The clinical value of fibrinogen and thromboelastography in the predictive assessment of the progression of persistent postpartum hemorrhage

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ABSTRACT

This study aims to explore the value of fibrinogen (FIB) and thromboelastography in evaluating persistent postpartum hemorrhage. A total of 130 parturients were divided into the control group (non-persistent postpartum hemorrhage, n=83) and the observation group (persistent postpartum hemorrhage, n=47), and the observation group was further divided into the mild bleeding group (n=30) and the severe bleeding group (n=17). FIB and D-dimer (D-D) were measured by an automatic coagulation analyzer, and the coagulation reaction time and coagulation time were measured by thromboelastography. FIB was decreased, while D-D levels, R value, and K value were increased in the observation group and the severe bleeding group ($p<0.05$). FIB was negatively correlated with the R and K values ($r=-0.957$, -0.921), while D-D was positively correlated with them ($r=0.943$, 0.968). Receiver operating characteristic curve analysis showed that the areas under the curve of FIB, D-D, R value, and K value were 0.861, 0.892, 0.943, and 0.976, respectively ($p<0.05$). FIB and thromboelastography parameters are related to the severity of persistent postpartum hemorrhage.

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Introduction

Postpartum hemorrhage is a serious complication in the field of obstetrics and gynecology; it is one of the major causes of maternal death and serious health problems worldwide.[1] Although the progress of medical technology and the improvement of nursing level in recent years have been helpful to reduce the risk of postpartum hemorrhage, in some cases, especially persistent postpartum hemorrhage, it is still a problem worthy of attention.[2-4] Persistent postpartum hemorrhage is defined as postpartum hemorrhage for more than 24 hours. Although its incidence is relatively low, its severity and influence should not be underestimated. Persistent postpartum hemorrhage may lead to excessive blood loss in the maternal body, and then lead to hypovolemic shock, endangering maternal life.[5,6] In addition to directly endangering maternal life, persistent postpartum hemorrhage will also lead to the disorder of coagulation function in blood vessels, which will increase the risk of maternal coagulation-related complications, such as thromboembolism.[7] Therefore, it is very important to predict and intervene in the progress of persistent postpartum hemorrhage as soon as possible to ensure maternal health. Fibrinogen (FIB) and thromboelastography (TEG) are two important indexes commonly used to evaluate coagulation function. FIB is a coagulation factor that is very important for the formation of thrombosis.[8] TEG is a comprehensive method to evaluate the process of blood coagulation and

fibrinolysis. By measuring the coagulation parameters at different stages, the state of coagulation function can be understood more comprehensively.[9,10]

In recent years, more and more studies have begun to pay attention to the potential value of FIB and TEG in predicting postpartum hemorrhage.[11] These studies mainly focus on analyzing the relationship between these indicators and postpartum hemorrhage, and their clinical significance in predicting the progress of postpartum hemorrhage at an early stage. However, the current research on the prediction of persistent postpartum hemorrhage, especially the prediction of progress, is still relatively limited. Therefore, this study aimed to explore the clinical value of FIB and TEG in predicting the progress of persistent postpartum hemorrhage. We collected a certain amount of maternal data and analyzed different coagulation indexes, especially the measurement of FIB and TEG parameters, to evaluate the relationship between them and the progress of persistent postpartum hemorrhage. Through this study, we hoped to further understand the role of these indicators in the pathogenesis of postpartum hemorrhage and provide a more scientific basis for the prediction and intervention of postpartum hemorrhage.

Patient selection criteria

From January 2021 to December 2022, 130 pregnant women who completed delivery in the Department of Obstetrics and Gynecology of our hospital were recruited as the research objects.[12] The age of pregnant women ranged from 21 to 40 years old, with an average age of 28.43±4.49 years. According to related clinical symptoms and diagnostic criteria of persistent postpartum hemorrhage, pregnant women were divided into a control group (non-persistent postpartum hemorrhage, n=83) and an observation group (persistent postpartum hemorrhage, n=47), and the observation group was divided into a mild hemorrhage group (n=30) and a severe hemorrhage group (n=17) according to the amount of hemorrhage. All invalids were informed of the protocol when they were enrolled in the study and signed informed consent.

