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ORIGINAL ARTICLE

Coagulation Index and Pregnancy Outcome in Gestational Diabetes Mellitus

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SUMMARY

Background: **The purpose of this study was to analyze the coagulation status of gestational diabetes mellitus (GDM) patients in combination with glucose levels and screen out indicators closely related to the severity of GDM and adverse pregnancy outcome.**
Methods: **The subjects of 110 GDM patients and 100 normal pregnant women were randomly selected. The results of prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), D-dimer (D-D), and plaque level test (PLT) in GDM patients and normal pregnant women (comparison group) were analyzed. The study screened out the coagulation indexes of GDM closely related to FPG and then analyzed the correlation between indexes and adverse prognosis.**
Results: **The results of PT were significantly lower in the GDM group. The PT was related to the severity of GDM and adverse pregnancy outcome.**
Conclusions: **The PT levels of GDM patients in the third trimester can be used as a reliable index for disease and prognosis evaluation.**
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KEY WORDS

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INTRODUCTION

Studies show that in order to adapt to the growth and delivery of the fetus, the coagulation indexes of pregnant women change, especially in the third trimester. For example, coagulation factor II, V, VII, VIII, IX, and X increase [1-3], FIB increases 40% - 50%, and it can increase to 4 - 5 g/L in late pregnancy. The increase of coagulation factors and the inhibition of FIB lead to a hypercoagulable state in the third trimester. Physiological hypercoagulability state is conducive to fibrin deposition on the arteries, uterine walls, and placental villi, helps to maintain the integrity of the placenta, and plays a physiological protective role in preventing rapid bleeding during and after delivery [4,5].

The incidence of adverse pregnancy outcomes in gestational diabetes mellitus (GDM) patients was significantly higher than that in normal pregnant women [6-8]. Offspring of GDM mothers not only have higher morbidity of adverse infant outcomes, but also have an increased risk of diabetes, obesity, and cardiovascular disease in their adult life [9-11]. A study shows that gestational diabetes presents as a significant antenatal risk factor for venous thromboembolism [12], GDM patients are more likely to have thrombus formation. Early detection of their coagulation status can prevent pathological pregnancy [13].

In order to observe the changes of coagulation status in GDM, guide clinical intervention in time, and effectively reduce the adverse outcome of DIC and other coagulation abnormalities, this experiment hopes to analyze the difference of coagulation indexes in combination with glucose levels between normal pregnant women and GDM patients and explore whether the severity of GDM is related to the degree of the coagulation disorder. At the same time, the correlation between coagulation indexes and the adverse outcomes of GDM patients was analyzed. The experiment hopes to seek more clinical prediction and monitoring indexes for GDM patients before delivery.

MATERIALS AND METHODS

The ethics committee of Beijing Shijitan Hospital, Capital Medical University approved the research project. We performed a retrospective analysis on data from the Laboratory Information System (LIS) at our hospital. The GDM patients (GMD group) met the diagnostic criteria of the American Diabetes Association (ADA) in 2011. The study group included 100 normal pregnant women (N group) and 110 GDM patients, all of whom had not used aspirin, contraceptives and other drugs that affect the coagulation and fibrinolysis system within one month before sampling. Exclusion criteria: (1) patients with acute or chronic infections, tumors, and cardiovascular diseases; (2) impaired glucose tolerance in the past; (3) severe liver and kidney dysfunction; (4) mental and intellectual impairment. One hundred and ten GDM patients were divided into two groups according to the FPG level of OGTT. The group with FPG ≤ 5.10 mmol/L was GM1, and the group with FPG > 5.10 mmol/L was GM2. The clinical characteristics of these subjects are compared in Table 1.

