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Original Research

Predictive Value of D-dimer in Preeclamptic Pregnant Women at Different Ages

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Abstract

Background: The aim of this study was to evaluate the relationship and impact of D-dimer levels and preeclamptic pregnancies at different ages in women. **Methods**: We conducted an observational retrospective cohort study of 325 pregnant women who delivered in Wenzhou People's Hospital from January 2018 to December 2021. Clinical data including age, neutrophils, lymphocytes, platelets, fibrinogen, gestational age, D-dimer/fibrinogen, blood pressure at admission, and fetal weight were collected from the medical record database. All measurements were made using the same methods. Data for continuous variables were expressed as X $\pm$ standard deviation (SD), and inter-group differences in continuous data were compared by independent sample *t*-test. Continuous variables that do not conform to the normal distribution, such as age and D-dimer, were expressed as median and quartile ranges. The relationship between D-dimer and preeclampsia pregnant women of different ages was evaluated by receiver operating characteristics (ROC) curve analysis. **Results**: Among the middle-aged pregnant women, the average D-dimer in the normotensive pregnancy group was (1.367 $\pm$ 0.03 mg/L), which was significantly lower than that in the preeclampsia group (2.087 $\pm$ 0.16 mg/L). The D-dimer/fibrinogen ratio was comparable between the young groups, but there was a difference between the middle-aged groups. Meanwhile, in middle-aged pregnant women, the predicted area of D-dimer for preeclampsia was 70.2% (95% confidence interval (CI) 60–80.43%, $p = 0.0002$) , which was significantly higher than that in the young group. **Conclusions**: Prenatal D-dimer levels may be associated with more accurate predictors of preeclampsia in middle-aged women than in young women.

Keywords: D-dimer; fibrinogen; fetal weight; preeclampsia

1. Introduction

Preeclampsia is a specific disease which is relatively common pregnancy complications and great harm to the mother and child [1], with an incidence of 2–8% [2]. The disease is characterized by hypertension (140/90 mmHg) after 20 weeks of gestation, with or without proteinuria (>0.3 g), and various complications of other systems (such as thrombocytopenia, liver impairment, renal impairment, pulmonary edema, emerging central nervous system abnormalities, or visual disturbances) [3]. Its risk factors include multiple pregnancies and maternal factors: race, age, obesity, gestational diabetes, chronic hypertension, assisted reproduction, kidney disease and autoimmune diseases [4,5]. The only way to treat the disease is to give birth, so means for early prediction, early prevention, and targeted prenatal monitoring are crucial. At present, the research on early prediction of preeclampsia at home and abroad still focuses on clinical research and measurement of angiogenesis spectrum. These include placental growth factor (PlGF), vascular endothelial growth factor, soluble fms-like tyrosine kinase (sFlt-1), fetal hemoglobin, cell-free fetal DNA (cff DNA), soluble fetal DNA angiotensin II type 1 receptor activating antibody (AT1-AA), proteomics, etc. In recent years, the proportion of older parturients in pregnant women has gradually increased. Blood hypercoagulability is a physiological phenomenon of pregnancy [6]. Vascular endothelial injury, one of the pathogenetic mechanisms of preeclampsia, activates platelets and coagulation factors to further aggravate blood hypercoagulation, thus facilitating thrombosis [7,8]. D-dimer reflects the dynamic process of fibrin polymerization and decomposition. Imbalance between the anticoagulant and coagulant promoting functions damages the endothelial function of placental trophoblastic cells [9]. Further increase of inflammatory mediators induces oxidative stress, resulting in placental dysfunction and adverse fetal outcomes [10]. D-dimer levels are high in women with preeclampsia, but no studies have been conducted to determine whether D-dimer levels are different in women with preeclampsia at different ages. Therefore, the purpose of this study was to evaluate the relationship between D-dimer during pregnancy and preeclampsia at different ages, and help to better predict the maternal and infant outcomes of preeclampsia pregnant women of different ages.

2. Materials and Methods

2.1 Study Population

We enrolled and analyzed the data of pregnant women who gave birth in Wenzhou People's Hospital between January 2018 and December 2021, and volunteered to be included in this retrospective cohort study. A total of 325 pregnant women were included, including 200 in the normotensive pregnancy group (preeclampsia control group) and 125 in the preeclampsia group, as shown in Fig. 1. This study was approved by the Hospital Research Ethics Committee.

