.3)

Data are mean ± standard deviation or n/total (%). * - $p < 0.05$ between groups.

DISCUSSION

With the adjustment of China's second-child policy in recent years, more and more Chinese women have been giving birth to second children. Of course, close attention is paid to health management during pregnancy, but the improvement of living standards has also brought about a series of negative factors for pregnancy, such as unhealthy diet and sleep habits, unhealthy living environments, etc. Previous research has clearly established maternal age as a risk factor for GDM [15,16]. In our study, the average age of the GDM group was 31.2 ± 4.3 years vs. 31.0 ± 4.0 years for the non-GDM group, with no significant difference between the groups. A possible reason is that none of the patients in our study population was older than 40 years. In both the GDM and non-GDM groups, the vast majority of women were giving birth before the age of 35 years. This tells us that age is a small factor in our research, and we should pay more attention to other factors that may reflect the risk of GDM.

Some studies have shown that weight or weight gain during pregnancy is highly correlated with GDM [17, 18]. Perhaps for this reason, some scholars have proposed that controlling weight gain during pregnancy can effectively reduce the occurrence of GDM. The pathogenesis of diabetes remains relatively unclear. It is generally acknowledged that diabetes is a disease related to inflammation and autoimmunity [19,20]. Some scholars classify obesity as an inflammatory disease, leading to the consideration of obesity as a risk factor for GDM [21]. Although BMI is one measurement of obesity, we

Table 2. Pregnancy outcomes among women with or without GDM.

Parameter	GDM (n = 324)	Non-GDM (n = 1,790)
Ante-partum fetal death *	1 (0.3)	2 (0.1)
Intra-partum fetal death *	0 (0)	0 (0)
Perinatal death *	0 (0)	0 (0)
Birth weight, g *	3,401 ± 428	3,379 ± 434
Birth height, cm *	49.9 ± 3.3	50.3 ± 3.1
Male *	157 (48.2)	889 (49.7)
Apgar score		
1 minute post-partum *	9.87 ± 0.47	9.85 ± 0.52
5 minutes post-partum *	9.96 ± 0.21	9.96 ± 0.25
10 minutes post-partum *	9.97 ± 0.19	9.94 ± 0.07
pH < 7.05 *	1 (0.3)	1 (0.1)
Admission to NICU *	36 (11.0)	188 (10.5)
Reasons for admission to NICU		
Asphyxia	1 (2.8)	21 (11.2)
Intraventricular hemorrhage	5 (13.9)	10 (5.3)
Jaundice *	13 (36.1)	74 (39.4)
Respiratory distress syndrome	3 (8.3)	10 (5.3)
Hypoglycemia *	2 (5.6)	10 (5.3)
Sepsis	1 (2.8)	10 (5.3)
Others *	11 (30.5)	53 (28.2)

Data are mean ± standard deviation or n/total (%). * - p < 0.05 between groups.

Table 3. Odds ratios for the ability of early pregnancy biomarkers to predict GDM.

Biomarkers	OR (95% CI)	p
FPG, mmol/dL	1.318 (1.228 - 1.416)	< 0.001
Vitamin A, mg/L	2.243 (0.228 - 3.169)	0.647
Vitamin E, mg/L	0.991 (0.899 - 1.093)	0.860
HbAlc, %	0.953 (0.378 - 2.430)	0.919
FT3, pmol/L	0.385 (0.203 - 0.727)	0.003
TPOAb, U/mL	0.995 (0.991 - 0.999)	0.018
TC, mmol/L	1.233 (0.755 - 2.011)	0.402
TG, mmol/L	2.050 (1.203 - 3.493)	0.008
UA, µmol/L	1.010 (1.003 - 1.018)	0.005
Ferritin, ng/mL	1.003 (0.997 - 1.009)	0.296

phenomenon unique to patients with GDM. It appears that more women are not following the guidance of obstetricians and gynecologists to control their weight, and a more casual diet and less exercise are likely common causes of this phenomenon. At the same time, the excessively fast pace of life and work has caused women to have less free time during pregnancy, limiting the available time for exercise. Of course, the degree of weight gain during different periods of pregnancy varies, and it is possible that a statistical analysis of

Table 4. Odds ratios for the ability of early pregnancy biomarkers to predict adverse pregnancy outcomes.