The results of PT, APTT, TT, FIB, D-D, and PLT in normal pregnant women and GDM patients were collected both in their first trimester and third trimester. PT, APTT, TT, FIB, and D-D items were analyzed by ACL TOP automatic coagulation analyzer (Instrumentation Laboratory, Milan, Italy). PLT was detected by Sysmex-2100 automatic hematologic analyzer (Sysmex Co., Ltd, Japan). The FPG results of OGTT were analyzed by Siemens ADVIA-2400 automatic biochemical analyzer (Siemens AG, Germany). The reference ranges of normal pregnant women in the third trimester used were as follows: 10.7 - 13.0 seconds for PT, 23.2 - 31.6 seconds for APTT, 14.9 - 18.7 seconds for TT, 3.46 - 6.00 g/L for FIB, 690 - 4,040 ng/mL for D-D, 125 - 350 x 10^9/L for PLT, and the FPG ≤ 5.1 mmol/L [14].

The clinical diagnosis of GDM patients (including the adverse pregnancy outcomes and other important clinical data) were collected from the hospital medical record system.

All statistical analyses were carried out on SPSS17.0. The measurement data were expressed by $\bar{x} \pm s$, and the count data were analyzed by *t*-test. The coagulation indexes of normal pregnant women and GDM patients were compared by independent sample *t*-test. The correlation of FPG and PT in GDM patients were analyzed by Pearson's correlation analysis, and the bilateral correlation $p < 0.01$ was statistically significant.

RESULTS

Comparative the coagulation results between the N group and GDM group in the first trimester, it shows that the results of PT, APTT, TT, FIB, D-D, and PLT in the GDM group were not significantly different from those in N group ($p > 0.05$, Table 2).

Comparative the coagulation results between two groups in third trimester (Figure 1), the results of PT in the GDM group were significantly lower than that in the N group ($p < 0.05$). The results of APTT, TT, FIB, D-D, and PLT in the GDM group were not significantly different from those in N group ($p > 0.05$).

The coagulation results in the N and GDM groups were obtained from 100 normal pregnant women and 110 GDM patients, respectively, in the third trimester. (A) The mean value of PT, APTT, and TT in the GMD group was lower than that in the N group, and the mean value of FIB was higher than that in the N group. There was a significant difference in PT between the N group and GDM group ($p < 0.05$). The results of APTT, TT, and FIB were not significantly different between the two groups ($p > 0.05$). (B) The mean value of D-D in the GMD group was higher than that in the N group, the mean value of PLT in GMD group were lower, but the differences were not statistically significant ($p > 0.05$).

Comparative analysis of coagulation results was performed between the GM1 and GM2 groups in third trimester, the mean value of PT in the GM2 group was significantly lower than that in the GM1 group ($p < 0.05$, Table 3 and Figure 2).

One hundred and ten GDM patients were divided into two groups according to the FPG level of OGTT. The group with FPG ≤ 5.10 mmol/L was GM1 (n = 87), and the group with FPG > 5.10 mmol/L was GM2 (n = 23). (A) Distribution of PT results in GM1 and GM2 groups was shown. The mean value of PT in the GM2 group was lower than that in the GM1 group. (B) There was a statistically significant difference in PT between the two groups ($p < 0.05$).

Table 1. Comparison of general clinical data ($\bar{x} \pm s$).

Parameters	N Group (n = 100)	GDM Group (n = 110)	GM1 group (FPG ≤ 5.10) (n = 87)	GM2 group (FPG > 5.10) (n = 23)
Age (years)	30.76 ± 3.49	33.19 ± 4.12	33.14 ± 3.91	33.39 ± 4.95
Pre-pregnancy BMI	22.60 ± 5.13	23.37 ± 3.65	22.63 ± 3.11	26.22 ± 4.18
Average gestational age	39.43 ± 1.52	39.22 ± 1.18	39.33 ± 1.14	38.78 ± 1.25
Average number of pregnancies	1.65 ± 0.83	2.13 ± 1.02	2.10 ± 1.07	2.22 ± 0.85
Average number of births	1.27 ± 0.45	1.42 ± 0.50	1.43 ± 0.50	1.39 ± 0.50

Table 2. Comparison of coagulation test results between N group and GDM group in first trimester ($\bar{x} \pm s$).