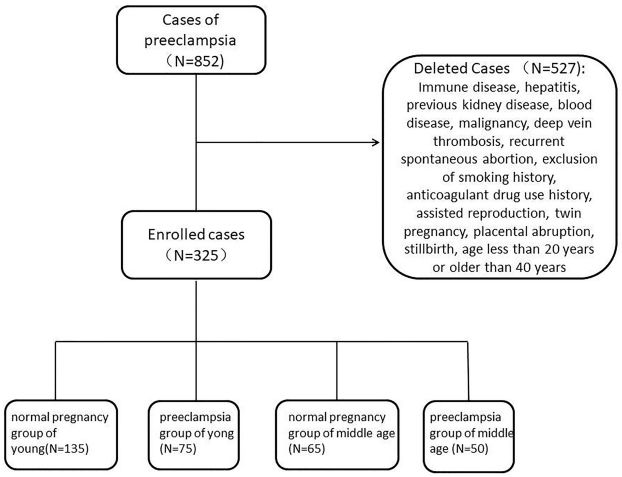

Fig. 1. Inclusion criteria and exclusion criteria for study population.

2.2 Inclusion Criteria and Exclusion Criteria for the Study

The inclusion criteria were based on the latest American College of Obstetricians and Gynecologists guidelines (ACOG), the diagnosis of preeclampsia [11] is the onset of hypertension after 20 weeks of gestation (systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg from two measurements taken more than four hours apart), with or without significant proteinuria ($\geq$300 mg/24 h or protein/creatinine ratio $\geq$0.3), the following conditions were observed: (1) thrombocytopenia (platelet $<$100,000/μL); (2) renal insufficiency (creatinine $>$1.1 mg/dL or baseline doubling); (3) liver function impairment (serum transaminase level is twice the normal value or upper abdominal pain); (4) brain symptoms (headache, visual impairment, convulsions); (5) pulmonary edema. Exclusion criteria were as follows: (1) twin and multiple pregnancies; (2) chronic hypertension, heart disease, kidney disease, diabetes, hyperthyroidism, connective tissue disease and blood disease; (3) smokers; (4) pregnancy caused by assisted reproductive technology; (5) trisomy 21, 18, 13 and other birth defects; (6) patients with a history of immunotherapy; (7) the case lacked critical information in the medical records; (8) patients who developed preeclampsia following delivery; (9) the age at pregnancy was above 40 years.

2.3 Sample Collection and Analysis

Clinical data including age, neutrophils, lymphocytes, platelets, fibrinogen, gestational age, D-dimer/fibrinogen, blood pressure at admission, and fetal weight were collected from the medical record database. Blood samples were collected prior to hospitalization for delivery, and tests for D-dimer and fibrinogen quantification were performed according to the manufacturer's guidelines. The D-dimer level was determined by immunoturbidimetric method, and the fibrinogen level was determined by Klaus method. All measurements were made using the same instruments and method. The Kolmogorov-Smirnov test was used to analyze the normality of the data. Data for continuous variables were expressed as X $\pm$ standard deviation (SD), and inter-group differences in continuous data were compared by independent sample *t*-test. Continuous variables that did not conform to the normal distribution, such as age and D-dimer, were expressed as median and quartile ranges. The area under the curve (AUC) calculated by the receiver operating characteristics (ROC) was used to assess predictive ability. Logistic regression analysis was used to determine the correlation between D-dimer and age and preeclampsia. SPSS 27.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and $p < 0.05$ was considered statistically significant.

3. Results

3.1 Comparison of Clinical Data of Study Population

A total of 325 pregnant women were enrolled in this study and divided into four groups according to their blood pressure and age: Normal blood pressure young group ($<$20 the age $<$30 years old, n = 135), normal blood pressure middle-aged group ($<$30 the age of $\leq$40, n = 65), preeclampsia young group ($<$20 the age $<$30 years old, n = 75), and preeclampsia middle-aged group ($<$30 the age of $\leq$40, n = 50). The demographic and basic characteristics of the four groups, including age, systolic blood pressure, diastolic blood pressure, neutrophils and other clinical biological indicators, are shown in Tables 1,2. There was no statistically significant age difference between the normotensive pregnancy group and the preeclampsia group.

3.2 D-dimer

The mean value of D-dimer in the normotensive pregnancy group was (1.412 $\pm$ 0.03 mg/L), which was slightly lower than that in the preeclampsia group (1.641 $\pm$ 0.07 mg/L), but the difference was not statistically significant ($p > 0.05$). However, among the middle-aged pregnant women, there was a statistically significant difference in D-dimer between the normotensive pregnancy group and the preeclampsia group ($p < 0.0001$), as shown in Fig. 2A. In the middle-aged-group, the mean value of D-dimer in the normotensive pregnancy group was (1.367 $\pm$ 0.03 mg/L), which was significantly lower than that in the preeclampsia group (2.087 $\pm$ 0.16 mg/L).