Biomarkers	OR (95% CI)	p
FPG, mmol/dL	1.214 (1.123 - 1.268)	< 0.001
Vitamin A, mg/L	0.717 (0.601 - 0.886)	0.037
Vitamin E, mg/L	0.852 (0.761 - 0.954)	0.005
HbAlc, %	0.775 (0.305 - 1.965)	0.591
FT3, pmol/L	1.354 (0.673 - 2.723)	0.396
TPOAb, U/mL	0.993 (0.986 - 1.001)	0.084
TC, mmol/L	1.223 (0.717 - 2.086)	0.461
TG, mmol/L	1.051 (0.520 - 2.127)	0.889
UA, µmol/L	1.010 (1.004 - 1.016)	0.002
Ferritin, ng/mL	0.998 (0.992 - 1.004)	0.530

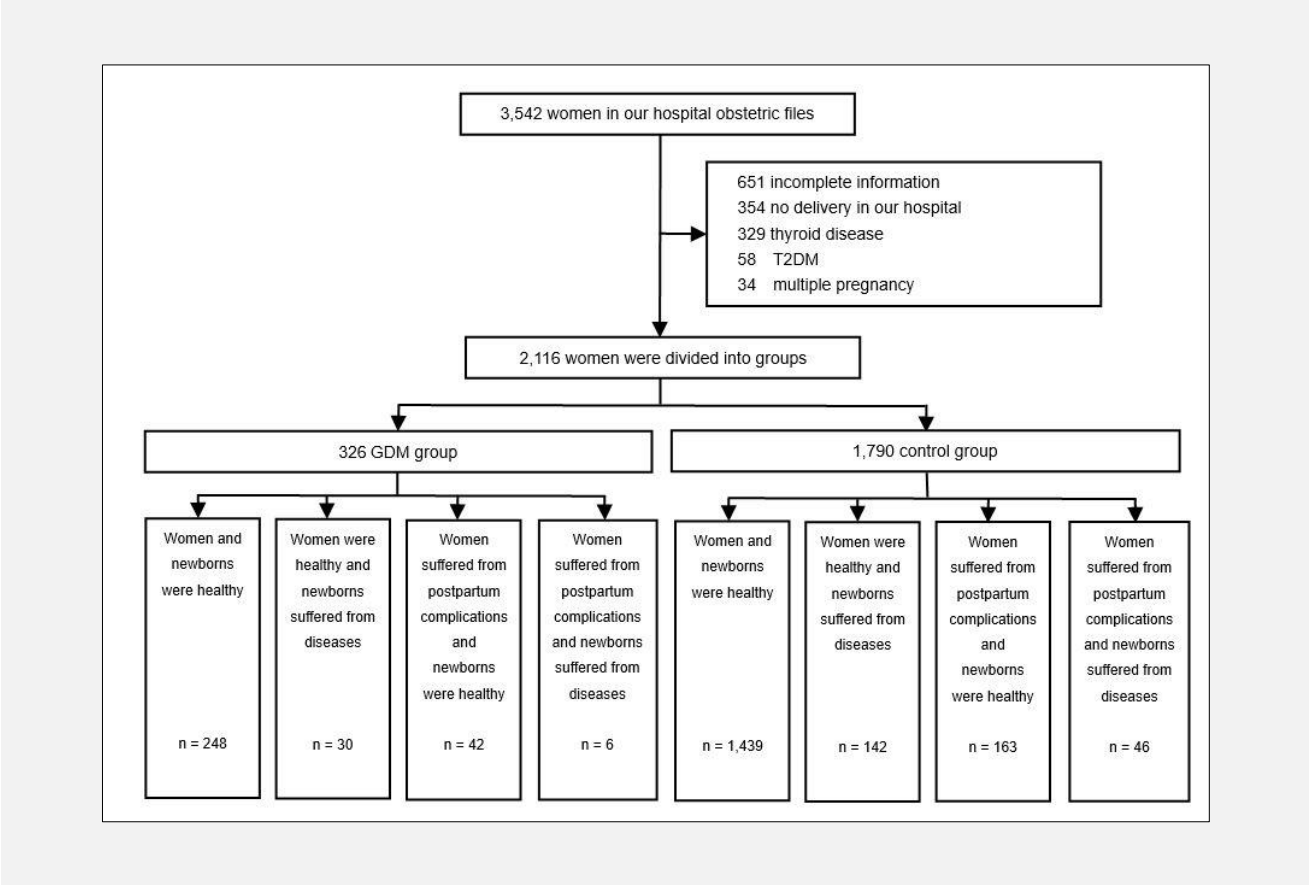

Figure 1. Flow diagram of the present study.

weight gain during different periods could provide more useful information. However, the present retrospective study was based on case records, and thus, weight gain could not be analyzed to this degree. Therefore, the effect of weight gain during pregnancy on the occurrence of GDM needs to be determined by prospective studies. Diabetes is a metabolic disease characterized by abnormal glucose metabolism in the body and abnormally el-

