

Blood Coagulation Indices in Twin Pregnancy Complicated with Preeclampsia

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ABSTRACT

Objective: To determine the regular changes of blood coagulation indices in twin pregnancy complicated with preeclampsia (PE).

Study Design: Descriptive study.

Place and Duration of Study: Fujian Provincial Maternity and Children Hospital from January 2014 to December 2017.

Methodology: A total of 180 twin pregnancies were enrolled in this study, including 40 diagnosed as PE, 50 as severe PE (sPE), and 90 as normal twin pregnancies. The changes of coagulation parameters of twin pregnant women in different gestational states and periods were retrospectively analysed.

Results: During the middle and late pregnancies in all groups, the PT (prothrombin time) decreased, and D-Di (D-dimers) increased gradually compared to early pregnancy ($p < 0.05$). When D-Di increased abnormally, adverse pregnancy outcomes increased. APTT (activated partial thromboplastin time) and TT (thromoplastin time) were shortened first and then significantly prolonged ($p < 0.05$). In the normal twin group, FIB was increased gradually from early pregnancy to mid-late pregnancy; in the PE group, FIB was increased and then decreased, especially in the sPE group ($p < 0.05$). There was no significant difference in coagulation function in early pregnancy ($p > 0.05$). FIB in sPE group was lower than that in other two groups in late pregnancy. TT in sPE group was higher than that in other two groups. D-Di and APTT in PE group and sPE group were higher than those in normal group ($p < 0.05$). The TT sensitivity was 68.8% with specificity 72.4%, at cut-off value of 13.48 s ($p < 0.01$).

Conclusion: The regular changes of blood coagulation indices in twin pregnancy complicated with PE had great predictive and diagnostic value of preeclampsia.

Key Words: Preeclampsia, Twin pregnancy, Coagulation indices.

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INTRODUCTION

Preeclampsia (PE) is a serious complication occurred in the middle and late pregnancy, and seriously affects the prognosis of mother and child. Its pathogenesis is complex and remains unknown.^{1,2} Patients with PE have abnormal hypercoagulation and hyperfunctional blood coagulation. The imbalance of coagulation and fibrinolysis systems is distinctive feature of PE. Therefore, the detection of these changes of blood coagulation indices for the guidance and prevention of PE has a certain clinical significance.³ As the assisted reproductive technology improves, studies have shown that the incidence of twin pregnancies and the incidence of concurrent PE have increased in recent years. Once

the coagulation and fibrinolytic systems are out of balance, the impact on maternal health is even greater because twin pregnancies carry a greater physical burden than single pregnancies.^{4,5} To date, no effective intervention other than termination of pregnancy has been identified, and the challenge of better treatment of PE in twin pregnancies is enormous. Therefore, it is important to identify the appropriate predictors of PE in twin pregnancy for the early prevention and treatment of PE.^{6,7}

The rationale of this study was to explore the dynamic changes in coagulation in twin pregnancies with PE, to identify possible associations with PE development, and to screen for possible predictors to guide the timely and reasonable diagnosis and treatment, improve maternal and infant prognosis.

The objective of the study was to determine the regular changes of blood coagulation indices in twin pregnancy complicated with pre-eclampsia (PE).

METHODOLOGY

Pregnant women who gave birth to twins were recruited between January 2014 and December 2017 during

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routine obstetric check-ups. The inclusion and diagnostic criteria were based on the ACOG guidelines.^{8,9} Inclusion criteria were twin pregnancies with preeclampsia or severe preeclampsia. Exclusion criteria were twin pregnancies with autoimmune diseases, chronic hypertension, chronic kidney disease, chronic liver disease, hematological diseases, and history of oral contraceptives, and without recent administration of low molecular weight heparin, aspirin and other drugs that affect blood clotting. Randomly selected 90 normal pregnant women with similar gestational age were as the control group. Informed consents were obtained from all participants. This study was a retrospective descriptive study and was reviewed and approved by the Ethics Committee of the Fujian Provincial Maternal and Child Health Hospital.

