Analysis of perinatal coagulation function in preeclampsia
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Abstract
To study the dynamic changes in perinatal coagulation function in patients with preeclampsia (PE).

The general data and coagulation indexes of 290 PE patients during the perinatal period (prenatal and 1 and 3 days postpartum) and 256 healthy pregnant women in the third trimester of pregnancy were investigated, and the data were analyzed.

Compared with healthy pregnant women, prothrombin time (PT), fibrinogen (FIB), platelet count (PLT), mean platelet volume (MPV), thrombocytocrit (PCT), maximum amplitude (MA), and coagulation index (CI) of PE patients decreased, and activated partial thrombin time (APTT), thrombin time (TT), D-dimer (DD), platelet distribution width (PDW) and K values increased before delivery (P < .05). APTT and FIB in PE patients were lower in the day 1 postpartum group than in the prenatal and postpartum day 3 groups, and TT, DD, and fibrin degradation products (FDP) were higher (P < .05). PCT and MPV were highest in the prenatal group (P < .05).

Compared with that of healthy pregnant women, the coagulation function of PE patients is in a relatively low-coagulation and high-fibrinolysis state on postpartum day 1, which increases the risk of postpartum hemorrhage and other adverse outcomes.

Abbreviations: APTT = Activated partial thrombin time, AT = antithrombin, CI = coagulation index, DD = D-dimer, FDP = fibrin degradation products, FIB = fibrinogen, LMWH = low molecular weight heparin, MA = maximum amplitude, MPV = mean platelet volume, PCT = thrombocytocrit, PDW = platelet distribution width, PE = preeclampsia, PLT = platelet count, PPH = postpartum hemorrhage, PT = prothrombin time, TEG = thrombelastogram, TT = thrombin time.

Keywords: coagulation function, low molecular weight heparin, postpartum hemorrhage, preeclampsia

1. Introduction
Preeclampsia (PE) is a common complication among pregnant women, with an incidence of approximately 5% to 8%.[1] If uncontrolled, the disease can progress to adverse consequences such as disseminated intravascular coagulation (DIC) and multiple organ failure (MOF).[2,3]

Vascular endothelial injury underlies the pathophysiological changes in PE patients.[4] Placental and immunologic abnormalities lead to the release of inflammatory cytokines in PE patients. Inflammatory factors cause inflammatory reactions, vascular endothelial injury, and exposure of collagen and tissue factors under the endothelium, leading to a series of changes in the coagulation, anticoagulation, and fibrinolytic systems, which then affect other systems,[5-6] leading to fetal death in utero, dysontogenesis, and other adverse obstetrical outcomes.

The commonly used laboratory tests of coagulation function in clinical practice include routine blood cell counts, coagulation factors, plasma fibrin degradation products (FDP), antithrombin (AT), and other indicators of coagulation, anticoagulation, and fibrinolytic functions. In addition, thromboelastography (TEG) can continuously and dynamically monitor the whole process of formation and degradation of blood clots.[7-8]

Administration of anticoagulants, such as low molecular weight heparin (LMWH) and AT, is an effective treatment for patients with severe PE complicated by DIC. It is gradually recognized clinically by blocking the malignant process of coagulation reaction.[9]

Many clinical studies have demonstrated the hypercoagulable state of healthy pregnant women in the third trimester.[10-11] To further assess coagulation function, postpartum hemorrhage (PPH), and risk of thrombosis in PE patients, we compared the third trimester coagulation function of PE patients and healthy pregnant women, assessed the changes of PE patients further assess coagulation function, postpartum hemorrhage, and risk of thrombosis in PE patients.

2. Materials and methods
2.1. Research subjects
The study subjects were 290 PE patients admitted to Sheng Jing Hospital of China Medical University from January to April 2018. General demographic and clinical data such as age, gestational week, number of gestation, and BMI were recorded, and the results of routine blood cell counts, blood coagulation
tests, TEG, and other indicators during the perinatal period (prenatal, postpartum day 1, and postpartum day 3) were also obtained. The control group consisted of 256 randomly selected healthy pregnant women in the third trimester admitted during the study period and their general data and coagulation indicators in the third trimester were recorded.

2.2. Inclusion and exclusion criteria
2.2.1. Inclusion criteria. The PE patients were women younger than 40 years old who met the diagnostic criteria for PE in the guidelines for diagnosis and treatment of hypertensive diseases in pregnancy [2014] [12]. The healthy pregnant women were between 24 and 40 years old, with a single fetus, normal fetal development, normal liver and kidney function, and without eclampsia, gestational diabetes mellitus, fetal growth restriction, or history of other adverse pregnancy conditions.