Admission criteria

Maintaining a normal pregnancy and successful delivery. Maternal women with complete clinical data. Pregnant women who had not found fetal abnormalities during prenatal examination. Pregnant women with 37-42 weeks. According to the clinical symptoms and the statistical results of blood measurement, it was preliminarily judged that the parturient in the observation group had or was suspected of persistent postpartum hemorrhage, was willing to participate in research, and was able to abide by the research program procedures.

Exclusion criteria

Patients with known coagulation system diseases or hemorrhagic diseases. Patients with premature delivery or other abnormal pregnancy. Patients with high-risk delivery complications (such as preeclampsia, placental abruption, *etc*.). Patients who had received anticoagulant therapy. Patients who had received whole blood or platelet transfusions. Patients with other serious basic diseases, such as severe heart disease and kidney disease.

Materials and Methods

Blood transfusion support therapy

The components of the patient's transfusion include suspended red blood cells and fresh frozen whole blood. The suspended red blood cells transfused by the patient are ≥8 U. After transfusing 8 U of suspended red blood cells, 800 mL of fresh frozen Whole blood should be matched. Suspended red blood cells: fresh frozen whole blood was infused at a ratio of 1:1, >1:1, and<1:1. During the infusion process, the patient's coagulation function and blood routine indicators were monitored every 2 hours, and the transfusion treatment plan was adjusted in a timely manner based on the examination results. When FIB is less than $1.0g \cdot L^{-1}$, 10 U cryoprecipitate is infused. When the platelet count (PLT) is less than 50×10^9/L, one therapeutic dose of PLT is collected by the infusion machine. If necessary, FIB and prothrombin complex are given to correct coagulation function and prevent DIC. During the process of infusing blood components, close attention should be paid to the patient's basic vital signs, bleeding situation, tolerance, and the occurrence of adverse reactions such as transfusion reactions. The data collection time for PPH is set after PPH and before transfusion.

Blood sample collection and index detection of surgical techniques

The collection of blood samples used sodium citrate tubes. In the morning of the second day after the operation, blood samples were collected from two groups of women. The horizontals of FIB and D-dimer (D-D) were tested by the CS-5100 automatic hemagglutination instrument. The reaction time (R) and coagulation time (K) were measured by the LEPV-8800 thromboelastometer (Aeroflex Corporation, Plainview, NY, USA).

Analysis of measurement results

The reaction time, coagulation time, FIB, and D-D levels of patients with persistent postpartum hemorrhage (the amount of bleeding within 24 hours after delivery ≥600 mL) and non-persistent hemorrhage were measured. Patients with persistent bleeding were divided into the severe bleeding group (n=17, the amount of bleeding within 24 hours after delivery ≥900 mL) and the mild bleeding group (n=30, the amount of bleeding within 24 hours after delivery □900 mL). By drawing diagnostic receiver operator characteristic (ROC) curves of FIB, D-D, reaction time, and clotting time in women with persistent bleeding, coagulation and TEG indicators were calculated to predict the area under the curve (AUC) of persistent bleeding.

Statistical analysis

SPSS22.0 (IBM, Armonk, NY, USA) statistical software was used to analyze the research data. The measurement data were expressed as mean ± standard deviation. A *t*-test was used for data with normal distribution or uniform

variance, and an approximate *t*-test was used for data with uneven variance. An F-test was used to compare the differences between groups. Chi-square test was used to compare the differences in counting data between groups. GraphPad Prism 8 software was used to draw graphs. A p-value <0.05 meant the difference was statistically significant.

Results

General data analysis

According to the general data of pregnant women, the average age of the control group was 28.75±4.33 years old, the average body mass index (BMI) was 23.18±1.95 kg/m^2, the average pregnancy cycle was 39.35±1.74 weeks, and the average number of births was 1.26±0.35, including 8 cases of gestational diabetes and 3 cases of gestational hypertension. The average age of the observation group was 29.56±5.18 years old, the average BMI was 23.65±2.02 kg/m^2, the average pregnancy cycle was 39.26±1.85 weeks, and the average number of births was 1.31±0.32, including 5 cases of gestational diabetes mellitus and 1 case of gestational hypertension. There was no distinguish in general information between the two groups (p>0.05) (Table 1).