Participants were divided into three groups: the normal twin pregnancy group, the PE twin pregnancy group, and the sPE twin pregnancy group. These groups were then divided into three subgroups according to the stage of pregnancy [early pregnancy $\leq 12+6$ weeks, midterm 13-27+6 weeks and third trimester 28-41 weeks]. Comparison of each test indicator was performed between and among the groups.

The changes of coagulation function including TT (thromboplastin time), PT (prothrombin time), APTT (activated partial thromboplastin time), FIB and D-Di (D-dimers) were analysed in different pregnant states and during different periods of pregnancy. The coagulation function was examined using American Beckman ACL7000 automatic coagulation analyzer and corollary reagents.

All statistical analyses were performed using SPSS 17.0 software. Measurement data were expressed as mean \pm standard deviation ($x \pm sd$). Homogeneity of variance of each group was performed using Levene' test. If the variance was uniform, one-way ANOVA was used for comparison among groups, and the LSD-t method was used for further comparison between two groups. If the variances were not consistent, the Kruskal-Wallis H test was used for inter-group comparisons, and Dunnett's T3 method was used for further comparison between the two groups. The area under the curve (AUC) was calculated with the receiver operating characteristic curve (ROC curve), the predictive variables were screened, and the diagnostic parameters (cut-off values) were calculated; $\alpha=0.05$ was used as the test level, and $p<0.05$ was regarded as statistically significant.

RESULTS

No significant differences in age and pre-pregnancy body mass index were observed among the three groups ($p > 0.05$). No significant differences were seen in the number of gestation days during examination in early pregnancy, middle pregnancy and late pregnancy ($p > 0.05$) Table I.

As the pregnancy progressed, PT gradually shortened, and the differences among the groups were statistically significant ($p < 0.05$). There were no statistical differences between the two groups ($p > 0.05$). In the middle and late pregnancy, PT was shorter in the PE and sPE groups than in the normal pregnancy group, and the differences were statistically significant ($p < 0.05$). From early pregnancy to middle-late pregnancy, no significant differences were

Table I: Comparison of general data of three groups of pregnant women.

	Normal (n=90)	PE (n=40)	sPE (n=50)	p
Age (years)	31.68 \pm 4.08	32.26 \pm 4.92	31.62 \pm 5.28	0.564
BMI at term (Kg/m ²)	21.24 \pm 3.06	20.76 \pm 3.25	21.32 \pm 3.16	0.283
Early pregnant test day (d)	56.96 \pm 16.7	59.85 \pm 15.5	57.82 \pm 15.6	0.207
Middle pregnant test day (d)	166.51 \pm 23.3	172.03 \pm 21.4	165.76 \pm 22.8	0.324
Late pregnant test day (d)	231.96 \pm 21.9	241.68 \pm 15.2	229.32 \pm 19.3	0.125

Table II: Changes in coagulation function parameters in three groups of pregnant women ($x \pm sd$).

Group	Case (n)	TT (s)	PT (s)	APTT (s)	FIB (g/L)	D-D (mg/L)
Normal group	90					
Early	21	13.19 \pm 1.01	10.83 \pm 0.60	30.05 \pm 2.85	3.62 \pm 0.66	0.17 \pm 0.13
Middle	30	12.73 \pm 1.02	10.14 \pm 0.42 ^a	27.06 \pm 1.96 ^a	4.42 \pm 0.76	0.56 \pm 0.34 ^a
Late	39	12.95 \pm 1.21	9.83 \pm 0.40 ^{ab}	28.21 \pm 2.52 ^{ab}	4.47 \pm 0.96 ^a	0.84 \pm 0.33 ^{ab}
PE group	40					
Early	14	13.05 \pm 1.34	10.85 \pm 0.74	30.25 \pm 3.42	3.66 \pm 0.88	0.20 \pm 0.18
Middle	12	12.89 \pm 1.10	9.90 \pm 0.44 ^{ac}	27.44 \pm 1.62 ^a	4.48 \pm 0.91 ^a	0.62 \pm 0.49 ^a
Late	14	13.15 \pm 0.97	9.62 \pm 0.33 ^{abc}	29.12 \pm 2.74 ^{bc}	4.35 \pm 0.70 ^a	1.05 \pm 0.80 ^{abc}
sPE group	50					
Early	20	13.18 \pm 1.22	10.68 \pm 0.62	30.44 \pm 3.05	3.71 \pm 0.70	0.20 \pm 0.19
Middle	20	13.15 \pm 1.20	9.81 \pm 0.48 ^{ac}	28.02 \pm 1.95 ^{ac}	4.26 \pm 0.82 ^a	0.66 \pm 0.64 ^a
Late	10	14.11 \pm 1.32 ^{cd}	9.44 \pm 0.46 ^{abcd}	29.36 \pm 2.83 ^{bc}	3.83 \pm 0.84 ^{cd}	1.49 \pm 1.32 ^{abcd}