Table 1. Demographic and clinical characteristics of participants (between 20 and 30 years of age).

Parameter	Normal pregnancy group	Pre-eclampsia group
The number of primipara	79	62
Age (Y)	26 (24, 28)	22 (25, 28)
Neutrophils (10^9/L)	6 (5.15, 6.75)	6.2 (5.1, 7)
Lymphocyte (10^9/L)	1.600 $\pm$ 0.03	1.759 $\pm$ 0.05
Platelets (10^9/L)	195 (165, 233)	198 (152.5, 235)
D-dimer (mg/L)	1.412 $\pm$ 0.03	1.641 $\pm$ 0.07
Fibrinogen (g/L)	4.045 $\pm$ 0.04	4.298 $\pm$ 0.08
D-dimer/fibrinogen	0.34 (0.27, 0.80)	0.35 (0.27, 0.47)
Fetal weight (g)	3361 $\pm$ 29.67	3048 $\pm$ 64.15
Systolic blood pressure (mmHg)	113.8 $\pm$ 0.5763	150.3 $\pm$ 1.263
Diastolic blood pressure (mmHg)	73.59 $\pm$ 0.58	97.33 $\pm$ 1.137

Table 2. Demographic and clinical characteristics of participants (between 30 and 40 years of age).

Paramete	Normal pregnancy group	Pre-eclampsia group
The number of primipara	11	19
Age (Y)	32 (31, 34)	33 (31, 36.75)
Neutrophils (10^9/L)	5.7 (5, 6.7)	5.65 (4.725, 7.175)
Lymphocyte (10^9/L)	1.515 $\pm$ 0.05	1.710 $\pm$ 0.06
Platelets (10^9/L)	174 (149, 199)	186.5 (154.75, 241)
D-dimer (mg/L)	1.367 $\pm$ 0.03	2.087 $\pm$ 0.16
Fibrinogen (g/L)	4.009 $\pm$ 0.06	4.240 $\pm$ 0.10
D-dimer/fibrinogen	0.34 (0.27, 0.40)	0.41 (0.30, 0.56)
Fetal weight (g)	3333 $\pm$ 38.87	2907 $\pm$ 116.5
Systolic blood pressure (mmHg)	113.8 $\pm$ 0.90	153.5 $\pm$ 1.50
Diastolic blood pressure (mmHg)	72.46 $\pm$ 0.73	95.66 $\pm$ 1.41

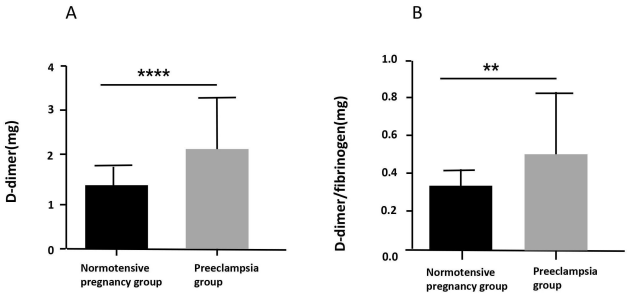

Fig. 2. D-dimer and D-dimer/fibrinogen in middle-aged pregnant women. (A) D-dimer in middle–aged pregnant women, ****: $p < 0.0001$. (B) D-dimer/fibrinogen in middle-aged pregnant women, **: $p < 0.01$.

3.3 D-dimer/Fibrinogen

The D-dimer/fibrinogen ratio was not different in the young group. However, there were differences among the middle-aged groups, as shown in Fig. 2B. The median and quad values of D-dimer/fibrinogen ratio were [0.34 (0.27, 0.80)] in the young normotensive pregnancy group, [0.35 (0.27, 0.47)] in the young preeclampsia group, [0.34 (0.27, 0.40)] in the middle-aged normotensive pregnancy group, and [0.41 (0.30, 0.56)] in the middle-aged preeclampsia group. The median and quad values of D-dimer/fibrinogen ratio were [0.34 (0.27, 0.40)] in the middle-aged normotensive pregnancy group, and [0.41 (0.30, 0.56)] in the middle-aged preeclampsia group. There was a statistical difference between the middle-aged pregnant women ($p = 0.0039$).