Comparison of maternal coagulation indicators

The levels of FIB and D-D were tested by an automatic hemagglutination instrument. The level of FIB in the observation group was lower than control group (p<0.05), and the level of D-D in the observation group was higher than control group (p<0.05) (Table 2).

Comparison of maternal thromboelastography indicators

The reaction time and coagulation time of pregnant women in both groups were detected by the thromboelastometer. Coagulation time and reaction time in the observation group were longer than control group (p<0.05) (Figure 1 and Table 3).

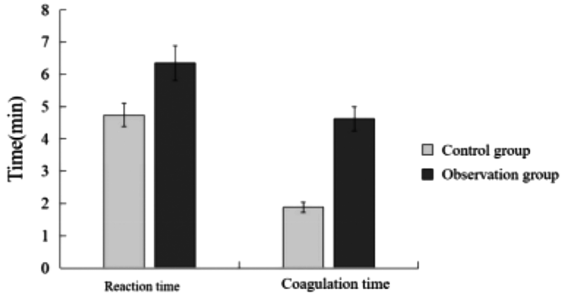

Figure 1. Comparison of maternal thromboelastography indicators.

Table 1. General data analysis.

Projects	Control group (n=83)	Observation group (n=47)	T-value/χ^2 value	p
Age (years)	28.75±4.33	29.56±5.18	4.117	0.552
Body mass index (kg/m^2)	23.18±1.95	23.65±2.02	3.206	0.135
Pregnancy cycle (weeks)	39.35±1.74	39.26±1.85	2.547	0.116
Birth order (times)	1.26±0.35	1.31±0.32	1.002	0.267
Gestational diabetes (%)	8(9.63%)	5(10.63%)	3.578	0.515
Pregnancy induced hypertension (%)	3(3.61%)	1(2.12%)	2.449	0.403

Table 2. Comparison of coagulation indexes of pregnant and lying-in women.

Groups	Fibrinogen (g/L)	D-dimer (mg/L)
Control group (n=83)	5.34±0.58	0.87±0.06
Observation group (n=47)	2.77±0.36	1.24±0.15
T-value	14.228	9.305
p	0.001	0.002

Table 3. Comparison of maternal thromboelastography indicators.

Groups	Reaction time (min)	Coagulation time (min)
Control group (n=83)	4.74±0.36	1.88±0.15
Observation group (n=47)	6.35±0.54	4.63±0.37
T-value	11.651	13.446
p	0.001	0.001

Comparison of coagulation indexes and thromboelastography indexes of pregnant women with persistent bleeding

The levels of FIB and D-D, reaction time, and coagulation time of pregnant women with persistent bleeding were detected by an automatic hemagglutination instrument and a thromboelastometer. The level of D-D in the severe bleeding group was higher than in the mild bleeding group ($p<0.05$), and the level of FIB in the severe bleeding group was lower than in the mild bleeding group ($p<0.05$). The coagulation time and reaction time in the severe bleeding group were longer than those in the mild bleeding group ($p<0.05$) (Table 4).

The correlation between coagulation index and thromboelastography index in women with persistent bleeding

Data analysis showed that FIB was negatively correlated with reaction time ($r=-0.957$, $p<0.001$) and coagulation time ($r=-0.921$, $p<0.001$). D-D was positively correlated with reaction time ($r=0.943$, $p<0.001$) and coagulation time ($R=0.968$, $p<0.001$) (*Supplementary Table 1*).

The predictive value of coagulation and thromboelastography indexes for persistent bleeding

The AUC of coagulation and TEG indexes was calculated by the ROC curve. The results showed that the diagnostic AUC of FIB, D-D, reaction time and coagulation time were 0.861 [95% confidence interval (CI) 0.632-0.975, $p<0.05$] and 0.892 (95% CI 0.615-0.883, $p<0.05$), 0.943 (95% CI 0.916-1.157, $p<0.05$), 0.976 (95% CI 0.963-1.204, $p<0.05$), respectively (*Supplementary Figure 1* and *Supplementary Table 2*).