a: $p < 0.05$, comparison within the groups, compared with early pregnancy; b: $P < 0.05$, comparison within the groups, compared with middle pregnancy; c: $p < 0.05$, comparison between the groups, compared with the normal group; d: $p < 0.05$, comparison between the groups, compared with PE group.

Table III (a): AUC for each variable in late pregnancy.

Test result variables	AUC	Standard error	p-value	95% CI	
				Lower limit	Upper limit
TT (s)	0.824	0.037	0.000	0.750	0.897
PT (s)	0.262	0.043	0.000	0.177	0.347
APTT (s)	0.556	0.054	0.286	0.451	0.661
FIB (g/L)	0.278	0.046	0.000	0.187	0.368
DD (mg/L)	0.546	0.054	0.377	0.439	0.653

Table III (b): Predictive value of each predictor of late pregnancy.

Predictor	Cut-off value	Sensitivity (%)	Specificity (%)	Peak of Youden index	OR value	95% CI		p-value
						Lower limit	Upper limit	
TT(s)	13.45	80.0	72.5	0.525	10.545	4.511	24.651	0.000
APTT(s)	28.25	58.0	58.8	0.168	1.249	0.613	1.892	0.590
DD (mg/L)	1.18	44.0	80.0	0.240	4.929	2.114	11.492	0.000

observed in TT among the groups ($p > 0.05$). There were no significant differences between the two groups ($p > 0.05$). In late pregnancy, TT was higher in sPE group than in other two groups, and the differences were statistically significant ($p < 0.05$). From early pregnancy to middle-late pregnancy, APTT was increased and then decreased in all groups, but it was still lower in late pregnancy than in early pregnancy. APTT was higher in PE and sPE groups than in the normal group, and the differences were statistically significant among the groups ($p < 0.05$). From early pregnancy to middle-late pregnancy, DD was gradually increased, and the differences were statistically significant ($p < 0.05$). No significant differences were seen in early and middle pregnancy among the groups ($p > 0.05$), while significant differences were observed in late pregnancy ($p < 0.05$). FIB was gradually increased in the normal group during pregnancy, and the differences were statistically significant among the groups ($p < 0.05$). FIB was increased and then decreased in PE and sPE groups, and it was still higher in late pregnancy than in early pregnancy. No

significant differences were observed in comparisons among the groups ($p > 0.05$). FIB was lower in sPE group than in other two groups in late pregnancy, and the differences was statistically significant ($p < 0.05$). Changes in coagulation function indicators are shown in Table II.

There were no obvious predictive values of the predictors in early pregnancy. Taking the ROC curve of PE in middle pregnancy, and the AUC of APTT and TT was 0.674 and 0.576 respectively, which has certain predictive significance, but the diagnostic accuracy was low. The ROC curve is shown in Figure 1. Taking the ROC curve of PE in late pregnancy, TT was an ideal predictor with an AUC of 0.824 and a cutoff value of 13.45s. TT predicted PE sensitivity of 80.0%, specificity of 72.5%, and odd ratio of 10.545 (Figure 1, Table III).