3.4 Fetal Birth Weight

The difference in fetal birth weight between the middle-aged normotensive pregnancy group and the middle-aged preeclampsia group was significant ($p < 0.0001$), as shown in Fig. 3A. In addition, the mean weight of the fetus in the middle-aged normotensive pregnancy group (3333 $\pm$ 38.87 g) and the mean weight of the fetus in the middle-aged preeclampsia group (2907 $\pm$ 116.5 g) was significantly lower than that in the middle-aged normotensive pregnancy group, and the difference was statistically significant ($p = 0.0002$), as shown in Fig. 3B.

3.5 Predictive Value of D-dimer for Preeclampsia in Pregnant Women of Different Ages

The relationship between D-dimer and pregnant women with preeclampsia at different ages was evaluated by ROC curve analysis. Table 3 shows detailed ROC curve analysis data. This model suggests that the predicted area of D-dimer for preeclampsia in middle-aged pregnant women is significantly higher than that in young women. Mean-

Table 3. PE was evaluated by D-dimer ROC curve.

Variable	Cut off value	Sensitivity of sensitivity	Degree of specificity	Area under curve	*p*	95% CI	
						Lower limit	Upper limit
D-dimer of youth group	1.86	28%	89%	0.596	0.02	0.5	0.6779
D-dimer of middle group	1.67	56%	84%	0.702	0.0002	0.6	0.8043

PE, preeclampsia; ROC, receiver operating characteristics; CI, confidence interval.

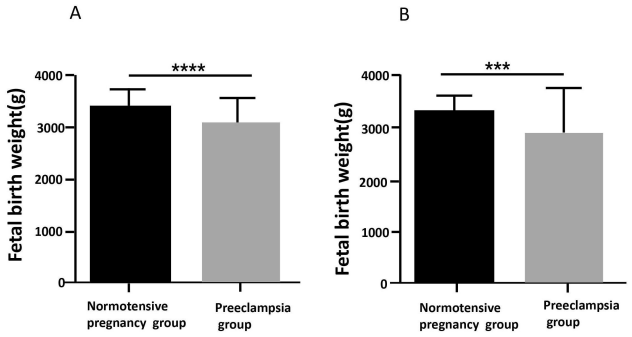

Fig. 3. Fetal weight of different age pregnant women. (A) Fetal weight of young pregnant women, ****: $p < 0.0001$. (B) Fetal weight of middle-aged pregnant women, ***: $p < 0.001$.

while, in middle-aged pregnant women, the predicted area of D-dimer for preeclampsia was 70.2% (95% confidence interval (CI) 60–80.43%, $p = 0.0002$) (Fig. 4). At the same time, logistic regression analysis was used to verify the correlation between D-dimer and preeclampsia again. The odds ratio (OR) value of D-dimer was 3.290 and was positively correlated with preeclampsia. The age also was positively correlated with preeclampsia which suggesting that D-dimer was more valuable in predicting preeclampsia in the middle-aged group (Table 4).

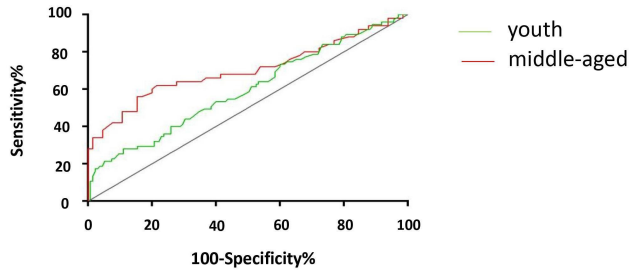

Fig. 4. ROC curve of D-dimer and pregnant women with preeclampsia at different ages.

4. Discussion

Preeclampsia is a pregnancy-specific disease that causes adverse outcomes for mothers and infants [12]. In order to predict preeclampsia earlier, many studies are still trying to find ideal markers [13]. It is well known that D-dimer is a potential predictor of preeclampsia [14], and we further clarified the predictive value of D-dimer in different age groups of preeclampsia. No similar studies have been reported.