Test results	N group	GDM group	t-value	p-value
PT (s)	11.60 ± 0.69	11.36 ± 0.55	3.625	0.058
APTT (s)	29.24 ± 2.52	28.75 ± 2.41	0.034	0.853
TT (s)	13.83 ± 1.01	13.43 ± 0.81	0.473	0.492
FIB (g/L)	3.74 ± 0.62	3.89 ± 0.56	0.662	0.417
D-D (ng/mL)	134.48 ± 117.28	141.37 ± 107.50	0.174	0.677
PLT (x 10^9/L)	256.10 ± 46.93	256.92 ± 62.97	3.676	0.057

Table 3. Comparison of PT between GM1 and GM2 group in third trimester ($\bar{x} \pm s$).

Test results	GM1 group	GM2 group	t-value	p-value
PT (s)	10.39 ± 0.41	10.12 ± 0.52	4.698	0.032

Table 4. Correlation analysis of FPG and PT in GDM patients.

Items		FPG	PT
FPG	Pearson's correlation	1	-0.285 **
	Significance (bilateral)		0.003
	N	110	110
PT	Pearson's correlation	-0.285 **	1
	Significance (bilateral)	0.003	
	N	110	110

Table 5. Comparison of the incidence (%) of adverse pregnancy outcomes between PT-H group and PT-L group.

Group	N	Caesarean section	Fetal distress	Pregnancy-induced hypertension syndrome (PIH)	Pre-eclampsia	Macrosomia	Premature rupture of membrane
PT-H group (PT ≥ 10.5)	57	21.1% (12)	3.5% (2)	3.5% (2)	3.5% (2)	5.3 (3)	14.0 (8)
PT-L group (PT < 10.5)	53	24.5% (13)	5.7% (3)	5.7% (3)	5.7% (3)	5.7% (3)	18.9 (10)

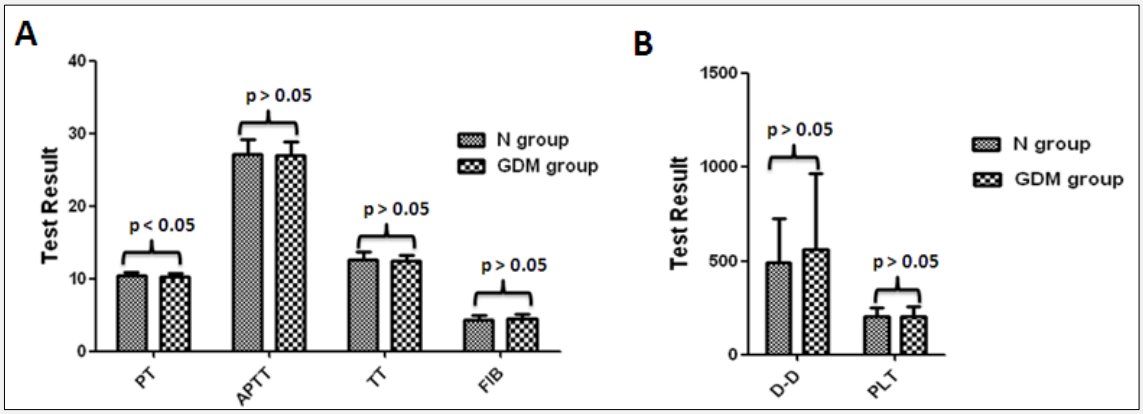

Figure 1. Comparison of coagulation results between the N and GDM groups in the third trimester.