DISCUSSION

The heavy uterine cavity pressure in twin pregnancies tends to trigger insufficient placental perfusion, resulting in placental ischemia and hypoxia synthesis and secretion of a large number of inflammatory factors, oxygen-free radicals into the mother's blood circulation, aggravating oxidative stress, and immune damage, triggering vascular endothelium Serious cell damage and dysfunction are more likely to induce hypertensive disorders in pregnancy than single pregnancy, and correspondingly increase the incidence of severe pre-eclampsia. Besides, twin pregnancies occur earlier, and the condition is more serious, which increases the risk of adverse outcomes such as postpartum hemorrhage and neonatal asphyxia.^{10,11} Therefore, screening and prediction of PE in twin pregnancies has become a widespread concern in clinical practice.

No obvious abnormality was seen in the blood coagulation status of the normal twin pregnancies in early pregnancy. In the middle and late pregnancy, the coagulation system and the fibrinolytic system underwent a series of changes to meet the needs of pregnancy. The content of FIB in the blood was gradually increased, which shortened the PT and APTT.

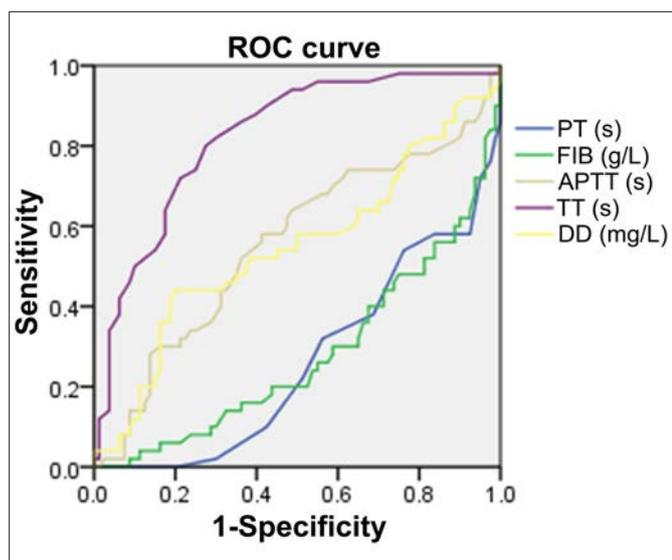


Figure 1: ROC curve of PE predicted by various parameters in late pregnancy.

Compensatory homeostasis in physiological hypercoagulability and low fibrinolysis returned to pre-pregnancy status after four weeks of delivery. This hypercoagulation is essential for the integrity of the placental function, delivery and postpartum hemostasis. But it also increases the risk of thrombosis. In this study, PT and APTT of the normal group were significantly shortened in middle and late pregnancy than in early pregnancy, while FIB and D-Di were significantly increased, suggesting the hypercoagulability of the blood.

The dysfunction of the coagulation system and the fibrinolytic system is an important feature of PE. With the progress of pregnancy, PT was gradually shortened in the middle and late pregnancy, and PT was shortened more significantly in PE and sPE groups than in the normal group ($p < 0.05$). Compared with the normal twin pregnancy group, TT, APTT and D-Di in late pregnancy showed obvious abnormalities in the PE group than in the normal group ($p < 0.05$). PT and APTT are indicators for detecting exogenous and endogenous coagulation systems respectively. D-Di is a specific degradation product of FIB. Its increased plasma content indicated enhanced fibrinolytic activity, and their abnormalities in PE suggested a serious imbalance between the coagulation system and the fibrinolytic system. D-Di was gradually increased in the middle and late pregnancy, and it was significantly higher in the sPE group than in other groups ($p < 0.05$). The abnormal increase of D-Di reflected the secondary fibrinolysis. Therefore, the detection of changes in D-Di level can be used as an auxiliary indicator for the diagnosis of PE, and also determine the severity of the disease and prognosis, providing a basis for twin pregnancy management and clinical diagnosis and treatment.^{12,13} TT mainly reflects the time of fibrinogen conversion to fibrin, and the content and activity of FIB in the blood. In general, TT and FIB have opposite trends, which is more obvious in the late pregnancy of PE. Pearson correlation analysis showed a significant negative correlation between TT and FIB ($r = -0.593$, $p < 0.001$). TT may be an ideal predictor of the onset and severity of PE.

