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Correlation between serum D-dimer andrisk of gestational diabetes mellitus

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This study has been carried out to investigate the correlation between serum D-dimer and the risk of gestational diabetes mellitus (GDM). A total of 308 pregnant women treated in our hospital from January 2018 to January 2020 were retrospectively analyzed. According to the diagnostic criteria for GDM, they were divided into normal blood glucose group (n=145) and GDM group (n=163). The level of serum D-dimer was measured by enzyme-linked immunosorbent assay at 5-12, 13-23, 24-28 and 29-37 weeks of pregnancy. The pregnant women who did not have GDM at 5-12 and 13-23 weeks of pregnancy but were diagnosed with GDM at and after 24 weeks of pregnancy were assigned to GDM-A group (n=18) and GDM-B group (n=26), respectively. The related factors affecting the occurrence of GDM was analyzed by multivariate logistic regression. The optimal threshold of D-dimer for the occurrence of GDM was predicted *via* receiver operating characteristic (ROC) curve. The level of serum D-dimer in GDM group was significantly higher than that in normal blood glucose group at 5-12, 13-23 and 24-28 weeks of pregnancy (P<0.05). The level of serum D-dimer at 24-28 weeks of pregnancy was negatively correlated with OGTT 0-min insulin (r=-0.756, P<0.05) and HOMA-IR (r=-0.693, P<0.05), but positively correlated with LDL-C (r=0.759, P<0.05). After adjustment of confounding factors such as pregnancy age, pre-pregnancy body mass index, *Acanthosis nigricans* and triglyceride, the level of serum D-dimer at 13-23 weeks of pregnancy was still an independent risk factor for the occurrence of GDM at and after 24 weeks of pregnancy (OR=0.731, 95% CI=0.503-0.760, P<0.05). Moreover, in GDM-B group, the level of serum D-dimer at 13-23 weeks of pregnancy could better predict the occurrence of GDM at and after 24 weeks of pregnancy, and the area under the ROC curve was 0.731.

Keywords: *Acanthosis nigricans*, D-dimer, Gestational diabetes mellitus, Pregnancy

Gestational diabetes mellitus (GDM) refers to the abnormal glucose metabolism or potential risk of abnormal glucose metabolism and the occurrence of DM during pregnancy, but the blood glucose returns to normal after delivery[1]. According to epidemiological data, the current incidence rate of GDM is up to 5% in China[2]. The relatively high level of blood glucose in pregnant women for a long time contributes to an abortion rate as high as 15-30%. Moreover, the risk of postpartum puerperal infection and expected risk of DM in pregnant women are increased, seriously affecting the quality of life of patients. During pregnancy, with the increase of gestational week and the continuous development of the fetus, maternal hormone levels and coagulation function will vary to a certain extent to meet the physiological needs of the mother. With variation in coagulation function in the patients, the risk of thrombosis will be elevated gradually. Thus, it is of great significance to strengthen blood monitoring in pregnant women. For the fetus, the incidence rate of macrosomia is as high as 25-42%, and the fetal malformation rate is 7-10 times that in normal pregnant women[3].D-dimer and fibrinogen are vital indices for clinical evaluation of coagulation function and fibrinolysis system. According to a study[4-9], a relatively high level of D-dimer in DM patients can facilitate the blood hypercoagulable state, thereby leading to thrombosis in the patients. Hence, in this study, the level of serum D-dimer was measured in pregnant women with GDM, and the correlation between serum D-dimer and glycolipid metabolism at different gestational weeks was investigated, so as to explore the efficiency of D-dimer for early prediction of the risk of GDM.

Experimental Section

General information

A total of 308 pregnant women treated in our hospital from January 2018 to January 2020 were

