

# Comparison of the D-dimer concentration in pregnant women with or without pulmonary thromboembolism

Seyed H. Borsi<sup>1</sup>, Maryam H. Shoushtari<sup>1</sup>, Mehrdad D. MalAmir<sup>1</sup>,  
Kambiz A. Angali<sup>2</sup>, Maryam S. Mavalizadeh<sup>3</sup>

<sup>1</sup>Departments of Pulmonology, <sup>2</sup>Biostatistics and Epidemiology, <sup>3</sup>Faculty of Medicine, Internal Medicine, Ahvaz Respiratory Research Center, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran

## ABSTRACT

**Introduction and Objectives:** Pulmonary thromboembolism is the third most common vascular disease after coronary heart disease and stroke and is approximately 10 times more common in pregnant women compared with the nonpregnant population at the same age. The purpose of the current work is to evaluate D-dimer plasma concentration in pregnant women with or without pulmonary thromboembolism. **Methods:** The present study was a cross-sectional study in which 100 pregnant women with suspected pulmonary embolism referred to Imam Khomeini Hospital in Ahvaz in 1398 were studied. After imaging and approving or rejecting a pulmonary embolism, simultaneously the D-dimer sample was taken from them; then the dimer level in each trimester was compared in positive or negative cases of pulmonary embolism. The SPSS software version 22 was used for data analysis. **Results:** The results showed that 12 patients in the study population had pulmonary embolism and 88 patients did not have pulmonary embolism. According to the results of patients with pulmonary embolism based on CT angiography results, there was no significant relationship with increasing gestational age and mean dimer level ( $P = 0.41$ ). But there was a significant relationship between gestational age and mean dimer level in the group with no pulmonary embolism ( $P = 0.0001$ ). There was no significant relationship between maternal age and mean dimer level in patients with pulmonary embolism ( $P = 0.376$ ) and without pulmonary embolism ( $P = 0.1$ ). Also, there was no significant relationship between the number of pregnancies in both groups with and without pulmonary embolism ( $P = 0.456$ ,  $P = 0.392$ ). **Conclusion:** Concomitant use of D-dimer and Wells' criteria can help us to diagnose or rule out pulmonary thromboembolism and minimize the risk of pregnant women being exposed to X-rays; given the biodiversity of the D-dimer of every woman during a natural pregnancy, repeated D-dimer measurements in the evaluation of thromboembolic pregnancy during pregnancy have no clinical application.

**Keywords:** D-dimer, pregnant, pulmonary thromboembolism

## Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a multifactorial disease with serious short-term and long-term complications and thus potentially fatal. On the other hand, pulmonary thromboembolism is the third most common

vascular disease after coronary artery disease and stroke, affecting 2–5% of people in their lives.<sup>[1,2]</sup> The mortality rate due to PE varies depending on factors such as age, underlying disease, etc.<sup>[3]</sup> PE is a common condition that cannot be diagnosed on the basis of clinical findings alone and due to the lack of sensitivity and specificity, the signs and symptoms of the disease continue to be classified as a potentially fatal disease, leading to more than 370,000 persons hospital admissions per year in the United States; the failure to diagnose PE leads to the sudden death of cardiovascular dysfunction and impaired quality of

**Address for correspondence:** Dr. Maryam S. Mavalizadeh, Faculty of Medicine, Department of Internal Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. E-mail: mavalymaryam@gmail.com

Received: 27-11-2019

Revised: 05-12-2019

Accepted: 07-01-2020

Published: 25-08-2020

### Access this article online

#### Quick Response Code:



Website:  
www.jfmpc.com

DOI:  
10.4103/jfmpc.jfmpc\_1070\_19

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**How to cite this article:** Borsi SH, Shoushtari MH, MalAmir MD, Angali KA, Mavalizadeh MS. Comparison of the D-dimer concentration in pregnant women with or without pulmonary thromboembolism. J Family Med Prim Care 2020;9:4343-7.