2.2.2. Exclusion criteria. Patients with smoking, alcohol, and drug use were excluded, as were those with medical conditions including chronic hypertension with pregnancy, acute and chronic hepatitis, acute and chronic kidney diseases, cardiovascular and cerebrovascular diseases, and endocrine and blood system diseases. Patients with other pregnancy complications were excluded.

2.3. Statistical analysis
Statistical software SPSS19.0 was used for statistical analysis, and measurement data were expressed as mean ± standard deviation. For data conforming to normal distribution, the mean between two groups was compared by independent sample t test, and the mean between multiple groups was compared by one-way Anova. The data that do not fit the normal distribution are compared after normal transformation. Counting data were represented by the number of cases and percentage, and the chi-square test was used for comparison between groups. P < .05 was considered to indicate a statistically significant difference.

2.4. Ethics
The Shengjing Ethics Committee has approved our study.

3. Results

3.1. General clinical characteristics
Compared with the general clinical characteristics of healthy pregnant women in the third trimester of normal pregnancy (Table 1), the gestational weeks, neonatal weight, and neonatal Apgar score (1 min and 5 min) of PE patients were significantly lower, and BMI, blood pressure (systolic and diastolic) was significantly higher (P < .001). Thirty-seven PE patients (12.76%) gave birth at 28–32 weeks gestation, 91 (31.38%) at 32–36 weeks, and 149 (51.38%) at 32–36 weeks; in contrast, the healthy pregnant women all delivered after 36 weeks. The difference was significant (P < .001). Among PE patients, there were 19 cases of stillbirth (6.20%). Postpartum hemorrhage, defined as blood loss greater than 1000 ml within 24 h after delivery, occurred in 13 cases (4.48%). There was no postpartum hemorrhage or stillbirth in the control group, and the difference was statistically significant (P < .05).

3.2. Comparison of clotting function between PE patients and healthy pregnant women in the third trimester of pregnancy
Compared with values in the healthy pregnant women, APTT, TT, DD, PDW, K were significantly increased, PT, FIB, PLT, MPV, PCT, MA and CI values in the PE patients were significantly shortened (P < .05, Table 2).

3.3. Comparison of prenatal coagulation index between PE patients at different gestational weeks and healthy pregnant women
PE patients were further stratified according to gestational week and compared with healthy pregnant women in terms of their

### Table 1
Comparison of general clinical characteristics between PE patients and healthy pregnant women in the third trimester.

| Project                  | PE (n = 290)   | Normal (n = 256) | P    |
|--------------------------|----------------|------------------|------|
| Age (y)                  | 30.09 ± 4.51   | 29.44 ± 3.74     | .067 |
| Gestational age (w)      | 35.48 ± 3.67   | 39.47 ± 0.91     | < .001 |
| Stratification of gestational age |                  |                  |      |
| 28–32W                   | 37 (12.76%)    | 0                | < .001 |
| 32–36W                   | 91 (31.38%)    | 0                | < .001 |
| >36W                     | 149 (51.38%)   | 256 (100%)       | < .001 |
| BMI                      | 27.70 ± 4.26   | 26.55 ± 3.17     | .012 |
| Blood tension (mmHg)     |                |                  |      |
| Systolic blood pressure  | 152.86 ± 19.77 | 117.86 ± 10.27   | < .001 |
| Diastolic blood pressure | 96.52 ± 13.40  | 76.1 ± 7.29      | < .001 |
| Gravdity                 | 1.87 ± 1.10    | 157.2 ± 0.87     | .106 |
| Parity                   | 0.18 ± 0.405   | 0.18 ± 0.413     | .974 |
| Neonatal weight (g)      | 2449.17 ± 985.26 | 3522.24 ± 397.73 | < .001 |
| Apgar score              |                |                  |      |
| 1 min                    | 9.21 ± 1.44    | 9.86 ± 0.67      | < .001 |
| 5 min                    | 9.79 ± 0.54    | 9.95 ± 0.36      | < .001 |
| Live births/stillbirth   | 272/19 (93.6%/6.20%) | 256/0 (100%/0)   | < .001 |
| Postpartum bleeding (ml) | 210.09 ± 109.63 | 198.89 ± 58.86   | .506 |
| PPH                      | 13/277 (4.48%/95.52%) | 0/256 (0/100%)    | < .001 |

