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Investigation of the relationship between changes in maternal coagulation profile in the first trimester and the risk of developing preeclampsia

Pei-Pei Jin [a,1], Ning Ding [a,1], Jing Dai [a], Xiao-Yan Liu [b,**], Pei-Min Mao [b,*]

[a] Department of Laboratory Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Department of Blood Transfusion, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

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ABSTRACT

Normal pregnancy is a hypercoagulable state with an increase in coagulation factor levels and a decrease in natural anticoagulation. However, a higher hypercoagulable state with prolonged activated partial thromboplastin time (APTT), prothrombin time (PT), increased D-dimer, and mean platelet volume is seen in women with preeclampsia at the time of onset. In addition, endothelial dysfunction occurs before the clinical symptoms of preeclampsia. Therefore, we undertook this study to investigate the coagulation profile in the first trimester in women who developed preeclampsia later. A total of 853 pregnant women with singleton births at the Obstetrics and Gynecology Hospital of Fudan University between January 2021 and December 2021 were included in this case-control study. In the comparison with the controls (n = 531), the mean value of D-dimer, APTT, thrombin time (TT), antithrombin (AT)), and fibrin degradation products (FDP) was significantly lower in preeclamptic women at the time of diagnosis (n = 322). The changes in the coagulation profile were not associated with the severity or the time of onset. The reduced values of D-dimer, AT, and FDP, and increased values of TT were also observed in the first trimester in women who developed preeclampsia later and were not associated with the severity, or the time of onset of preeclampsia. After adjusting for maternal age and BMI, the values of D-dimer and AT in the first trimester were correlated to the risk of developing preeclampsia. Our findings suggest that there is an abnormal maternal response to the hemostatic system in early gestational age in women who developed preeclampsia later and measuring the coagulation profile could be an additional predictive marker of preeclampsia.

1. Introduction

Preeclampsia, a human-specific pregnancy disorder affects 2%–7% of all pregnant women after 20 weeks of pregnancy [1] and in response to 60,000 maternal deaths worldwide [2]. Preeclampsia is one of the leading causes of maternal and neonatal morbidity and mortality worldwide (14%), especially in developing countries [3]. Although the underlying mechanism of this pregnancy disorder is still unclear, maternal vascular endothelial cell dysfunction is suggested to be associated with the development of clinical symptoms of

* Corresponding author.
** Corresponding author.
E-mail addresses: liuxiaoyan1480@fckyy.org.cn (X.-Y. Liu), maopeimin1503@fckyy.org.cn (P.-M. Mao).
[1] P. Jin and N. Ding contributed equally to this work.

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preeclampsia [4].

Normal pregnancy is a hypercoagulable state with an increase in coagulation factor levels and a decrease in natural anti-coagulation, and this physiological change aims to prevent excessive maternal blood loss at delivery (reviewed in Ref. [5]). However, women with preeclampsia may develop coagulopathy, predisposing them to bleed complications. Vascular endothelial dysfunction can lead to abnormal coagulation [6,7], as it results in exposing collagen fibers and triggering platelet aggregation and adhesion [7]. These changes could result in placental ischemia and hypoxia, and cause placental villi degeneration and necrosis, which release coagulation substances and activate the exogenous coagulation system [8]. Reduced placental perfusion due to the failure of vascular remodeling contributes to the pathogenesis of preeclampsia. These studies highlighted that imbalance of coagulation activity, in particular, the alterations in coagulations in the early stage of pregnancy is associated with the development of preeclampsia [5]. In addition, abnormal enhancement of blood coagulation activity has been also suggested to be involved in the pathogenesis of pre-eclampsia, because of the increased frequency of venous thromboembolic events, thrombotic placental abnormalities, and thromboxane production in this population [9]. As a consequence of an imbalance of coagulation activity, multiple thrombi and rapid depletion of platelets, prothrombin, fibrinogen (FIB), and other coagulation factors could have occurred during pregnancy [10,11].