The level of D-dimer is high during pregnancy, which is a normal physiological phenomenon. Our study also confirmed that the level of D-dimer in the preeclampsia group was significantly higher than that in normotensive pregnancy [8]. Further studies found that the D-dimer levels of preeclampsia women over 30 years of age were significantly higher than those of preeclampsia women below 30 years of age. D-dimer is the final degradation product of fibrin, reflecting the level of polymerization and decomposition of fibrin [15]. In order to increase placental blood perfusion, the body compensatively promotes vascular constriction, resulting in high blood pressure and further promoting the occurrence of preeclampsia [16]. Placental ischemia can increase the production of sFlt-1, angiotensin II (Ang II) type 1 autoantibodies and TNF-α, leading to maternal vascular endothelial dysfunction [17]. Studies have shown that reducing the placental arterial perfusion pressure in rats can induce a rat model of preeclampsia, resulting in restricted fetal growth and development [18]. In addition, increased placental vascular resistance forces the muscular segment of the artery to maintain narrowing and contraction, increases maternal circulation and placental lipid peroxidation, and decreases antioxidant activity, which further increases lipid peroxidation and decreases antioxidant activity [19]. Studies have shown that the end products of fatty acid oxidation in maternal plasma, umbilical cord plasma and placental tissue of pregnant patients with fetal growth restriction are higher than those in healthy pregnant patients [20]. We also showed that the fetal birth weight of pregnant women with preeclampsia was significantly lower than that of the normotensive pregnancy group, which had a certain impact on the infant.

The damage of vascular endothelial cells is the basic pathological change of preeclampsia. D-dimer levels have been found to correlate with C-reactive protein (CRP) [21]. Elevated D-dimer is likely associated with vasculitic status. PTX3 is a novel inflammatory marker, which can lead to the prothrombotic state caused by endothelial dysfunction [22]. In studies of disease severity in COVID-19 patients, PTX3 is positively correlated with plasma D-dimer and is involved in coagulation dysfunction [23]. Silvia Galbiati *et al.* [24] found that serum PTX3 was significantly elevated in pregnant women with preeclampsia, which supports our conclusion.

Table 4. Regression analysis of age, number of deliveries, D-dimer and preeclampsia.

Variables in the Equation									
		B	SE	Wald	df	Sig	Exp(B)	95% CI for Exp(B)	
								Lower limit	Upper limit
Step 1[a]	Age	0.040	0.033	1.411	1	0.235	1.040	0.975	1.111
	D-dimer	1.191	0.251	22.434	1	<0.001	3.290	2.010	5.385
	Delivery (1)	–0.154	0.292	0.279	1	0.597	0.857	0.483	1.520
	Constant	–3.391	1.113	9.290	1	0.002	0.034		

a. Variable(s) entered on step 1: Age, D-dimer, Delivery.

B, beta; df, degree of freedom; SE, standar erro; CI, confidence interval.

In the acute phase caused by tissue and blood vessel injury, fibrinogen is a key component of thrombosis and hemostasis [25]. By detecting plasma fibrinogen γ chain concentration, Zhu Yuli *et al.* [26] found that fibrinogen synthesis and degradation disorders may be one of the important mechanisms of preeclampsia. This was inconsistent with our experimental results, which showed that the mean fibrinogen in the preeclampsia group was higher than that in the normotensive pregnancy group, but the difference was not statistically significant. Meanwhile, the ROC curve showed that the predicted area was larger in the middle-aged pregnancy group. In the middle-aged pregnant women, the D-dimer cutoff value was 1.86 µg/mL, the sensitivity was 28%, and the specificity was 89%. The cutoff value of D-dimer was 1.67 µg/mL, the sensitivity was 56%, and the specificity was 84%. Hence, D-dimer has a higher predictive value for preeclampsia in older pregnant women. In order to exclude the interference of other variables, such as the time of delivery of primipara or menpara, age and so on, we used multiple regression method to verify the above conclusions.

Elevated D-dimer was an independent factor associated with increased incidence of venous thromboembolism, myocardial infarction, and cerebral infarction [27]. If the D-dimer of pregnancy body is high, it is easy to activate the coagulation system. The mother-to-fetus interface vascular endothelium is easy to be damaged. Next, amniotic fluid enters the maternal circulation through potential channels, leading to the occurrence of amniotic fluid embolism. Research shows that preeclampsia increases the risk of an ominous complication such as amniotic fluid embolism [28].

If D-dimer is high in an older pregnant woman during prenatal examination, the clinician should closely monitor the pregnancy blood pressure, urine routine, placental growth factor, etc. Notably, this was the first study to describe the D-dimer levels associated with blood pressure differences among pregnant women of different ages. However, the sample size of this study was so small that the results could be biased. Large prospective trials are needed to investigate the predictive value of D-dimer in preeclampsia at different ages.

5. Conclusions

Prenatal D-dimer level maybe associated with preeclampsia occurrence in pregnant women over 30 years of gestational age than in women before 30 years of age.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

The experimental ideas are designed by TTL. HPZ and TTL interpretate the data for work and write the discussion of the manuscript. YJH designed and made critical revisions to the paper. SHC and JYZ collected and analyzed data. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Wenzhou People's Hospital (approval number: 2021-346).

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Conflict of Interest

The authors declare no conflict of interest.

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