BMI = Body Mass Index, PE = preeclampsia, PPH = postpartum hemorrhage.
blood coagulation indexes before pregnancy. With the increase in gestational weeks, PT in the PE patients showed an increasing trend but were lower than in the healthy pregnant women, TT and PDW gradually decreased but were higher than in the healthy pregnant women, and MA values in the PE groups were all significantly lower than in the healthy pregnant women ($P < .05$). Also, the APTT and DD of the PE groups were both higher than in the healthy pregnant women. FIB, PLT, MPV and PDW gradually increased and there was no statistical difference between the greater than 36 weeks group and the healthy pregnant women ($P > .05$). Other indicators of TEG were also close to the normal level of normal pregnant women with the increase of gestational weeks. Further pair comparison among the three groups of PE patients showed that the PT and TT of the first two groups were statistically different from those of the group over 36 weeks; the FIB, MPV and PDW were statistically different between the 28–32w group and the group over 36W; the PLT and PCT were statistically different between the 32–36w group and the group over 36W ($P < .05$, Table 3).

### 3.4. Coagulation index changes in PE patients in the perinatal period

The clotting index changes in PE patients during the perinatal period (prenatal, day 1, and day 3 after delivery) were analyzed. APTT and FIB were significantly lower in the day 1 group than in the prenatal and day 3 group ($P < .05$), and there was no statistical difference between the prenatal and day 3 groups. TT, DD, and FDP were significantly larger in the day 1 after delivery group than in the prenatal and day 3 groups ($P < .05$), while there was no significant difference between the prenatal and day 3 groups. PCT and MPV showed a trend of gradual decrease, significantly greater in prenatal than in day 1 group and day 3 group ($P < .05$), and no statistical difference between day 1 and day 3 groups ($P > .05$). The data on TEG related indicators were insufficient in the day 3 group, and the MA value in the prenatal group was significantly greater than in the day 1 group ($P < .05$). There was no statistical difference between the remaining data, including relatively prolonged PT on day 1 after delivery, PLT showed a trend of first decrease and then increase, and PDW showed an overall trend of increase (Table 4).

### 4. Discussion

The coagulation dysfunction of PE patients is the result of multiple factors, including heredity and environment. In order to prevent PPH and other adverse obstetric outcomes in women in the third trimester of normal pregnancy, physical reserves of clotting substances are increased, and a state of hypercoagulability is maintained. On the basis of the relatively stable hypercoagulability of normal pregnant women, PE patients fail to establish the appropriate immune tolerance, and the fetus as a...
semi-graft causes immune rejection; meanwhile, uterine spiral arteriolar recast disorder; placenta ischemia and hypoxia lead to the release of inflammatory factors and vascular endothelial injury.[14] A large number of tissue factors, vascular hemophilia factors, and other factors are released to initiate local endogenous and exogenous coagulation pathways, and the risk of thrombosis is increased. PE patients are in a local pathological hypercoagulable state, which is equivalent to the hypercoagulable period of DIC.[15] If the condition of PE patients continues to progress, the local high coagulation state of the blood causes the consumption of coagulation substances, leading to the body into the consumptive low coagulation state. At this time, the body’s blood clotting material reserve is insufficient, and the risk of PPH increases. Unlike the causes of PPH in the third trimester of normal pregnancy, hypercoagulability and fibrinolysis are the main causes of PPH in PE patients, while most of the former are due to placental causes or birth canal damage.[16]

It has been reported that PE patients have coagulation dysfunction in the third trimester of pregnancy, and adverse maternal outcomes such as PPH and even DIC and MOF, as well as adverse fetal outcomes such as fetal death in utero, fetal growth restriction, stillbirth.[17] In our study, the systolic and diastolic blood pressure of PE patients were significantly higher than in healthy pregnant women, and the gestational age, neonatal weight, and neonatal Apgar score of PE patients were significantly lower than those of healthy pregnant women, which accords with the results of previous reports.[18] In addition, PE patients had a higher incidence of stillbirth and postpartum hemorrhage than healthy pregnant women, and BMI of PE patients was higher than that of normal pregnant women (P < .05), while in the 2020 edition of guidelines for the diagnosis and treatment of hypertension during pregnancy, it is recommended that overweight pregnant women control their body weight to a BMI of 18.5–25 and abdominal circumference < 80 cm to reduce the risk of the disease during a second pregnancy.