It has been reported that a higher hypercoagulable state with prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT) and increased D-dimer and mean platelet volume is seen in women with preeclampsia at the time of onset [12–14]. However, an imbalance in the coagulation activity and the alterations in coagulation could occur early before the presence of the clinical symptoms in women with preeclampsia [5]. Whether these changes are also seen in the early stage of pregnancy in women who developed preeclampsia later has not been fully investigated. Therefore, we undertook this case-control study to investigate the changes in coagulation activity in the early stage of pregnancy in women who developed preeclampsia later.

2. Methods

2.1. Subjects

In this case-control study, 322 women with preeclampsia and 531 healthy pregnant women were included. Gestation-matched healthy pregnant women were randomly selected by Excel software from 8549 healthy pregnancies with a singleton live birth at the hospital of Obstetrics and Gynaecology, the Fudan University of China between January 2021 and December 2021. Pregnant women with medication that may affect coagulation function (such as anti-vitamin K treatment), and pregnant women with chronic hypertension, cardiovascular disease, severe anemia or immune disorder, and untreated endocrine diseases were excluded. All healthy pregnant women did not have any abnormal coagulation test results. The first trimester in this study refers to the period before 12 weeks of pregnancy.

Maternal clinical data of the study including maternal age, body mass index (BMI), parity, the time of onset, systolic and diastolic blood pressure, delivery weeks, and, birthweight were collected from the hospital electronic databases. Preeclampsia was defined as systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg with proteinuria or liver dysfunction following the current international guideline from the International Society for the Study of Hypertension in Pregnancy (ISSHP) [15]. Early onset of pre-eclampsia was defined as the time of onset before 34 weeks of gestation. Severe preeclampsia was defined when the systolic is $\geq$160 mmHg or diastolic is $\geq$110 mmHg.

This study was approved by the research ethics committee of the Obstetrics and Gynecology Hospital Affiliated to Fudan University (2022-81). Written informed consent was obtained from all participants.

2.2. Coagulation functional test

At the first prenatal visit (10–12 weeks of gestation) or at the time of onset of preeclampsia, 2 ml of peripheral blood was collected into blood collecting vessels containing sodium citrate anticoagulant. The blood samples were centrifuged at 3000 rpm for 15 min. All peripheral blood samples were processed within 2 h after collection. PT, APTT, thrombin time(TT), FIB, dmere-ier , AT, and fibrin degradation products (FDP) was measured using an CS 5100 fully automated hemagglutinate analyzer and supporting reagents (Sysmex Corporation). PT, APTT, FIB and TT are detected by coagulation method, D-dimer and FDP are detected by immuno-turbidimetry, and AT is detected by chromogenic substrate method. In addition, the international standardized ratio (INR) was calculated by the value of PT/normal control PT) ^ ISI. The coefficient of variation (CV%) was less than 10% for all the assays.

2.3. Statistical analysis

Data for continuous variables are presented as mean and SD. The Cohen's d Effect Size is calculated using mean, standard deviation and sample size. We use the RAND(.) function in EXCEL software to generate random numbers. Multivariate Logistic regression analysis was used to investigate the effect of D-dimer, AT, and TT on the development of preeclampsia using SPSS software. $P < 0.05$ was considered statistically significant.

3. Results

The clinical parameters of the study cohort are summarized in Table 1. The maternal age in women who developed preeclampsia later was 31.8 years, which was significantly older than the controls (28.7 years, $p < 0.001$). The mean gestational age at diagnosis of

preeclampsia was 34^{+3} weeks, and the mean delivery weeks of preeclamptic women were 37^{+4} weeks. The BMI was significantly higher in women who developed preeclampsia later (24.2 vs 20.6 kg/m^2, $p < 0.001$). Of 322 women who developed preeclampsia, 36 (11%) women had severe preeclampsia, and 87 (27%) had early-onset preeclampsia.