Discussion and Conclusions

Postpartum hemorrhage refers to the situation that which the vaginal bleeding of the parturient exceeds 500 mL (or the bleeding exceeds 1000 mL within 2 hours after the end of labor) within 24 hours after delivery due to insufficient uterine contraction, torn cervix or perineum, incomplete endometrial stripping, and other reasons. It is one of the major reasons that threaten maternal life. Postpartum hemorrhage is a common but serious complication in obstetrics and gynecology, which poses a threat to maternal and neonatal health.[13-15]

The results showed that the level of FIB in the observation group was lower than in the control group, which may reflect the weakening of platelet function and blood clot formation during postpartum persistent bleeding. FIB, as a key coagulation protein, is very important for maintaining normal coagulation function.[16] The abnormal reduction may lead to a decrease in thrombosis ability, thus increasing the risk of postpartum hemorrhage.[17] However, the increase in maternal D-D level in the observation group may reflect the disorder of postpartum coagulation and the enhancement of thrombolysis. D-D is a product of fibrin degradation, and its rise may indicate abnormal degradation of fibrin and abnormal activation of the coagulation system. These results further highlight the important role of FIB and D-D in postpartum hemorrhage. The role of these indexes in postpartum hemorrhage is further discussed. The abnormal changes of FIB and D-D may be related to the disorder of the coagulation system. Factors such as poor postpartum uterine contraction and insufficient uterine wound contraction may lead to uncontrollable bleeding, which may lead to disorders of coagulation function.[18] The increase of D-D may be due to the abnormal degradation of fibrin, which leads to the formation of fibrin polymer, thus activating the process of thrombosis and dissolution. These changes may further affect platelet aggregation and thrombin activation, leading to the aggravation of postpartum hemorrhage.

Further analysis found that the coagulation time and reaction time of the observation group were longer than those of the control group, indicating that the coagulation function of the observation group was impaired. These findings provided a deeper understanding of the study, revealing the close relationship between FIB, D-D, coagulation time, and reaction time and the severity of persistent postpartum hemorrhage. The discovery of this correlation had important guiding significance in clinical practice, which was helpful to more accurately evaluate the risk of maternal bleeding and formulate individualized intervention strategies. The coagulation time and reaction time of the observation group were longer than those of the control group, suggesting that the coagulation function of the observation group was obviously impaired. This may be related to the dysfunction of the coagulation system caused by postpartum hemorrhage. In the process of postpartum hemorrhage, the blood vessels of the uterine wound need to be closed by coagulation, and the impairment of coagulation function may lead to a decrease in platelet aggregation and vasoconstriction, which will further aggravate the bleeding situation.[19,20] In terms of severity, the level of D-D rose, the level of FIB reduced, and the coagulation time and reaction time prolonged in the severe bleeding group, which further supported that these indexes were related to the severity of bleeding. The increase of D-D may be due to the abnormal degradation of

Table 4. Comparison of coagulation indexes and thromboelastography indexes in women with persistent bleeding.

Groups	Fibrinogen (g/L)	D-dimer (mg/L)	Reaction time (min)	Coagulation time (min)
Mild bleeding group (n=30)	5.57±0.60	1.03±0.08	5.49±0.43	3.52±0.36
Severe bleeding group (n=17)	2.15±0.22	1.46±0.13	7.03±0.61	5.25±0.44
T-value	9.251	14.706	14.622	11.419
p	0.004	0.001	0.001	0.001

fibrin caused by bleeding, thus activating the thrombolysis process. The decrease in FIB level may lead to a decrease in thrombosis ability, while the prolongation of coagulation time and reaction time further shows the disorder of coagulation function. The consistency of these results reveals the importance of these indicators in evaluating the severity of persistent postpartum hemorrhage. Further discussion on the relationship between these indicators and the severity of postpartum hemorrhage will help clinicians to identify high-risk parturients more accurately and take early intervention measures. In actual clinical practice, these indicators can be used as a powerful tool to predict the severity of postpartum hemorrhage and help doctors quickly judge the condition of the parturient and make appropriate treatment plans. In addition, these results also provide clues for further study on the pathogenesis of postpartum hemorrhage, which is helpful to deeply understand the role of coagulation dysfunction in postpartum hemorrhage.