Compared with healthy pregnant women, PE patients had decreased PT, FIB, PLT, MPV, and PCT; increased DD, APTT, TT and PDW; all of the differences were statistically significant (P < .05). These differences indicate a relatively hypocoagulable state in patients with PE. APTT, TT prolongation and PLT and FIB reduction were also reported by Chen.[19] In contrast, Wang Shuang[20] reported that PE patients were in a state of high coagulation and low anticoagulation in the third trimester compared with healthy pregnant women, which differs from our results. The results of our study suggest that the coagulation material was consumed; fibrinolytic activity was enhanced, and platelet levels showed compensatory increase. Shortening of the PT may be related to vascular endothelial injury and massive release of tissue factors that activate the exogenous coagulation pathway.[21] In our PE patients, the TEG K value was prolonged and the MA and CI values were decreased, which basically accords with the changes in the conventional coagulation indicators, indicating that compared with the healthy pregnant women, the PE patients had a coagulation substance deficit in the third trimester of pregnancy. At this time, the body is generally in a state of relatively low coagulation and high fibrinolysis compared with normal pregnant women, and the coagulation state is unstable and the compensatory ability is poor. The number of postpartum hemorrhage is significantly increased also suggests that a large amount of clotting substances are consumed during childbirth, so it is necessary to intervene in advance for PE patients to avoid excessive consumption of clotting factors. For PE patients who fail to interrupt the excessive consumption of coagulation substances early, the coagulation indexes should be corrected to the level above the lower limit of normal pregnant women’s coagulation function before delivery to ensure that there are enough coagulation factors to participate in hemostasis.

Considering that although PE patients and normal pregnant women were in the same third trimester, the gestational span of PE patients was large, so the gestational age of PE patients was stratified to compare the differences in blood coagulation function in different gestational age intervals, and then compared with the normal pregnant women respectively. It can be seen that with the increase of gestational age, the clotting state of PE patients in the third trimester is similar to that of healthy pregnant women. FIB, PLT, MA, PCT, MA, and CI values of PE patients in

| Table 4 | Coagulation index changes in PE patients in the perinatal period. |
|---------|---------------------------------------------------------------|
|         | Prenatal (n = 165)                                          | Day 1 after delivery (n = 240) | Day 3 after delivery (n = 110) | P1   | P2   | P3   |
| PT (s)  | 9.71 ± 0.61                                                 | 9.82 ± 0.74                    | 9.76 ± 0.68                     | .149 | .627 | .454 |
| APTT (s)| 28.49 ± 2.95                                                | 27.63 ± 4.39                   | 28.90 ± 4.48                    | .035 | .403 | .006 |
| FIB (g/L)| 4.23 ± 0.76                                                 | 3.80 ± 0.83                    | 4.49 ± 0.95                     | .<001 | .042 | .<001 |
| TT (s)  | 15.13 ± 0.75                                                | 15.46 ± 1.08                   | 15.24 ± 0.81                    | .<001 | .341 | .037 |
| DD (mg/L)| 807.6 ± 644.35                                              | 1981.5 ± 4268.96               | 1072.94 ± 1377.91               | .<001 | .085 | .007 |
| FDP (mg/L)| 13.5 ± 13.32                                               | 59.49 ± 72.64                  | 18.62 ± 23.96                   | .002 | .483 | .004 |
| AT (%)  | 62.25 ± 15.85                                               | 63.68 ± 17.71                  | 73.67 ± 14.46                   | .833 | .140 | .094 |
| PLT (×10^9/L)| 179.91 ± 65.14                                             | 169.95 ± 61.07                | 182.96 ± 73.07                  | .131 | .683 | .058 |
| MPV (fl) | 10.55 ± 1.54                                                | 9.99 ± 1.58                    | 9.28 ± 1.54                     | .<001 | .<001 | .<001 |
| PCT (%) | 0.19 ± 0.07                                                 | 0.17 ± 0.06                    | 0.16 ± 0.06                     | .<001 | .<001 | .650 |
| PDW (%) | 15.96 ± 2.64                                                | 16.28 ± 2.22                   | 16.37 ± 2.28                    | .181 | .199 | .915 |
| R (min) | 5.44 ± 1.11                                                 | 4.83 ± 0.73                    | .140                           |
| K (min) | 1.63 ± 1.28                                                 | 2.99 ± 2.23                    | .161                           |
| Angle   | 68.98 ± 5.88                                                | 59.44 ± 13.68                  | .115                           |
| MA      | 67.69 ± 6.97                                                | 45.20 ± 25.68                  | .<001                           |
| CI      | 1.65 ± 1.69                                                 | 1.07 ± 3.15                    | .062                           |
| LY30 (%)| 0.83 ± 1.76                                                 | 1.98 ± 2.27                    | .430                           |

P1: prenatal group vs Day 1 after delivery group; P2: prenatal group vs Day 3 after delivery group; P3: Day 1 after delivery group vs Day 3 after delivery group.

