Am J Transl Res 2025;17(2):1106-1113
www.ajtr.org /ISSN:1943-8141/AJTR0161054

Original Article

Coagulation indices for predicting hypertensive pregnancy disorders

Xuejun Kou[1*], Qirong Li[2*], Zhonggui Pan[3], Jing Yang[2]

[1]Department of Cardiology, Shandong Provincial Third Hospital, Jinan 250031, Shandong, China; [2]Department of Obstetrics and Gynecology, Jinan Maternity and Child Care Hospital, Jinan 250001, Shandong, China; [3]Department of Geriatrics, Yantai Penglai District Hospital of Traditional Chinese Medicine, Yantai 265600, Shandong, China. [*]Equal contributors and co-first authors.

Received October 10, 2024; Accepted January 2, 2025; Epub February 15, 2025; Published February 28, 2025

Abstract: Objectives: To study the correlation between coagulation function indicators at 28-34 weeks of gestation and the occurrence, progression, and severity of hypertensive disorders in pregnancy (HDP), and to explore their potential predictive value for HDP. By analyzing the changes in coagulation function indicators during pregnancy, HDP can be detected early, the progression of HDP can be delayed, and the prognosis of mothers and infants can be improved. Methods: This retrospective analysis encompassed 300 pregnant women who underwent antenatal examinations at the obstetrics outpatient department of Jinan Maternity and Child Care Hospital between October 2020 and October 2023. A total of 182 pregnant women diagnosed with HDP were selected as the observation group. Meanwhile, 118 healthy pregnant women from the same period served as the control group. General clinical data of all participants, such as age, gestational age, number of pregnancies, and number of deliveries, were collected. After an overnight fast, blood samples were drawn from all participants and immediately sent for testing to assess coagulation function indicators. Subsequently, these indicators were analyzed to explore their potential predictive value for the occurrence and severity of HDP. Results: Platelet count (PLT), thrombin time (TT), and fibrinogen (Fib) were identified as independent prognostic factors for pregnant women with HDP. Additionally, pregnant women with HDP had a higher incidence of premature delivery, full-term birth, vaginal delivery, cesarean section, postpartum hemorrhage, fetal growth restriction, neonatal asphyxia, and perinatal death. Conclusion: PT (Prothrombin Time), activated partial thromboplastin time (APTT), TT, Fib, and international normalized ratio can reflect the severity of hypertensive disorders in pregnancy.

Keywords: Coagulation indexes, hypertensive disorders, pregnancy, clinical significance

Introduction

Hypertensive disorders during pregnancy (HDP) constitute a group of multi-system pregnancy complications typified by hypertension, edema, proteinuria, and platelet aggregation [1]. This syndrome entails vasoconstriction, giving rise to elevated maternal blood pressure, diminished uterine blood flow, impairment of placental vascular endothelial integrity, and activation of the coagulation cascade. As the disease advances, 10%-20% of gestational hypertension cases can progress to preeclampsia, which impacts approximately 7-10% of pregnant women. HDP represents a substantial risk factor for increased morbidity and mortality in both mothers and fetuses [2]. The onset and progression of HDP are unpredictable, rendering accurate prediction and targeted prevention highly advantageous for enhancing maternal and fetal outcomes.

During the early phase of pregnancy, the levels of various coagulation factors rise. Prothrombin time (PT), thrombin time (TT), and coagulation factors I, II, V, VII, VIII, IX, and X all increase. Factor VII can rise to over 10 times its normal value, while factors VIII and X can increase to 100%-300% and 120%-180% of their normal levels, respectively. Fibrinogen (Fib) levels can also increase by 2-3 times (3-7 g/L) [3-5]. At the same time, the anticoagulation function in pregnant women decreases, evidenced by a reduction in antithrombin III (ATIII) activity, a

https://doi.org/10.62347/NBXU9802

pronounced elevation in D-dimer concentration, and a marked decrease in activated protein C (APC) [6]. These alterations culminate in a hypercoagulable state, potentially heightening the risk of thrombosis [7]. Additionally, studies have shown that the blood of patients with pregnancy-induced hypertension (PIH) is in a hypercoagulable state, which bolsters red blood cell aggregation and reduces their deformability, further increasing blood viscosity in these patients [8-10]. However, the coagulation traits might differ based on the subtype or severity of pregnancy-induced hypertension, a topic that has yet to be thoroughly explored.