life.<sup>[4,5]</sup> It is also 4–16 times more common in pregnant woman compared to other women at the same age group. The risk factors for this disease include cigarette smoke, malignancy, obesity, old age, long periods of inactivity, and the history of surgery.<sup>[5]</sup> The incidence of VTE during pregnancy is 1 person per 1000 pregnancies.<sup>[6]</sup> Due to important changes that occur during pregnancy (such as swelling of the legs and pain and discomfort as common symptoms in this period), diagnostic methods, devices, and facilities are changing during this time, and clinical diagnosis of VTE is not reliable at this time.<sup>[7]</sup> D-dimer is used as an important diagnostic test, especially to rule out VTE in nonpregnant patients; however, the usefulness of this test for the VTE diagnostic algorithm during pregnancy has not been fully explored. Several studies in this area have indicated that reaching a D-dimer concentration of 500 µg/L necessitates the use of routine imaging for diagnosis (but no specific interval for different trimmers is mentioned).<sup>[8]</sup> Venous ultrasound is an excellent diagnostic method with high sensitivity and specificity for the diagnosis of DVT, but there are several main reasons for a better evaluation of the D-dimer for diagnosis in pregnant women. The use of venous ultrasound is highly dependent on the operator, the accuracy of the device, and the experience of the operator. It is also commonly used in large centers and is often difficult to find in small centers without advanced facilities. On the other hand, the lower price, the ease of use, and the better interpretation of the results make D-dimer more attractive.<sup>[9]</sup> Several studies have been carried out in recent years, including the study by Choi *et al.*, which examined the D-dimer level of 152 pregnant women suspected of having VTE with 100% dimer sensitivity and the specificity of this tests was 42%; they suggested that larger groups need to be studied to better evaluate the results.<sup>[10]</sup> However, the purpose of the current work is to evaluate D-dimer plasma concentration in pregnant women with or without pulmonary thromboembolism.

## Methods

In this cross-sectional study, 100 pregnant women with suspected PE referred to Imam Khomeini Hospital in Ahwaz in 2019 were studied. Information for this study was gathered from trimester of each pregnant patient who presented with symptoms of PE and underwent imaging by a physician considering high suspicion of PE, after imaging and approving or rejecting a PE, at the same time a sample of D-dimer was taken from them. Then the D-dimer level in each trimester was compared in positive or negative cases of PE. The SPSS software version 22 was used for data analysis. Therefore, to compare dimer with and without PE in each trimester, two-way ANOVA and post-hoc tests were used to compare the two groups. Regression and correlation were also used for the correlation analysis.

## Results

In this study, 100 pregnant women were divided into 5 groups according to their age: 11% in the under-20 age group, 24% in the age group of 20–25 years, 26% in the age group of 26–30 years, 27% in the age group of 31–35 years, and 12% over 35 years.

Table 1 lists the results of pregnancy patients confirmed on the basis of positive results of pulmonary vascular CT angiography; a comparison of the dimer number with maternal age is given. According to the results of the correlation table, relation between maternal age and mean D-dimer in patients with PE was not significant ( $P = 0.376$ ).

On the other hand, Table 2 shows the results for pregnant women whose results were negative for pulmonary vascular angiography. The correlation between D-dimer and age of the mother indicated no significant correlation between dimer number and age of the mother ( $P = 0.1$ ).

Another variable considered in this study was the number of pregnancies (gravida). Accordingly, patients were divided into four groups; the results for the percentage of pregnancy rate (gravida) as well as the correlation between the D-dimer levels with the pregnancy number variable are presented in Table 3. Twenty cases of pregnant women with pulmonary vascular CT angiography, PE, were compared between the number of pregnancies and the dimer number. There was also a correlation between the variable number of pregnancies and the dimer level in 88 pregnant patients whose results were negative

**Table 1: Comparison of the D-dimer number with maternal age in pregnancy women confirmed on the basis of positive results of pulmonary vascular CT angiography**