enrolled. According to the diagnostic criteria for GDM, the patients were divided into normal blood glucose group (n=145) and GDM group (n=163). In addition, based on the gestational week when D-dimer was measured, they were further grouped as follows: 5-12 weeks of pregnancy [normal blood glucose group (n=46) and GDM group (n=39)], 13-23 weeks of pregnancy [normal blood glucose group (n=55) and GDM group (n=47)], 24-28 weeks of pregnancy [normal blood glucose group (n=23) and GDM group (n=32)], and 29-37 weeks of pregnancy [normal blood glucose group (n=21) and GDM group (n=45)]. Besides, the pregnant women who did not develop GDM at 5-12 weeks of pregnancy but were diagnosed with GDM at and after 24 weeks of pregnancy were assigned to GDM-A group (n=18), while those who did not develop GDM at 13-23 weeks of pregnancy but were diagnosed with GDM at and after 24 weeks of pregnancy were assigned to GDM-B group (n=26). None of the subjects developed type 1 DM (T1DM) or T2DM, or suffered from diseases affecting blood glucose levels, such as hyperthyroidism, Cushing syndrome and pancreatitis. All of them had no acute complications such as diabetic ketoacidosis, or have serious impairment of heart, liver or kidney function. The diagnostic criteria for GDM were based on the criteria in the Chinese Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus (2017 Edition)[10]. The pregnant women who underwent 75-g oral glucose tolerance test (OGTT) at 24-28 weeks of pregnancy and met any one of the following standards were diagnosed with GDM: 5.1 mmol/L ≤ fasting plasma glucose (FPG) <7.0 mmol/L, OGTT 1-h PG ≥10.0 mmol/L, or 8.5 mmol/L ≤ OGTT 2-h PG <11.1 mmol/L.

Collection of clinical data

The pregnancy age, height, pre-pregnancy weight, maximum pre-pregnancy weight, pre-pregnancy body mass index (BMI), family history of DM in first-degree relatives and the occurrence of neck and/or axillary *Acanthosis nigricans* were recorded.

Fasting venous blood was collected after fasting and water deprivation for 8 h. The FPG, glycated albumin (GA), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were detected by enzymic methods using the automatic biochemical instrument in our hospital. Apolipoprotein A1 (APO-A1) and APO-B were determined *via* immunity transmission turbidimetry, glycosylated hemoglobin (HbAlc) was measured by means of high-performance liquid chromatography, and fasting insulin was detected by chemiluminescent microparticle immunoassay.

All the pregnant women were subject to 75-g OGTT at 24-28 weeks of pregnancy for the diagnosis of GDM, and OGTT 0-, 60- and 120-min PG and insulin were measured. According to the suggestions in the Guideline, pregnant women with a high risk of hyperglycemia, including those with histories of GDM and macrosomia, obesity, polycystic ovary syndrome, and a family history of DM in first-degree relatives, should be screened for glycometabolism by 75-g OGTT before 24 weeks of pregnancy in advance.

Measurement of serum D-dimer level

When the fasting biochemical indices were collected, the blood samples were collected in the serum separator tube, and stored in a refrigerator at -80° after centrifugation. The serum level of D-dimer in the patients was measured using an ACL TOP 700 automatic coagulation analyzer (Instrumentation Laboratory, USA).

Assessment of insulin resistance (IR) and islet β cell function

IR index [homeostasis model assessment of IR (HOMA-IR)] and islet β cell function index (HOMA-β) were evaluated using the formulas as follows[11]: HOMA-IR = insulin (μU/mL) × FPG (mmol/L)/22.5, and HOMA-β = [20 × insulin (μU/mL)]/FPG (mmol/L) − 3.5].

Statistical analysis

SPSS 26.0 software was utilized for statistical analysis. Kolmogorov-Smirnov test was adopted to test the normality of each variable. The measurement data in line with normal distribution were expressed as($\bar{\chi}\pm s$), while those in line with skewed distribution were expressed as [median (upper and lower quartiles)], and independent-samples *t*-test (normal distribution) or Mann-Whitney U test (skewed distribution) was conducted for comparison between two groups. The enumeration data were expressed as [n (%)], and χ^2 test was performed for the comparison between two groups. Pearson or Spearman correlation analysis was employed to evaluate the correlation between serum D-dimer and each index. Multivariate logistic regression was used to analyze the related factors affecting the occurrence of GDM. The receiver operating characteristic (ROC) curve was adopted to predict the optimal threshold of D-dimer

for the occurrence of GMD. P<0.05 suggested that the difference was statistically significant.

Results

General data

The pregnancy age, pre-pregnancy weight, maximum pre-pregnancy weight, pre-pregnancy BMI and the incidence rate of neck and/or axillary *Acanthosis nigricans* were significantly higher in GDM group than those in normal blood glucose group (P<0.05) (Table 1).

Glycolipid metabolism-related indices

Patients in GDM group had OGTT at the gestational week of (20.32±7.91) weeks. It was found that the levels of OGTT 0-, 60- and 120-min PG, OGTT 0-min insulin, HbAlc and GA, and HOMA-IR in GDM group were significantly higher than those in normal blood glucose group, while HOMA-β was lower in GDM group than that in normal blood glucose group, showing statistically significant differences (P<0.05). Moreover, the level of TG in GDM group was higher than that in normal blood glucose group, but there were no statistically significant differences in the levels of TC, HDL-C, LDL-C, APO-A1 and APO-B between the two groups (P>0.05) (Table 2).