Therefore, the aim of this study was to analyze the correlation between coagulation function indicators at 28-34 weeks of gestation and the occurrence, progression, and severity of HDP, and to explore their prospective predictive value for HDP. By analyzing the changes in coagulation function indicators during pregnancy, HDP can be detected early, the progression of HDP can be delayed, and the prognosis of both mothers and infants can be improved.

Materials and methods

Case selection

A total of 300 pregnant women who underwent antenatal examinations at the obstetrics outpatient department of Jinan Maternity and Child Care Hospital from October 2020 to October 2023 were recruited for this study. Of these, 182 pregnant women meeting the established inclusion and exclusion criteria and diagnosed with HDP were assigned to the observation group. Meanwhile, 118 healthy pregnant women from the same period served as the control group. The study was approved by the Ethics Committee of Jinan Maternity and Child Care Hospital.

Inclusion criteria: 1) Women who met the diagnostic criteria for hypertensive disorders in pregnancy and severe preeclampsia [11]: ① Gestational hypertension: Blood pressure (BP) ≥ 18.7/12.0 kPa (140/90 mmHg), first detected during pregnancy and returning to normal within 12 weeks postpartum; no proteinuria (-). Patients may exhibit other signs of preeclampsia, such as upper abdominal discomfort or thrombocytopenia. ② Preeclampsia was categorized into mild and severe forms. Mild: After 20 weeks of pregnancy, BP ≥ 18.7/12.0 kPa (140/90 mmHg), urine protein ≥ 300 mg/24 h or positive (+) on measurement stick; Severe: BP ≥ 21.3/14.7 kPa (160/110 mmHg), urine protein ≥ 2.0 g/24 h or (++), serum creatinine > 106.08 μmol/L (1.2 mg/dL), platelet count < 100 × 10^9/L, microvascular hemolysis (elevated LDH), elevated ALT or AST, persistent headache, brain or visual dysfunction, or persistent upper abdominal pain. ③ Eclampsia: Convulsions occurring in women with preeclampsia, not attributable to any other cause. ④ Chronic hypertension complicated with preeclampsia: Women who did not have proteinuria before 20 weeks of pregnancy but developed proteinuria ≥ 300 mg/24 h later; or women who had hypertension and proteinuria before 20 weeks, with a sudden increase in proteinuria, elevated BP, or a platelet count < 100 × 10^9/L. ⑤ Pregnancy with chronic hypertension: BP ≥ 18.7/12.0 kPa (140/90 mmHg) detected before pregnancy or before 20 weeks of gestation, or hypertension first diagnosed after 20 weeks of pregnancy that persists until 12 weeks postpartum. 2) Singleton pregnancy in women aged 18 years or older. 3) Women who conceived naturally.

Exclusion criteria: 1) Pregnant women with concurrent hypertension, chronic kidney disease, or liver disease. 2) Pregnant women with intrahepatic cholestasis of pregnancy, liver diseases, heart conditions, or blood disorders. 3) Pregnant women who had received antihypertensive treatment or medications affecting the autonomic nervous system prior to admission. 4) Pregnant women with a history of underlying conditions before or during pregnancy (such as diabetes, heart disease, liver or kidney dysfunction, disseminated intravascular coagulation, thyroid dysfunction, aplastic anemia, thrombocytopenic purpura, etc.). 5) Pregnant women who gave birth before 28 weeks of gestation for any reason. 6) Pregnant women with immune dysfunction or hereditary diseases.

Data collection

During antenatal check-ups, 5 ml of blood was drawn from the cubital vein of pregnant women using EDTA-K2 anticoagulant vacuum blood collection tubes. The collected venous blood was partitioned, labeled, and stored in a 4°C refrigerator. Subsequently, the blood was promptly centrifuged at 4,000 r/min for 10 minutes, and the serum was stored in a -70°C

Table 1. Comparison of the general conditions of pregnant women between the two groups

General characteristics	Observation group (n=182)	Control group (n=118)	t/χ^2	p
Age	32.62±2.96	33.16±3.75	1.401	0.162
< 35	106 (58.24%)	68 (57.63%)		
≥ 35	76 (41.76%)	50 (42.37%)		
BMI	29.02±2.31	28.67±2.05	1.326	0.186
< 28	90 (49.45%)	71 (60.17%)		
≥ 28	92 (50.55%)	47 (39.83%)		
Twin pregnancy	24 (13.19%)	5 (4.24%)	6.566	0.010
Single pregnancy	158 (86.81%)	113 (95.76%)		
Education level (college or above)	76 (41.76%)	50 (42.37%)	0.799	0.371
Gravida			0.003	0.953
≥ 2	87 (47.80%)	56 (47.46%)		
< 2	95 (52.20%)	62 (52.54%)		
Parity			3.770	0.052
≥ 1	98 (53.85%)	50 (42.37%)		
< 1	84 (46.15%)	68 (57.63%)		
Systolic blood pressure	176.93±7.71	138.32±3.68	50.756	0.000
Diastolic blood pressure	109.83±6.03	95.40±3.42	23.641	0.000