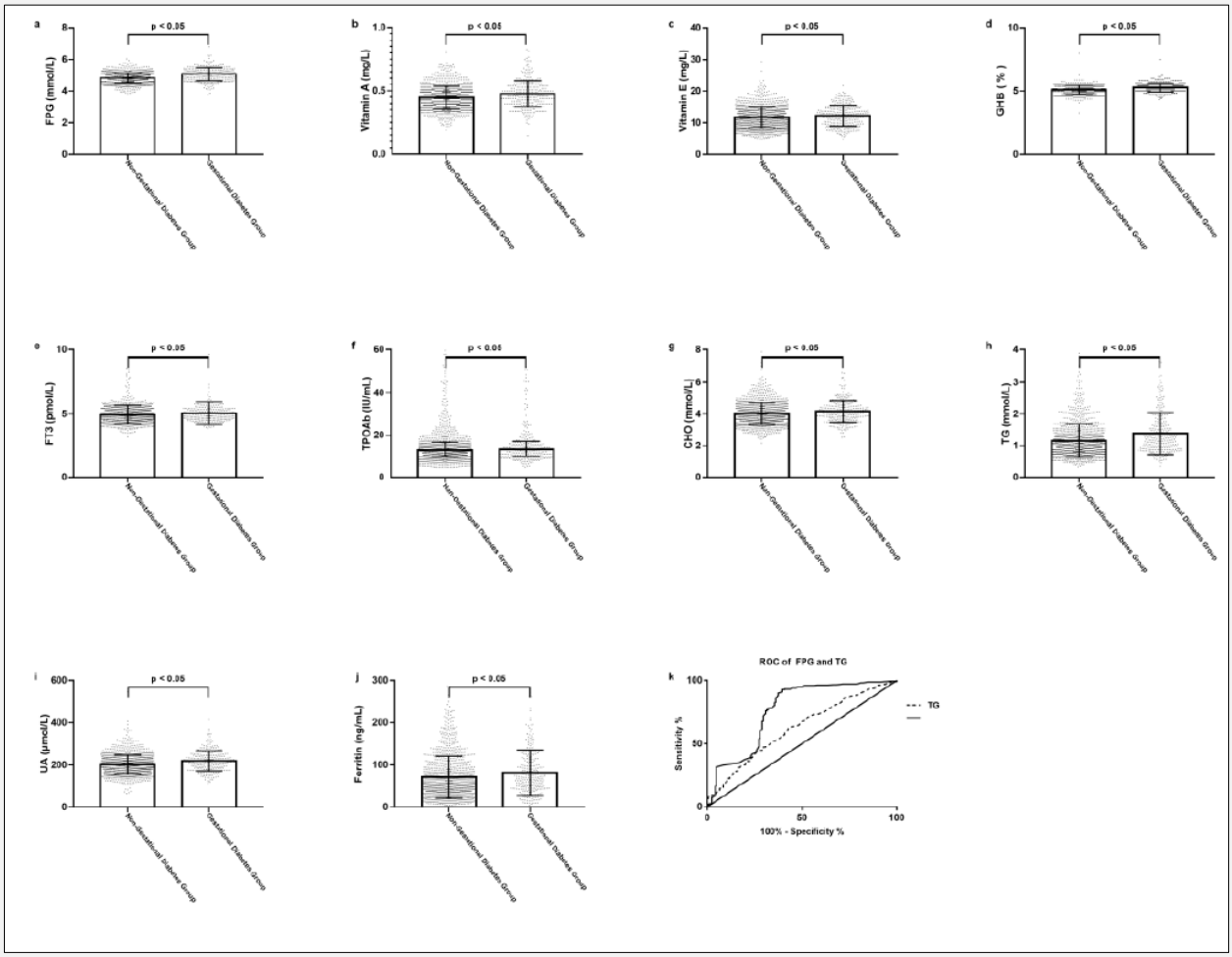

Figure 2. a - j. Comparisons of biomarker levels between the GDM and non-GDM groups, and (k) ROC curve analysis of the predictive value of FPG and TG

Linear regression analysis was performed to identify biomarkers in early pregnancy that can accurately predict GDM in the second and third trimesters of pregnancy, after adjustment for possible confounding factors (e.g., age, doctors, eating habits, etc.).