PTE positive	n	Mean	Minimum	Maximum
<20	1	12,300	12,300	12,300
20-25	1	13,640	13,640	13,640
26-30	4	10,805	8200	14,600
31-35	4	14,320	10,600	17,530
More than 35	2	16,050	15,700	16,400
Total	12	13,211	8200	17,530

**Table 2: Comparison of the D-dimer number with maternal age in pregnant women whose results were negative for pulmonary vascular CT angiography**

PTE negative	n	Mean	Minimum	Maximum
<20	10	36,150	1590	5370
20-25	23	32043	1170	6080
26-30	22	40,332	1370	8430
31-35	23	41,409	1450	11,940
More than 35	10	46,370	2790	8220
Total	88	38,658	1170	11,940

**Table 3: Correlation between the D-dimer levels with the pregnancy number**

Gravid	n	Mean	Minimum	Maximum
1	2	15,420	13,640	17,200
2	3	14,433	12,300	16,400
3	4	12,745	10,600	17,530
More than 3	3	11,140	8200	15,700
Total	12	13,211	8200	17,530

for pulmonary vascular CT angiography. The results showed that there was no significant relationship between the number of pregnancies in both groups with and without PE with D-dimer level ( $P = 0.392$ ,  $P = 0.456$ ).

In the present study, another variable was investigated that the results of frequency percentage and statistical analysis results are presented in Table 4. All patients were divided into three trimesters according to LMP-based pregnancy; among 100 patients, 20% in the first trimester (first 12 weeks), second trimester 13–24 weeks was 32% and third trimester 25 weeks to delivery was 48% frequency was obtained.

Therefore, to analyze the data, the patients were divided into two groups with (confirmed) PE comprising 12 of the study population and 88 patients with no PE. According to the results presented in Table 4, no significant relationship was found between patients with PE based on CT angiographic findings with increasing gestational age and mean D-dimer level ( $P = 0.41$ ). On the other hand, analysis for the other group was performed on 88 pregnant women with PE who were not detected and the results showed a significant association between increasing gestational age and mean dimer level ( $P = 0.0001$ ).

## Discussion

D-dimer is a minor protein product, which is found in circulation in negligible amounts because of endogenous fibrinolysis.<sup>[11]</sup> Many studies have examined the level of D-dimer during pregnancy<sup>[10-12]</sup> and showed that D-dimer values were higher during pregnancy compared to nonpregnancy. In addition, increased levels of D-dimer were observed in the third trimester of normal pregnancy.<sup>[10]</sup> However, the reason for the increase in the amount of D-dimer during pregnancy may be continuous coagulation, and fibrinolysis increases the production of intrinsic and extrinsic coagulation factors during normal placental growth.<sup>[13,14]</sup> This results in a physiological increase in the concentration of D-dimer in the blood of the mother during pregnancy until delivery, which is not necessarily associated with thromboembolic complications.<sup>[15,16]</sup> Therefore, the present study was performed on 100 pregnant women who were suspected of having PE according to the Wells' criteria, one of the most important results being that of the 12 pregnant women who had PE-positive CT angiography, the mean dimer number was  $13,210 \pm 3100$ ,