Note: BMI: body mass index.

freezer. Using the ACL-200 fully automatic coagulation analyzer from Coulter Company in the United States, along with reagents such as 500 ml Hemosil™ Reference Emulsion, Hemosil™ APTT Lyophilized silica, 1L Test™ PT-Fibrinogen HS, Hemosil Calibration plasma, Hemosil™ Calcium Chloride, the coagulation indexes including PT, activated partial thromboplastin time (APTT), Fib, TT, and international normalized ratio (INR) were detected.

Outcome measurements

The primary indices encompassed coagulation indices, which were detected by the ACL-200 fully automatic coagulation analyzer. These coagulation indices comprised PT, APTT, Fib, TT, and INR. The secondary indexes included the age, pregnancy and childbirth history, body mass index (BMI), systolic and diastolic blood pressure, gestational weeks at delivery, etc., along with biochemical index parameters such as routine blood and liver function. A fully automatic blood analyzer was utilized to detect hemoglobin (Hb), hematocrit (HCT), variations in red blood cell distribution width (RDW-CV), platelet count (PLT), plateletcrit (PCT), mean platelet volume (MPV), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum C-reactive protein (CRP), and urine protein in the pregnant women.

Statistical methods

Statistical analysis was carried out using IBM SPSS Statistics 27.0 software. Categorical variables were presented as percentages [n (%)], and comparisons were made using the chi-square test or Fisher's exact test. Firstly, normality and homogeneity of variance tests were conducted on the measurement data. For data following a normal distribution, the results were expressed as mean ± standard deviation (mean ± SD), and one-way analysis of variance (ANOVA) was employed. Pairwise comparisons between groups were performed using the least significant difference (LSD) method. Pearson correlation analysis was applied to examine the correlation between variables that followed a normal distribution. For non-normally distributed data, the results were expressed as median (P25, P75). A *p*-value of < 0.05 was regarded as statistically significant.

Results

Comparison of general conditions of the pregnant women in both groups

The baseline demographic and clinical characteristics are shown in **Table 1**. There were no significant difference between the two groups

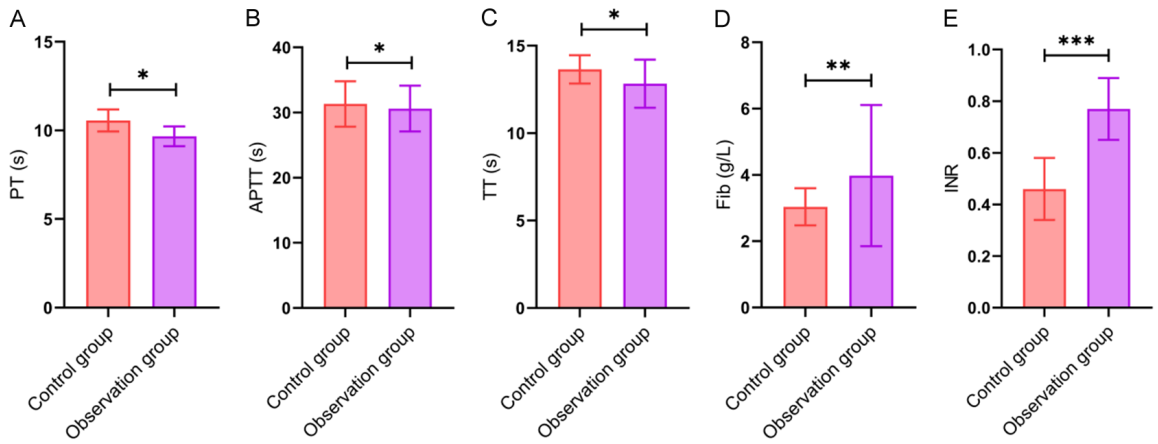

Figure 1. Comparison of coagulation indexes between the two groups. (A) PT, (B) APTT, (C) TT, (D) Fib, (E) INR. Note: PT: prothrombin Time, APTT: activated partial thromboplastin time, Fib: fibrinogen, TT: thrombin time, INR: international normalized ratio. *P < 0.05, compared to the control group. **P < 0.01, compared to the control group. ***P < 0.001, compared to the control group.