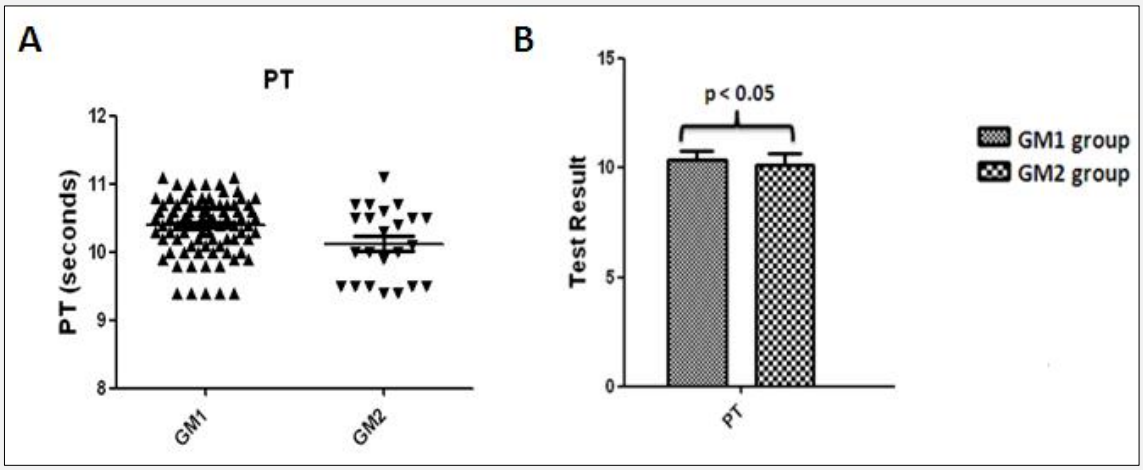

Figure 2. Comparison of PT between GM1 and GM2 groups in the third trimester.

The trend between FPG and the reciprocal of PT in the third trimester of the N group, GM1 group, and GM2 group was shown in Figure 3. As shown in Figure 3, there was a good change trend between FPG and the reciprocal of PT.

The trend of PT reciprocal was the same as that of FPG in the three groups. Compared with the N group, the PT value decreased in the GM1 group and more significantly in the GM2 group.

The correlation analysis of FPG and PT in the GDM patients was analyzed (Table 4). There was a significant correlation between FPG and PT in the GDM patients (bilateral, $p < 0.01$).

According to PT results, 110 GDM patients were divided into PT high group (PT-H, PT $\geq$ 10.5) and PT low group (PT-L, PT < 10.5). The incidence and number of adverse pregnancy outcomes in PT-H group and PT-L group were compared in Table 5.

The results showed that the incidence of caesarean section, fetal distress, PIH, pre-eclampsia, and premature rupture of the membrane in the PT-L group was significantly higher than that in the PT-H group. The inci-

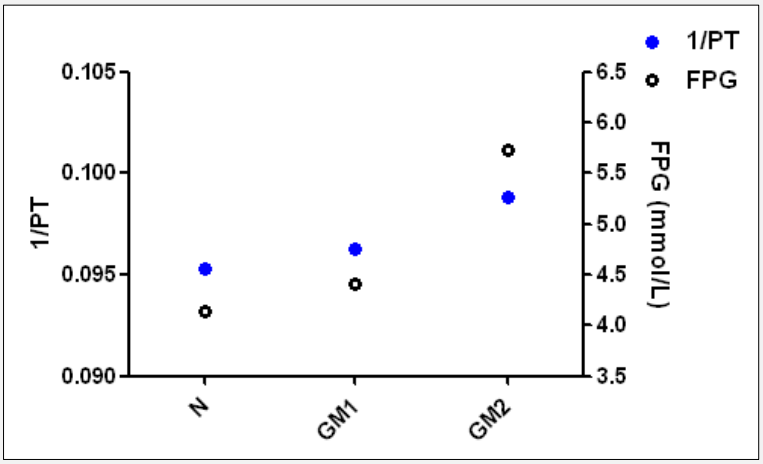

Figure 3. Trend of FPG and the reciprocal of PT in N group (n = 100), GM1 group (n = 87), and GM2 group (n = 23).

dence of macrosomia in the PT-L group was higher than that in the PT-H group, but with little difference. It is considered that fetal weight is mainly related to blood glucose level of GDM patients.