PT, Activated partial thrombin time; AT, antithrombin; CI, coagulation index; DD, D-dimer, FDP, fibrin degradation products, FIB, fibrinogen, MA, maximum amplitude, MPV, mean platelet volume, PCT, thrombocytocrit, PDW, platelet distribution width, PLT, platelet count, PT, prothrombin time, TT, thrombin time.
different gestational age strata were all lower than in healthy pregnant women, reflecting a state of decreased coagulation factor function, reduced platelet number and function, and increased fibrinolysis. These findings may be due to the early gestational age and the failure of coagulation factors to reach the peak of synthesis, or they may be due to the consumption of coagulation substances caused by the local microthrombosis characteristic of the primary disease. Local microthrombosis leads to insufficient oxygen supply to the placenta, resulting in fetal dysplasia and an increase in premature births, again indicating the necessity of early anticoagulant therapy for PE patients. Both mechanisms may lead to insufficient blood coagulation reserve before delivery in PE patients, increasing the risk of PPH.

Further analysis of the dynamic changes of clotting indicators in the perinatal period of PE patients showed that due to the consumption of clotting substances during delivery, FIB levels were lowest at day 1 after delivery. At this time, the coagulation function of the body was weakened, while fibrinolytic activity was enhanced. TT, DD, and FDP reached the highest level 1 day after delivery, then gradually declined, and MPV and PCT gradually decreased ($P < .05$). In addition, at day 1 after delivery, PLT was at its lowest point and PDW was higher than before, also indicating the process of platelet consumption and continuous synthesis of new platelets. There was no statistical difference in the TEG-related indicators, but compared with the values in the prenatal period, the postpartum K value was prolonged, MA and CI were shortened, and LY30 was increased, indicating a state of low coagulation and high fibrinolysis, which is roughly consistent with previously reported findings. These indicators together suggest that day 1 after delivery is a high-risk stage for postpartum hemorrhage. If measures are taken in the early clinical stage to ensure that the prenatal coagulation substances are not overconsumed, the risk of bleeding can be greatly reduced in patients at day 1 after delivery, and coagulation function can gradually recover at postpartum day 3.

In addition, in the comparison between different gestational age groups, the PT, FIB, TT and platelet-related indexes in the first two groups were statistically different from those in the group $>36$W. FIB showed an increasing trend, and the generation of fibrinogen during delivery was accelerated after 28W. There was no difference in DD among the groups or compared with the normal pregnant women, which may be due to the large standard deviation of DD, suggesting the need for individual observation. DD is an effective indicator to reflect the secondary fibrinolytic activity of the body and suggest deep vein thrombosis. In the early establishment of the coagulation interval of normal pregnant women in the third trimester of pregnancy, the reference interval of DD was 254–1337ug/L, and it is suggested to pay attention to the risk of DIC in patients higher than the upper limit of this interval. If measures are taken in the early clinical stage to ensure that the prenatal coagulation substances are not overconsumed, the risk of bleeding can be greatly reduced in patients at day 1 after delivery, and coagulation function can gradually recover at postpartum day 3.

Therefore, we suggest that early application of anticoagulant therapy should be considered in combination with the results of coagulation function test in prenatal period to prevent thrombosis and the consumption of coagulation factors.

5. Conclusion
In conclusion, compared with healthy pregnant women, PE patients are in a state of coagulation dysfunction in the third trimester of pregnancy. In addition, if not controlled, PE may progress from hypercoagulation and local thrombosis, to the consumption of clotting substances, and even to a hypocoagulable state. Before delivery, PE patients had less clotting substances than healthy pregnant women, increasing the risk of PPH and other adverse obstetric outcomes. Through dynamic analysis of the perinatal coagulation function of PE patients, we found that day 1 after delivery is a high-risk stage for parturient women, and the risk of bleeding and thrombosis coexist. Therefore, we suggest that early application of anticoagulant therapy be considered in combination with the results of coagulation function test in prenatal period to prevent thrombosis and the consumption of coagulation factors.

Author contributions
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