The coagulation profile at diagnosis in women with preeclampsia is summarized in Table 2. The mean value of D-dimer or APTT or AT or TT or FDP was significantly lower in women with preeclampsia, compared to controls ($p < 0.001$, or $p < 0.001$, or $p = 0.0004$, or $p < 0.0001$ or $p = 0.006$, respectively). In contrast, there was no difference in the mean value of PT, INR, and FIB between preeclamptic women and controls. We then investigated the changes in the value of -dimerd, APTT, AT, and FDP at diagnosis in women with preeclampsia according to the severity or the time of onset of preeclampsia. The mean value of D-dimer, APTT, and AT was not associated with the severity or the time of onset, while the mean value of FDP was significantly lower in severe preeclampsia, compared to mild preeclampsia (6.26 mg/L vs 6.48 mg/L, $p = 0.029$). The Common Language Effect Size is a non-parametric effect size, specifying the probability that one case randomly drawn from the one sample has a higher value than a randomly drawn case from the other sample. In the calculator, we take the higher group mean as the point of reference. For example, the probability that randomly selected healthy pregnant women have higher serum D-dimer than randomly selected preeclamptic pregnant women is 0.542.

We next investigated whether there was a change in the coagulation profile D-dimer, APTT, AT, and FDP) in the first trimester between the two groups. As shown in Table 3, the mean value of D-dimer, AT, and FDP in the first trimester was significantly reduced in women who developed preeclampsia later, compared to women who did not develop preeclampsia later ($p < 0.002$). In contrast, the mean value of TT in the first trimester was significantly increased in women who developed preeclampsia later, compared to women who did not develop preeclampsia later ($p < 0.0001$). However, there was no difference in the mean value of APTT between the two groups. The changes in the value of D-dimer, TT, AT, and FDP in the first trimester were not associated with the severity or the time of onset of preeclampsia (Supplementary Tabs. 1 and 2).

Multivariate logistic regression analysis showed that after adjusting for maternal age and BMI, the values of D-dimer and AT were significantly correlated with the risk of developing preeclampsia (Table 4). While the values of TT were not correlated with the risk of developing preeclampsia, after adjusting for maternal age and BMI.

4. Discussion

In this case-control study, we found the reduced values of D-dimer, APTT, AT, TT, and FDP in women with preeclampsia at the time of diagnosis, compared to controls. The reduced values of D-dimer, AT, and FDP, and increased values of TT were also observed in the 1st trimester in women who developed preeclampsia later, compared to those women who did not. The changes in the coagulation profile in the first trimester were not associated with the severity or time of onset of preeclampsia.

During normal pregnancy, the physiological adaptation could induce some differences in the hemostatic system [16,17]. While, coagulation disorder and endothelial cell dysfunction are closely associated with the pathogenesis of preeclampsia, and platelet activation could occur in the early stage of pregnancy in women who developed preeclampsia later [18–20]. Endothelial cell dysfunction leads to platelet aggregation and adhesion resulting in abnormal coagulation activity [19]. Increased platelet adhesion and aggregation rates to endothelial cells were seen in women with preeclampsia [21]. This is mainly because the massive activation of platelet-activating factors leads to aggregation and consequently releases the reaction with platelets by further releasing platelet-activating factors in the circulation and inhibiting of prostacyclin synthesis.

D-dimer is one of the protein fragments produced when a blood clot needs to be dissolved, which can help to rule out the potential thrombotic condition. APTT is used to detect the activity of the endogenous blood coagulation system, mainly to detect the concentration of blood coagulation factors IX, XI, and XII. It is used to monitor the dosage of heparin in clinical practices. In addition, AT is a protein in the blood that blocks forming of abnormal blood clots. It can help the balance between bleeding and clotting. FDP are substances that remain in the bloodstream after a blood clot is dissolved. TT measures the time for forming a clot. In this case-control study, we found that the values of D-dimer, TT, APTT, AT, and FDP were significantly reduced in women with preeclampsia at the time of diagnosis. Our study supported a previous study that reported an association between deficiency of AT and preeclampsia [22] and lower values of APTT in preeclampsia [23]. While other studies showed increased values of D-dimer, APTT, and TT in women with preeclampsia [24,25] or no difference in the values of APTT between the normotensive pregnancy and preeclampsia [26]. We do not

Table 1
Demographics of the study cohort.