In this study, the Pearson correlation coefficient was used to analyze the correlation between FIB and reaction time and coagulation time. It was found that FIB was negatively correlated with these two indexes, while D-D was positively correlated with them. FIB was negatively correlated with reaction time and coagulation time, which meant that the decrease in FIB level was related to the extension of coagulation time. FIB is an important precursor to form fibrin clots during coagulation, and coagulation time is an important parameter to measure coagulation function.[21,22] The decrease of FIB may mean that the ability of blood to form fibrin clots is weakened during coagulation, which may lead to the prolongation of coagulation time. This may be because in the case of persistent postpartum hemorrhage, a large amount of FIB is consumed, which affects the coagulation system. Secondly, D-D is positively correlated with reaction time and coagulation time, which means that the increase in D-D level is related to the extension of coagulation time. D-D is the product of fibrinolysis, and its increase may reflect the abnormal degradation of fibrin and the process of thrombolysis.[23,24] The prolonged coagulation time may be related to the dysfunction of the coagulation system, which leads to the prolonged coagulation time of blood.[25-27] This positive correlation may be due to the accelerated degradation of fibrin in the case of postpartum hemorrhage, which leads to an increase in D-D level, and also affects the normal function of the coagulation system, leading to the extension of coagulation time. The consistency of these results strengthens the role of FIB, D-D, coagulation time, and reaction time in postpartum coagulation function.[28-31] The relationship between these indexes reveals that the function of the maternal coagulation system may be affected by many factors, including the decrease of FIB level and the increase of D-D level. Further research can explore the relationship between these changes and the mechanism of postpartum hemorrhage and provide a more accurate basis for clinical intervention.[32,33]

By calculating the ROC curve, the predictive value of FIB, D-D, reaction time, and coagulation time for persistent postpartum hemorrhage was evaluated. The results show that the diagnostic AUC of these indexes is high, which shows that they have certain clinical value in predicting persistent postpartum hemorrhage. The high diagnostic AUC value shows that these indexes have high accuracy and discrimination in predicting persistent postpartum hemorrhage. This means that these indicators can distinguish the possibility of persistent postpartum hemorrhage to a certain extent and provide clinicians with an auxiliary judgment tool. Specifically, the high AUC values of FIB, D-D, reaction time, and coagulation time indicate that they may have good application potential in the diagnosis of postpartum coagulation dysfunction. These results have important clinical significance for early diagnosis and intervention of postpartum hemorrhage. Once the abnormal changes of these coagulation indexes occur in the parturient, doctors can take measures earlier to reduce or avoid the risk of persistent postpartum hemorrhage. For example, for pregnant women with high D-D level and prolonged coagulation time, more active intervention measures, such as infusion of coagulation factors or other appropriate treatments, can be considered to prevent further aggravation of bleeding.

This study has some limitations. Specifically, blood samples were collected the day after the intervention. This timing arrangement means that the measured values may, at least to some extent, be influenced by ongoing bleeding events, rather than merely representing predictive factors for their occurrence. Therefore, the results of this excellent study seem to provide more information about the risk of postpartum hemorrhage progression rather than its early prediction. In this regard, future studies that can obtain coagulation data either before the onset of bleeding or immediately after it begins would be highly valuable.

To sum up, our results emphasize the importance of FIB and TEG in predicting persistent postpartum hemorrhage. These indexes have potential clinical application value in evaluating maternal coagulation function and bleeding risk.

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Online supplementary material:

Supplementary Figure 1. X-ray plain film analysis of the receiver operator characteristic curve predicted by coagulation and thromboelastography indexes for persistent bleeding.

Supplementary Table 1. Study on the correlation between coagulation index and thromboelastography index in parturients with persistent bleeding.

Supplementary Table 2. Comparison of coagulation indexes and thromboelastography indexes in women with persistent bleeding.