It is well known that PE patients have abnormally increased coagulation substances and clotting activity.^{14,15} However, the study found that FIB in the PE group was increased and then decreased in the PE group; and was significantly higher in the middle pregnancy than in the early pregnancy, when compared with that in the normal twin pregnancy group. Although FIB was still higher in the late pregnancy than in the early pregnancy, but lower than in the middle pregnancy. This trend was more obvious in the sPE group. The results indicated that with the progression of PE disease, the fibrinolytic system was activated and gradually increased, the consumption of clotting factor FIB was increased, decompensation occurred, and FIB showed a downward trend. If the disease continued to develop, serious complications

such as HELLP syndrome appeared. FIB consumption is significantly reduced, leading to DIC and MODS. The reason may lie in that increased liver burden of PE patients in the late pregnancy leads to a decrease in FIB synthesis. On the other hand, the hypercoagulable state and microthrombosis in the circulatory system also consume a large amount of FIB. The coagulation and fibrinolysis systems of PE patients have experienced severe and complex changes, rather than simply increasing the procoagulant substance.^{16,17}

Coagulation function indicators experienced significant changes in the early pregnancy, began to show abnormalities in the middle pregnancy, and had the greatest change in the late pregnancy. These indicators showed greater changes in the severe PE group. The study data showed that TT and APTT were optional predictors in the second trimester, but the diagnostic accuracy was low. In the third trimester of pregnancy, the specificity of DD is higher, but the sensitivity is poor; TT is the most predictive and has a high diagnostic value. In the middle and late pregnancy, TT may be a more reliable indicator for early prediction of PE.

In the current study, the authors focused on PT, D-Di, APTT, TT and FIB because they were classical indicators in blood coagulation system and they often presented with significant differences between twin pregnancy with PE and singleton. However, the recent reports mostly limited to singleton. Due to the heterogeneous pathophysiology and genetic factors, no single indicator is sufficient for the prediction and diagnosis of twin pregnancies with PE.¹⁸ Few studies identified that serum markers ubiquitously used in singleton pregnancy may be useful in twin pregnancy with PE.¹⁹ But their clinical application and analysis have never been fully demonstrated to date.

At present, most of the researches on the predictive indicators of PE at home and abroad are retrospective studies on singleton pregnancy. The coagulation indicators with predictive value in these studies on PE included TT, APTT, and D-Di.²⁰⁻²³ Han L *et al.* performed a retrospective study in 174 women with singleton pregnancy (53 cases of mild PE, 42 cases of severe PE, and 79 cases of normal pregnant women).²⁴ The ROC curve analysis showed that TT had the highest predictive value for PE (AUC: 0.743) with a cut-off value of 12.65s, which is recommended as a potential indicator for early monitoring of the onset and severity of PE. In this study, the cut-off value of TT in late pregnancy was 13.45 s, which was higher than that of Han L *et al.* The reason may lie in the difference in preeclampsia between singleton and twin pregnancies. The changes in blood coagulation indicators were more obvious and the condition was more serious in twin pregnancies with PE of late pregnancy.

The present study has some shortcomings. The sample size of twin pregnancies with and without PE was very

small due to the low prevalence of PE. In the foreseeable future, a much larger sample size is needed to unveil the underlying mechanism of changes of blood coagulation indices in twin pregnancy with PE.

CONCLUSION

Normal twin pregnancies have a physiological hypercoagulable state in the middle and late pregnancies. When combined with PE, systemic arteriolar spasm and vascular endothelial cells are severely damaged, which may cause abnormalities of the internal and external coagulation system, abnormal blood hypercoagulability, consumption of blood coagulation factors such as platelets and fibrinogen. The reason may be the difference between preeclampsia in singleton and twin pregnancies. The change of coagulation index of PE in late pregnancy with twin pregnancy is more obvious and the condition is more serious.

ETHICAL APPROVAL:

This study has been reviewed and approved by the Ethics Committee of the Fujian Provincial Maternal and Child Health Hospital.

PATIENTS' CONSENT:

Informed consents were obtained from all participants.

CONFLICT OF INTEREST:

Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

JY: Lead and conceived the project.

ZL: Contributed to design articles, collected and analysed data, and authored the manuscript.

HZ, LL: Contributed to collect and analyse data.

LC: Helped perform the analysis with constructive discussions.

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