Table 2. Comparison of biochemical indexes between the two groups

	Control group (n=118)	Observation group (n=182)	t	p
Ca	1.60±0.10	2.04±0.08	42.771	0.000
Cr	55.13±6.51	65.02±15.19	6.685	0.000
BUN	3.90±1.03	4.73±0.71	8.553	0.000
UA	387.72±60.83	442.70±58.18	7.853	0.000
DBil	4.12±0.70	4.06±0.74	0.684	0.494
Bil	4.23±1.31	4.38±1.18	1.016	0.310
Alb	32.76±2.24	28.70±3.22	11.842	0.000
Glb	26.03±1.73	26.98±2.39	0.732	0.057
ALT	19.14±25.02	22.62±18.73	1.376	0.170
AST	26.07±12.61	28.13±21.13	0.957	0.339
LDH	218.94±38.12	262.13±56.64	7.281	0.000
Cholesterol	6.89±1.03	7.83±1.10	7.426	0.000
Hb	119.79±15.01	119.37±11.55	0.275	0.783
HCT	34.69±2.06	35.08±1.73	1.771	0.078
PLT	184.00±31.15	174.43±35.12	2.409	0.017

Note: Ca: calcium, Cr: creatinine, BUN: Blood Urea Nitrogen, UA: Uric Acid, DBil: Direct Bilirubin, Bil: Bilirubin, Alb: Albumin, Glb: Globulin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, LDH: Lactate Dehydrogenase, Hb: Hemoglobin, HCT: Hematocrit, PLT: Platelet.

in terms of education level (college or above), body mass index, and gravida (all P > 0.05).

Comparison of coagulation indices between the two groups of women

In the comparison of various coagulation indexes, the levels of PT, APTT, TT, Fib, and INR in the observation group were all significantly lower than those in the control group (all P < 0.05) (**Figure 1**).

Comparison of biochemical indices between the two groups

In the observation group, compared with the control group, the Ca, serum Cr, BUN, and serum UA levels were significantly higher (all P < 0.05), while the Alb and cholesterol levels, as well as the PLT count, were significantly lower (all P < 0.05), (**Table 2**). Additionally, the serum LDH level was markedly elevated (P < 0.05).

Comparison of coagulation indices between the mild and severe preeclampsia group

In the comparison of coagulation indexes between the mild and severe preeclampsia groups (**Figure 2**), the PT and APTT levels were significantly higher in the mild preeclampsia group (P < 0.05), while the TT level was lower, and the Fib and INR levels were significantly lower in the severe preeclampsia group (all P < 0.05).

Logistic regression analysis

The results of the logistic regression analysis of factors associated with HDP indicated that PLT (95% CI 1.001-1.016; P=0.017), TT (95% CI

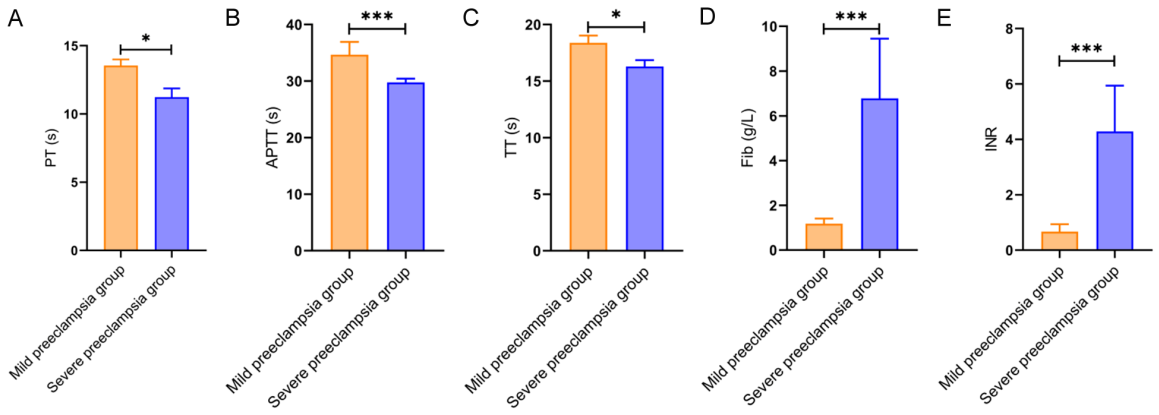

Figure 2. Comparison of coagulation indexes between mild and severe preeclampsia group. (A) PT, (B) APTT, (C) TT, (D) Fib, (E) INR. Note: PT: prothrombin Time, APTT: activated partial thromboplastin time, Fib: fibrinogen, TT: thrombin time, INR: international normalized ratio.*P < 0.05, compared to the control group. ***P < 0.001, compared to the control group.