	Controls (n = 531)	Preeclampsia (n = 322)	*p* value
Maternal age (years, mean/SD)	28.7 ± 2.6	31.8 ± 4.6	$p < 0.001$
BMI (kg/m^2)	20.68 ± 2.8	24.16 ± 4.0	$p < 0.001$
Systolic blood pressure at diagnosis (mmHg, mean/SD)	<140	146 ± 11.4	N/A
Diastolic blood pressure at diagnosis (mmHg, mean/SD)	<90	93 ± 9.5	N/A
Time of onset (weeks, mean/SD)	N/A	34^{+3}±0.6	N/A
Delivery time (weeks, mean/SD)	39^{+1} ± 0.15	37^{+4} ± 0.2	$p < 0.05$
Birth weight (g, mean/SD)	3359 ± 423	3040 ± 589	$p < 0.001$
Parity			$p > 0.05$
P = 1	437 (82%)	266 (82.6%)	
P ≥ 2	94 (18%)	56 (17.4%)	

Table 2
The difference in the coagulation profile between the two groups in the 3rd trimester.

	Preeclampsia (n = 322)	Controls (n = 531)	Effect Size	*p* values
D-dimer (mg/L, mean/SD)	2.12 ± 1.56	2.31 ± 1.09	0.148	$\mathbf{p < 0.0001}$
INR	0.8756 ± 0.04	0.8736 ± 0.05	−0.043	$p = 0.3237$
PT (second, mean/SD)	10.43 ± 0.61	10.4 ± 0.61	−0.049	$p = 0.4653$
APTT (second, mean/SD)	25.73 ± 2.13	26.84 ± 8.98	0.154	$\mathbf{p < 0.0001}$
TT (second, mean/SD)	17.07 ± 1.174	17.76 ± 6.66	0.13	$\mathbf{p < 0.0001}$
AT (%, mean/SD)	82.64 ± 13.1	85.65 ± 10.69	0.258	$\mathbf{p = 0.0004}$
FIB (g/L, mean/SD)	4.27 ± 0.76	4.25 ± 0.69	−0.028	$p = 0.441$
FDP (mg/L, mean/SD)	6.46 ± 3.98	6.86 ± 3.18	0.739	$\mathbf{p = 0.006}$

Abbreviation: INR = international normalized ratio, PT = prothrombin time, APTT = activated partial thromboplastin time, TT = thrombin time, AT = antithrombin, FIB = fibrinogen, FDP = fibrin degradation products.

Table 3
The difference in the coagulation profile between the two groups in the 1st trimester.

	Preeclampsia (n = 322)	Controls (n = 531)	Effect Size	*p* values
D-dimer (mg/L, mean/SD)	0.379 ± 0.24	0.420 ± 0.26	0.162	$\mathbf{p = 0.002}$
APTT (second, mean/SD)	26.22 ± 1.97	26.08 ± 1.65	−0.079	$p = 0.817$
TT (second, mean/SD)	17.33 ± 1.09	17.15 ± 0.74	−0.203	$\mathbf{p = 0.016}$
AT (%, mean/SD)	89.95 ± 10.43	92.69 ± 9.33	0.281	$\mathbf{p = 0.0002}$
FDP (mg/L, mean/SD)	1.59 ± 1.29	2.283 ± 1.37	0.517	$\mathbf{p < 0.0001}$

Abbreviation: APTT = activated partial thromboplastin time, TT = thrombin time, AT= antithrombin, FDP = fibrin degradation products.

Table 4
Multivariate logistic regression analysis on the effect of D-dimer, APTT, and TT with the risk of developing preeclampsia.