DISCUSSION

In clinical routine detection of coagulation indexes, PT is the most commonly used screening test for the extrinsic coagulation system. The value of PT reflects the levels of factor I, II, V, VII, X, and acquired coagulation factors. PT shortening often indicates that the blood is in a hypercoagulable state. Its pathological state is often related to deep vein thrombosis and early DIC.

Due to the normal physiological need of pregnancy and childbirth, the hemostatic system creates a physiological hypercoagulable state. The coagulation function is relatively increased, but the anticoagulation function of blood is relatively reduced [4,15]. Research shows that, with the increasing gestational age, the coagulation function is gradually strengthened, and the anticoagulation function is relatively weak [16]. The levels of various hormones change, in particular, the level of estrogen increases significantly. Estrogen can increase the production of coagulation factors and fibrinogen, and decrease the level of antithrombin [17,18]. In recent years, the clinical research on the abnormal coagulation function in pregnancy and the adverse outcome of pregnancy has increased gradually. Some scholars believe that the abnormal coagulation function in pregnancy is closely related to diffuse intravascular coagulation (DIC), PIH, macrosomia, preterm delivery, vascular thrombosis [19-21], and the pathological hypercoagulable state of blood tending to thrombosis [1,22]. Vascular endothelium damage in GDM patients can also activate fibrin and coagulation, and the hypercoagulable state of blood is more obvious.

In this study, all subjects did not use aspirin, contraceptives, and other drugs that affect the coagulation and fibrinolysis system within one month before sampling. Aspirin and low molecular weight heparin (LMWH) are commonly used in pregnancy. Aspirin, as a non-steroidal cyclooxygenase inhibitor, has been shown to reduce the expression of thromboxane A2 in pregnant women [23]. The aspirin treatment of pregnant women can effectively improve the hypercoagulable state and reduce the occurrence of adverse pregnancy outcomes [24]. Similarly, LMWH can inhibit the activities of thrombin IIA and coagulation factor Xa to achieve anticoagulation [25]. Because LMWH does not pass through the placenta, the application of LMWH can not only ensure the therapeutic effect of pregnant women with hypercoagulable state, but also takes into account the safety of the fetus [26,27]. Studies show that the use of LMWH in pregnancy can significantly prolong APTT [28].

The results of PT, APTT, TT, FIB, D-D, and PLT were compared between normal pregnant women and GDM patients in the first trimester. There was no significant difference between the two groups. GDM is definitely diagnosed in the second trimester of pregnancy. When the blood glucose in the early stage of the disease was better, the coagulation indexes of PT, APTT, and TT were lower than those of normal pregnant women, but the difference was not statistically significant.

The coagulation indexes and PLT results of normal pregnant women and GDM patients in the third trimester were compared. The results showed that the PT in-

dex was significantly different between the two groups. After further grouping the GDM group according to FPG, the difference of PT between the GM1 and GM2 groups was still significant. Among N, GM1, and GM2 groups, the change trend of PT reciprocal was the same as that of FPG. These results indicate that PT results are not only related to GDM, but also to the degree of GDM.

CONCLUSION

The research shows that the results of PT, APTT, TT, and PLT in normal pregnant women and GDM patients in the third trimester were shorter than those in their first trimester. The results of FIB and D-D increased with the increase of gestational age. The PT results of GDM patients in the third trimester decreased more significantly. Therefore, the clinician should strengthen the detection of thrombus markers and intervene in thrombus formation occurs in GDM patients [29]. The monitoring of coagulation indexes in the third trimester of GDM patients plays an active role in evaluating the prognosis and judging the development of the disease, especially in reducing the adverse pregnancy outcomes.

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Declaration of Interest:
The authors declare that they have no conflict of interest.

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