Serum D-dimer levels at different gestational weeks

At 5-12, 13-23, 24-28 and 29-37 weeks of pregnancy, the level of serum D-dimer in GDM group was significantly higher than that in normal blood glucose group, showing statistically significant differences (P<0.05) (Table 3).

Correlations between serum D-dimer and glycolipid metabolism-related indices

At 24-28 weeks of pregnancy, the level of serum D-dimer was negatively correlated with OGTT 0-min insulin (r=-0.756, P<0.05) and HOMA-IR (r=-0.693, P<0.05), and positively correlated with LDL-C

Table 1 —General data of patients

	GDM group (n=163)	Normal blood glucose group (n=145)	Statistical value	P
Pregnancy age (Y)	31.8±4.0	30.5±3.8	2.915	0.004
Pre-pregnancy index				
Weight (kg)	62.8±3.1	58.1±3.2	13.081	0.000
Maximum weight (kg)	64.6±5.1	59.9±5.4	7.852	0.000
Height (cm)	162.8±7.3	162.4±9.8	0.409	0.683
BMI (kg/m^2)	23.9±3.1	22.1±2.8	5.322	0.000
Maximum BMI (kg/m^2)	24.7±4.0	22.7±3.2	4.806	0.000
Family history of DM [n (%)]	26 (15.95)	22 (15.17)	0.035	0.851
Acanthosisnigricans [n (%)]	72 (44.17)	33 (22.76)	15.660	0.000

Table 2 — Glycolipid metabolism-related indices [median (upper and lower quartiles)]

Index	GDM group (n=163)	Normal blood glucose group (n=145)	Z	P
OGTT 0-min PG (mmol/L)	5.50 (5.11,5.81)	4.61 (4.47,4.80)	13.298	0.000
OGTT 60-min PG (mmol/L)	9.64 (8.39,10.43)	7.42 (6.79,8.30)	7.182	0.000
OGTT 120-min PG (mmol/L)	8.22 (7.03,9.40)	6.63 (5.91,7.41)	7.438	0.000
OGTT 0-min insulin (mU/L)	11.44 (8.09,14.20)	6.87 (5.39,8.69)	7.221	0.000
HOMA-IR	2.75 (1.85,3.61)	1.38 (1.10,1.79)	9.021	0.000
HOMA-β	110.50 (75.39,156.85)	132.32 (101.29,171.28)	3.298	0.017
HbAlc (%)	5.29 (4.99,5.56)	4.89 (4.69,5.11)	7.982	0.000
GA (%)	12.93 (11.40,13.90)	11.40 (10.20,12.80)	4.931	0.000
TC (mmol/L)	5.17 (4.55,5.73)	4.98 (3.76,6.30)	0.872	0.287
TG (mmol/L)	2.09 (1.39,3.10)	1.33 (1.04,2.20)	2.983	0.023
HDL-C (mmol/L)	1.66 (1.32,1.95)	1.70 (1.45,2.18)	0.763	0.382
LDL-C (mmol/L)	2.69 (2.21,3.33)	2.75 (1.93,3.47)	0.654	0.419
APO-A1 (g/L)	2.05 (1.64,2.32)	1.92 (1.54,2.48)	0.402	0.668
APO-B (g/L)	0.90 (0.73,1.07)	0.81 (0.55,1.05)	1.298	0.074

Table 3 — Serum D-dimer levels at different gestational weeks [mg/L, median (upper and lower quartile)]

Gestational week (week)	Normal blood glucose group		GDM group		Z	P
	n	D-dimer	n	D-dimer		
5~12	46	0.34 (0.11,0.43)	39	2.44 (1.81,2.87)	4.242	0.000
13~23	55	0.33 (0.09,0.34)	47	2.43 (1.84,2.81)	4.302	0.000
24~28	23	0.35 (0.13,0.36)	32	2.45 (1.92,2.94)	4.323	0.000
29~37	21	0.32 (0.15,0.33)	45	2.18 (1.87,2.69)	4.172	0.000
5~37	145	0.33 (0.14,0.34)	163	2.34 (1.86,2.78)	4.298	0.000

(r=0.759, P<0.05), but had no correlation with the other indices (P>0.05).