Table 3. Logistic regression analysis of factors associated with HDP

Correlation factor	B	SE	Wald	p	OR	95% CI
PLT	0.008	0.004	5.655	0.017	1.009	1.001-1.016
PT	0.983	0.813	0.015	0.904	1.018	0.057-1.256
APTT	0.103	0.055	3.754	0.059	1.109	0.996-1.235
TT	2.652	0.336	62.273	0.000	14.182	7.340-27.403
Fib	1.006	0.165	37.136	0.000	0.366	0.265-0.505
INR	0.144	0.268	0.003	0.957	1.056	0.437-2.435

Note: HDP: hypertensive disorders in pregnancy, PLT: Platelet, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time, TT: Thrombin Time, Fib: Fibrinogen, INR: International Normalized Ratio.

Table 4. Comparison of delivery outcomes between the two groups

Delivery outcome	Observation group (n=182)	Control group (n=118)	χ^2	p
Premature delivery	70 (38.46%)	27 (22.88%)	7.942	0.005
Full-term birth	112 (61.54%)	91 (77.12%)	-	-
Vaginal delivery	68 (37.36%)	63 (53.39%)	7.475	0.006
Cesarean section	114 (62.64%)	55 (46.61%)	-	-
Postpartum hemorrhage	64 (35.16%)	22 (18.64%)	9.555	0.002

Table 5. Comparison of perinatal outcomes between the two groups

Neonatal outcome	Observation group (n=182)	Control group (n=118)	χ^2	p
Fetal growth restriction	68 (37.36%)	16 (13.56%)	20.119	0.000
Fetal distress	40 (16.48%)	28 (23.73%)	0.125	0.723
Neonatal asphyxia	30 (16.48%)	9 (7.63%)	4.965	0.026
Perinatal death	20 (3.85%)	3 (%)	7.215	0.007

7.340-27.403; P < 0.001), and Fib (95% CI 0.265-0.505; P < 0.001) are independent prognostic factors affecting pregnant females with HDP (**Table 3**).

Comparison of delivery outcomes and perinatal outcomes between the two groups

As shown in **Table 4**, the observation group exhibited a higher rates of premature delivery, full-term birth, vaginal delivery, cesarean section, and postpartum hemorrhage (all P < 0.05). Furthermore, the incidences of fetal growth restriction (FGR), neonatal asphyxia, and perinatal death in the observation group was significantly elevated (all P < 0.05) (**Table 5**).

Discussion

In our study, we determined that PLT, PT, FIB, and INR served as independent prognostic factors for pregnant women with hypertensive disorders of pregnancy (HDP). Additionally, PT, APTT, TT, FIB, and INR were identified as independent prognostic factors in women with severe preeclampsia. Further-

more, pregnant women with HDP had a greater incidence of premature delivery, full-term birth, vaginal delivery, cesarean section, postpartum hemorrhage, FGR, neonatal asphyxia, and perinatal death. These findings hold significant implications for comprehending the role of coagulation disturbances in the pathophysiology of HDP and its associated complications, as well as for clinical management.

It is well established that HDP is correlated with altered coagulation profiles, shifting towards a hypercoagulable state [12]. The identification of PLT, PT, FIB, and INR as independent prognostic factors in this study underlines the crucial importance of coagulation function in the management of HDP. Elevated levels of fibrinogen (FIB), an acute-phase reactant, are frequently observed in preeclampsia and HDP [13]. FIB is associated with increased blood viscosity, which can augment the risk of thrombotic events, such as deep vein thrombosis (DVT) and pulmonary embolism, in these patients [14]. Likewise, PT and INR, indicators of clotting ability, are often prolonged in preeclamptic patients, suggesting impaired coagulation and a potential for bleeding complications, especially during delivery. PLT is another vital marker. In preeclampsia, thrombocytopenia (low platelet count) is commonly encountered, particularly in severe cases [15]. This thrombocytopenia can heighten the risk of bleeding during labor and delivery. A significant discovery in our study was the role of PLT in the prognosis of HDP, indicating that monitoring platelet levels could be pivotal for assessing the severity of the disease and predicting complications like postpartum hemorrhage.