	Not adjusted (OR, 95% CL)	Age-adjusted (OR, 95% CL)	BMI adjusted (OR, 95% CL)	Age and BMI adjusted (OR, 95% CL)
D-dimer	0.465 (0.280–0.773), $p = 0.003$	0.376 (0.210–0.673), $p = 0.001$	0.562 (0.319–0.990), $p = 0.046$	0.457 (0.246–0.849), $p = 0.013$
AT	0.971 (0.957–0.986), $p < 0.001$	0.963 (0.947–0.979), $p < 0.001$	0.971 (0.955–0.987), $p < 0.001$	0.963 (0.946–0.981), $p < 0.001$
TT	1.255 (1.074–1.468), $p = 0.004$	1.201 (1.015–1.421), $p = 0.033$	1.164 (0.981–1.381), $p = 0.083$	1.134 (0.945–1.360), $p = 0.177$

Abbreviation: OR: odds ratio, CL: confidence interval, TT = thrombin time, AT= antithrombin.

know the exact reason for the difference between our study and other studies. One possibility was the sampling time. In those studies, the sampling time was not mentioned. In contrast, the sampling time in our current study was the same as the diagnosis without delay. The values of APTT and TT were significantly decreased through the gestational age [27] and the values of D-dimer were significantly increased through the gestational age [27,28]. In addition, the sample size was relatively small in those studies, compared with our current study (less than 100 preeclampsia in those studies vs 321 preeclampsia in our study).

Maternal endothelial cell dysfunction happens before the presence of the clinical symptoms of preeclampsia. Therefore, it is important to investigate whether the changes in the coagulation profile occur in the first trimester of pregnancy, which has not been investigated yet in the literature. In our current study, we found reduced values of D-dimer, AT, and FDP and increased values of TT in the first trimester in women who developed preeclampsia later, compared to women who did not. No difference in the values of APTT in the first trimester was observed between women who developed preeclampsia later and who did not could be due to the maternal adaptation in the hemostatic system during pregnancy. However, after adjusting for maternal age and BMI which could affect the hemostatic system, we found that D-dimer and AT were significantly correlated with the risk of developing preeclampsia. Our data, therefore, suggests that the changes in the coagulation profile in the early stage of pregnancy may be able to be an additional predictive marker for early diagnosis of preeclampsia.

The abnormal values of D-dimer, APTT, TT, and FDP were not associated with the development of severe or early onset preeclampsia in the first trimester, suggesting the similarity of the mechanism in causing the changes in the coagulation profile between the subtypes of preeclampsia. In our current study, we reported the hypercoagulable state at the early stage of pregnancy in women who developed preeclampsia later.

4.1. Strengths and weaknesses

Clinicians should give high priority to PT and INR levels in early pregnancy. For pregnant women with decreased PT and INR detected at the first obstetric examination, enhanced monitoring during subsequent pregnancies is needed, which is clinically important to reduce PE and avoid adverse pregnancy outcomes.

It is well-known that treatment with low molecular weight aspirin at early gestational age in women with high risk of developing preeclampsia is widely reaccommodated [29]. Our research is a single-center research, which needs to be verified by larger multi-center research in the future, and further studies are still needed to determine whether the detection of PT and INR can provide a

strong reference for determining the optimal time to take aspirin.

5. Conclusion

Preeclampsia is associated with vascular endothelial dysfunction which consequently increasing the risk of thromboembolism. In this case-control study with relatively large sample size, we are first time to report the reduced values of D-dimer and AT in early gestational age in women who developed preeclampsia later, after adjusted for maternal age and BMI, and these changes were significantly correlated with the risk of developing preeclampsia. Our results suggest that coagulation testing in the first trimester in women who developed preeclampsia later has important clinical significance, coagulation testing may be an additional predictor of preeclampsia, improving preventive screening and patient safety.

Author contribution statement

Pei-Pei Jin: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper. Ning Ding; Jing Dai: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data. Xiao-Yan Liu; Pei-Min Mao: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e17983.

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