Risks of GDM after 24 weeks of pregnancy based on serum D-dimer level

After adjustment of the confounding factors such as pregnancy age, pre-pregnancy BMI, *Acanthosis nigricans* and TG, the level of serum D-dimer at 13-23 weeks of pregnancy was still an independent risk factor for the occurrence of GDM at and after 24 weeks of pregnancy. For every 1 mg/L increase in the concentration of serum D-dimer in 13-23 weeks of pregnancy group, the risk of GDM at and after 24 weeks of pregnancy was increased by 56.3% (OR=1.563, 95% CI=1.035-2.229, P<0.05). The level of serum D-dimer at 5-12 weeks of pregnancy had no significance for assessing the risk of GDM at and after 24 weeks of pregnancy (P=0.614).

Predictive efficiency of serum D-dimer level for GDM

The level of serum D-dimer at 13-24 weeks of pregnancy in GDM-B group could better predict the occurrence of GDM at and after 24 weeks of pregnancy, and the area under the ROC curve was 0.731 (95% CI=0.503-0.760) (Fig. 1). The optimal threshold, sensitivity and specificity of D-dimer were 2.132 mg/L, 78.0 and 80.9%, respectively. The level of serum D-dimer in pregnant women at 5-12 weeks of pregnancy had no significance for the early prediction of GDM at and after 24 weeks of pregnancy, and the area under the ROC curve was 0.477 (P=0.602).

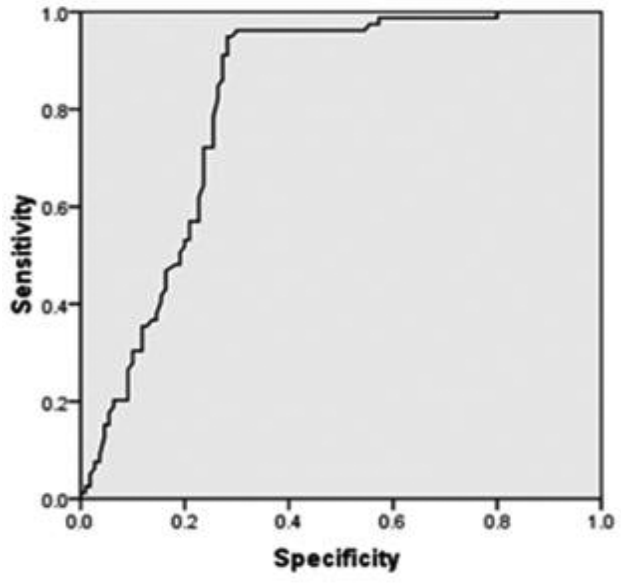

Fig. 1 —ROC curve of serum D-dimer at 13-23 weeks of pregnancy in predicting GDM at and after 24 weeks of pregnancy.

Discussion

The incidence rate of GDM shows an upward trend annually. According to the epidemiological survey by the International Diabetes Federation, the incidence rate of GDM among women worldwide has reached 14.2%[12] while that in China (17.5%) is much higher than the global level. The instability of blood glucose during pregnancy results in increased risks of spontaneous abortion, premature delivery, intrauterine asphyxia and death. According a study[13], the risk of complications in pregnant women with GDM who are not treated in time is markedly increased, and the morbidity rate of perinatal infants is also dramatically related to the time of treatment. Hence, it is necessary to have early prediction of GDM in patients, and then intervene with reasonable and effective measures. Studies on the pathogenic factors and screening indices of GDM have been widely carried out in China and abroad[14]. Currently, GDM is mainly diagnosed by FPG and 75-g OGTT. However, FPG only reflects the instantaneous blood glucose level, whereas the blood glucose in the body is easily affected by many factors. Besides, OGTT requires collecting blood for multiple times, so the operation is tedious. In addition, OGTT is vulnerable to many factors, such as stress, glucose intake and vomiting after taking glucose, resulting in low repeatability and poor compliance in patients, and even undiscovered severe GDM that endangers fetal health due to high blood glucose load in the pregnant women[15]. Early screening for GDM can prevent adverse outcomes of pregnant women, fetuses and newborns. If the risk of GDM can be predicted by some serological markers in the first and second trimesters of pregnancy, it will help clinicians identify the high-risk population of GDM and perform early intervention to improve pregnancy outcome.