Severe preeclampsia represents a more severe form of HDP, with markedly altered coagulation profiles. The identification of PT, APTT, TT, FIB, and INR as independent prognostic factors in severe preeclampsia implies that these markers can assist in predicting the progression and potential complications of the disease. Specifically, APTT and TT offer crucial insights into the intrinsic and common coagulation pathways [16]. Deviations in these clotting times may mirror endothelial dysfunction and excessive activation of the coagulation cascade, which are fundamental aspects of preeclampsia pathophysiology [17, 18]. The combination of PT, APTT, INR, and FIB affords a comprehensive overview of the coagulation status of a pregnant woman with HDP or severe preeclampsia. These markers could be incorporated into a multifaceted strategy to evaluate the risk of maternal and fetal complications, guiding clinical decision-making, particularly concerning the optimal timing of delivery and the management of anticoagulation during labor.

Our study also revealed that pregnant women with HDP experienced a higher prevalence of several adverse pregnancy outcomes, namely premature delivery, full-term birth, vaginal delivery, cesarean section, postpartum hemorrhage, FGR, neonatal asphyxia, and perinatal death. These findings align with prior research demonstrating a heightened risk of adverse pregnancy outcomes in women with HDP [19-21]. Women with HDP, especially those with severe preeclampsia, are more prone to preterm birth, either because early delivery is essential to safeguard maternal health or due to placental dysfunction [22]. The elevated incidence of FGR observed in HDP patients is intimately linked to placental insufficiency, which compromises the nutrient and oxygen supply to the fetus, increasing the risk of prematurity and low birth weight [23]. The increased frequency of cesarean section in HDP patients can be attributed to several factors, including fetal distress, inadequate uterine relaxation, or the need for early delivery to avert complications in both the mother and fetus [24, 25]. Coagulation anomalies, such as thrombocytopenia, prolonged PT, and impaired fibrinogen levels, contribute to an increased risk of postpartum hemorrhage [26, 27]. Women with severe preeclampsia, in particular, are at a higher risk owing to the interaction between coagulation dysfunction and uterine atony [28]. The altered placental function in HDP leads to reduced oxygen and nutrient delivery to the fetus, resulting in FGR and, in more severe cases, neonatal asphyxia [29]. FGR is a common complication of preeclapiensia and is often associated with perinatal death, as reduced placental blood flow hampers fetal development and leads to poor outcomes.

The findings of our study indicate that monitoring coagulation markers like PLT, PT, FIB, and INR is beneficial not only for assessing the severity of HDP and preeclampsia but also for

forecasting pregnancy outcomes. Abnormal coagulation parameters may suggest an elevated risk of maternal and fetal complications, including postpartum hemorrhage, FGR, and neonatal asphyxia. These markers ought to be taken into account in conjunction with other clinical manifestations, including blood pressure and urine protein levels, in the management of women with HDP. Regular surveillance of coagulation parameters could assist in guiding clinical decision-making, specifically regarding the optimal timing of delivery and the management of anticoagulation therapy during labor.

This study does have certain limitations. Firstly, it might have been constrained by the sample size and the selection of the study population, potentially resulting in a lack of comprehensive representation and generalizability. Secondly, environmental factors and concurrent underlying diseases that could also impact coagulation function might not have been thoroughly accounted for and controlled, influencing the accuracy and interpretation of the results. Moreover, a single study might not precisely capture the dynamic alterations in coagulation status throughout the pregnancy process, and longitudinal follow-up studies could be required for a more profound understanding. Therefore, more large-sample, multi-center randomized controlled trials are warranted to elucidate the clinical significance of coagulation indicators in HDP. In conclusion, PT, APTT, TT, Fib and INR can reflect the severity of hypertensive disorders in pregnancy. These findings underscore the necessity for meticulous monitoring and management of coagulation function in pregnant women with HDP, aiming to enhance pregnancy outcomes and mitigate the risks associated with these conditions.

Disclosure of conflict of interest

None.

Address correspondence to: Jing Yang, Department of Obstetrics and Gynecology, Jinan Maternity and Child Care Hospital, No. 2 Jianguo Xiaojing 3 Road, Jinan 250001, Shandong, China. Tel: +86-0531-89029424; E-mail: yj_1023@126.com

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