evated blood glucose levels. It is often associated with abnormal lipid metabolism and insulin resistance. Diabetes also affects the small blood vessels and nerves of the body, resulting in abnormal development of small blood vessels, inner nerve paresthesia, etc. [22]. During pregnancy, the body's blood lipid levels show physiological increases in order to maintain a normal pregnancy. A previous study [22] reported that the increases in blood lipids during pregnancy mainly involved TC and TG, with the increase in TG possibly being greater, which is consistent with our research results. We observed that FPG and TG in the first trimester differed significantly between the GDM and non-GDM groups. Although according to the existing diagnostic guidelines, which provide no diagnostic standard for FPG in early pregnancy, our results indicate that if the FPG of a pregnant woman in the first trimester is between 4.7 and 5.1 mmol/L, careful attention should be paid to this situation. A FPG level in this range does not correspond to a diagnosis of GDM in these pregnant women, but may predict the later occurrence of GDM. We observed a significant difference in TG levels between the GDM and non-GDM groups in the first trimester also. Our research showed that higher values of FPG and TG are independent risk factors for GDM and adverse pregnancy outcomes. GDM is not a sudden disease, but rather a chronic cumulative disease. Pregnant women with GDM may have abnormal blood sugar and blood lipid

levels in the first trimester, although the degree of such changes may be very small. If elevated FPG and TG levels are detected during this period, close attention should be paid to determine whether intervention is appropriated, with the goal of reducing the occurrence of GDM and adverse pregnancy outcomes.

According to the recognized diagnostic criteria, hypothyroidism diagnosis depends on laboratory examinations. Even when no clinical manifestation is observed, when a TSH level between 2.5 - 10.0 mlU/L in early pregnancy or 3.0 - 10.0 mlU/L in middle and late pregnancy is measured in combination with a reduced FT4 level or a TSH level > 10.0 mlU/L is observed independent of the FT4 level, a diagnosis of hypothyroidism in pregnancy can be made [23]. Pregnant women with hypothyroidism are more likely to suffer from abortion, anemia, pregnancy-induced hypertension, placental abruption, postpartum hemorrhage, and other obstetric complications. Untreated hypothyroidism during pregnancy can increase the risk of premature delivery, low birth weight, neonatal respiratory distress syndrome, and embryonic or perinatal death [24]. More attention is given to TSH and FT4 than to FT3 in the monitoring of hypothyroidism. In our study, no significant differences in TSH and FT4 concentrations were observed between the GDM and non-GDM groups, and women with a relatively high FT3 appeared to have a lower risk of GDM. FT3 is mainly produced by deiodination of thyroxine (T4), and a decrease in the amount of T4 will inevitably lead to a decrease in the amount of FT3. However, the FT4 levels of the women were in the normal range, and the phenomenon of reduced FT3 levels in this context warrants close attention. Clinicians need to monitor laboratory indicators of thyroid function in the first trimester to avoid the possibility of GDM caused by reduced FT3. At the same time, FT3 cannot be increased indefinitely, as excessive FT3 will cause hypothyroidism. Therefore, in the first trimester, FT3 should be carefully monitored and managed.

Both vitamin A and vitamin E have anti-oxidative effects. During the embryonic developmental process, vitamin A and vitamin E play a promoting role. During the complete pregnancy process, pregnant women need to ensure that they have enough vitamin A and vitamin E to support the normal development of an embryo. Deficiency in vitamin A and vitamin E can lead to impaired fetal development or fetal malformations [25]. In our study, we found that the levels of vitamin A and vitamin E in the first trimester were independent predictors of adverse pregnancy outcomes, with an inverse relationship between these levels and adverse outcomes. Accordingly, dietary supplementation with adequate amounts of vitamin A and vitamin E during pregnancy is likely beneficial to pregnant women and fetuses. To avoid related side effects though, it is necessary to supplement vitamin A and vitamin E reasonably during pregnancy and to monitor the levels of these vitamins via regular blood testing.

There are some limitations to the present study. First, the retrospective design does not allow for the collection of data on important covariates, such as nutritional status. We cannot yet determine whether the monitoring of the indicators observed will improve the incidence of GDM and pregnancy outcomes. Prospective studies are needed to overcome this limitation. Second, we do not know what types of health products or drugs the pregnant women took during the observed pregnancies, and thus, we cannot assess their potential impacts on our results. Third, our study was a single-center study, and the results may not be universally applicable. Finally, the clinical situation of the newborns was assessed by reading the clinical case records, and it is possible that some case records were inaccurate or incomplete.

CONCLUSION

In conclusion, screening of blood biomarkers in early pregnancy may be beneficial for reducing the occurrence of GDM and adverse pregnancy outcomes. For women in whom a slight increase in FPG (> 4.7 mmol/L) or TG (> 1.83 mmol/L) is detected in early pregnancy, immediate intervention is advisable. FPG and TG levels in early pregnancy were found to be potentially valuable indicators of later GDM. Additionally, our results indicate that vitamin A, vitamin E, and FT3 levels need to be maintained within reasonable ranges throughout pregnancy. An abnormal level of any of these indicators could increase the risk of GDM or adverse pregnancy outcomes.

Declaration of Interest:
The authors declare that they have no competing interests.

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