GDM refers to the abnormal glucose tolerance of varying degrees that occurs or is discovered for the first time during pregnancy. Hyperglycemia in GDM patients contributes to the increase of inflammatory factors such as TNF-α, IL-6, CRP and D-dimer, which alters the structure of vascular endothelial cells, resulting in increased microvascular permeability, increased leakage of plasma and small molecular proteins, decreased insulin transport and increased IR, and thereby causing vascular endothelial injury. Moreover, the damaged vascular endothelium and the inflammatory factors activate the coagulation-fibrinolysis system in the patients. If this pathophysiological disorder in patients is not

ameliorated and continues to develop beyond the compensatory capacity of the anticoagulation system, thrombosis may be induced[16,17]. D-dimer is produced by the specific degradation of cross-linked fibrin, and its level reflects the intensity of secondary fibrinolytic activity, so D-dimer is considered as a molecular marker of hypercoagulable state and hyperfibrinolysis *in vivo*[18,19]. According to a previous study[20], there is a correlation between D-dimer level and GDM screening. The results of this study revealed that the level of serum D-dimer in GDM group was significantly higher than that in normal blood glucose group at 5-12, 13-23, 24-28 and 29-37 weeks of pregnancy. However, the level of serum D-dimer in GDM group was decreased at 29-37 weeks of pregnancy, which may be due to the improvement of IR induced by the decreased placental function in the third trimester of pregnancy. In this study, it was also found that the level of serum D-dimer at 24-28 weeks of pregnancy was negatively correlated with fasting insulin and HOMA-IR, and positively correlated with LDL-C.

There were some limitations in this study. Firstly, retrospective collection may result in selective bias and incomplete clinical data. Secondly, no long-term postpartum follow-up of the subjects was conducted in this study, so the long-term incidence rates of metabolic syndromes, such as DM and hypertension, cannot be obtained. In the future, postpartum follow-up will be carried out to further study the variation in serum D-dimer during pregnancy and after delivery and the outcome of postpartum glycolipid metabolism.

To sum up, the level of serum D-dimer at 13-23 weeks of pregnancy is an independent risk factor for the occurrence of GDM at and after 24 weeks of pregnancy. When D-dimer level is over 2.132 mg/L, the incidence rate of GDM is higher. Therefore, D-dimer may be a serological marker before the occurrence of GDM.

References

1 Wang Y, Zhang L, Teng Y, Zhang J, Yang L, Li J, Lai J, Zhao Y & Wu Y, *J Environ Sci*, 69 (2018) 5.
2 Ming-Xia G, Yong X U & Jun-Yan WU, Maternal and Child Health Care of China, 2016.
3 Sui-Yi Z, *China Mod Med*, 3-4 (2017) 10.
4 Min W, Yong-Yi BI, Zhi-Yan L U, *Chinese J Microcirculation*, 2015.
5 Murugan E, Rani D P G & Yogaraj V, *Colloids Surf B Biointerfaces*, 114 (2014) 121.
6 Murugan E, Rani D P G, Srinivasan K & Muthumary J, *Expert Opin Drug Deliv*, 10 (2013)1319.
7 Murugan E, Yogaraj V, Rani D P G & Sinha A K, *RSC Adv*, 5 (2015) 106461.
8 Murugan E, Akshata C R & Stephy A, *Adv Mater Proc*, 2 (2012) 176.
9 Murugan E, Rani D P G, Yogaraj V, Sudhandiran G & Babu D, *Ceram Int*, 48 (2022)16000.
10 Chinese Diabetes Society, *Chinese J Pract Intern Med*, 38 (2018) 292.
11 Matthews DR, Hosker J P, Rudenski A S, Naylor B A, Treacher D F & Turner R C, *Diabetologia*, 28 (1985) 412.
12 Dixon J B, Zimmet P, Alberti K G & Rubino F, *J Diabetes*, 3(2011)263.
13 Hong C, Yichen L & Jian H, *J Mod Med Health*, 2015.
14 Nielsen KK, Kapur A, Damm P, De Courten M & Bygbjerg IC, *BMC Pregnancy Childbirth*, 14 (2014) 1.
15 Van Leeuwen M, Opmeer BC, Yilmaz Y, Limpens J, Serlie M J & Mol BW, *Euro J Obstet Gynecol Reprod Biol*, 154 (2011) 130.
16 Shen Y, Peake P W& Kelly J J, *Nephrology*, 10 (2010) 599.
17 Nommsen-Rivers LA, Dolan LM & Huang B, *J Acad Breastfeed Med*, 7 (2012) 43.
18 Dan L, *J Hainan Med Univ*, 2013.
19 Izci-Balserak B & Pien GW, *Curr Opinion Pulmon Med*, 16 (2010) 574.
20 Ahmed M S, Jadhav A B, Hassan A & Meng Q H, *ISRN Inflamm*, 2012 (2012) 953461