compared to 88 cases who had negative CT angiography and their mean dimer was  $3860 \pm 1950$ . It was significantly higher. In a 2016 review study of 1585 patients, Crawford *et al.*<sup>[17]</sup> aimed to assess the relationship between patients' age and dimer level. Their results also showed that the dimer level increased with increasing age of the patients, but this was not significant, which is consistent with the results of the present study. In a cohort study of Hedengran *et al.* on 4117 pregnant women, the results reported that the level of dimer increased during pregnancy such that in the third trimester this difference was significantly higher in pregnant women with DVT than healthy controls, which is consistent with the present study.<sup>[18]</sup> But in the final report of the Hedengran study, it was concluded that due to the biological diversity of each woman's dimer during natural pregnancy, repeated measurements of dimer in the evaluation of thromboembolism during pregnancy have no clinical application. Parilla *et al.*<sup>[19]</sup> also reported in a 2016 report that concurrent use of dimer and Wells' criteria could help us diagnose and rule out pulmonary thromboembolism. They measured the D-dimer level in 17 pregnant women and found that in the third trimester, the dimer level reached its highest level in people with PE and was significantly different from healthy people. So they reported that the simultaneous use of dimer and Wells' criteria could be of great help to us and minimize the risk of pregnant women being exposed to X-rays. Nishi *et al.*<sup>[14]</sup> performed a study on 1131 pregnant women and measured the dimer level at weeks 6–14 and 30–34. The results of this study showed the numerical mean of the dimer in pregnant mothers without DVT in the first and third trimester was  $1100 \pm 1000 \mu\text{g/L}$  and  $2200 \pm 1100 \mu\text{g/L}$  and in pregnant women with DVT was  $1400 \pm 800$  and  $2600 \pm 2000$  respectively. The numerical mean of the dimer in the third trimester of pregnant women with DVT was significantly higher than healthy controls, but this was not the case for the first trimester,<sup>[14]</sup> which is consistent with the present study. On the other hand, the numerical mean of the dimer increased in the third trimester compared to the first trimester, indicating that the dimer increases with increasing gestational age, which is the case for the present study. It is likely that the increase of the dimer in the first trimester is due to the increase in coagulation factors, because of the increase in estrogen. On the other hand, it seems that in the third trimester, the increase of the dimer is due to a disturbance of the pelvic blood flow due to a rapid growth of the effects on the uterus and the estrogen.

Nishi *et al.* also reported that the dimer content in twins was higher in the third trimester than in monomers (Singleton  $2200 \pm 1600$ ; twin  $3700 \pm 2500$ ), but that was not the case in the first quarter. In the present study, all pregnant women were singleton.

Kovac *et al.*<sup>[20]</sup> examined 89 healthy pregnant women between the ages of 18–40 in 2009 and pregnant women in three trimesters. Twelve pregnant women also had thromboembolism. Dimensions of healthy pregnant women in the first trimester was  $2220 \pm 640$ , second trimester was  $3260 \pm 1310$ , and third trimester was  $4750 \pm 1690$ ; Kovac's study showed that with increasing gestational age, the amount of dimer was significantly

**Table 4: Comparison between D-dimer level and gestational age**

Trimester		n	Mean	Minimum	Maximum
PTE positive	T1	1	17,200	17,200	17,200
	T2	4	13,150	8.20	16,400
	T3	7	12,677	9.52	17,530
	Total	12	13,211	8.20	17,530
PTE negative	T1	19	2.1442	1170	3640
	T2	28	3.4082	1.39	5420
	T3	41	4.9761	1.93	11,940
	Total	88	3.8658	1.17	11,940

increased in healthy women, which is statistically significant, and this is consistent with the present study. The mean of dimer for thromboembolic pregnant women in the first trimester was  $15,960 \pm 950$ , second trimester  $13,300 \pm 7000$ , and third trimester  $11,570 \pm 3740$ ; the results of this study are in line with the present study. Morse *et al.* conducted a study of 48 healthy pregnant women (compared to healthy nonpregnant women) in 2004 to examine the mean of the dimer number.<sup>[21]</sup> They reported dimer levels in the first trimester,  $1910 \pm 250$ ,  $3930 \pm 720$  in second trimester, and  $5440 \pm 960$  in third trimester. The dimer content increased significantly with increasing gestational age, consistent with the present study, and the numerical mean of the dimer in all three trimesters in the Kovac study was somewhat similar to the present study.

## Conclusion

According to the results of this study, the mean of D-dimer in pregnant women with PE is significantly higher than those without PE. In the case of pregnant women without PE, the numerical mean of the dimer per trimester increases with increasing gestational age, which is significant, but this is not the case for pregnant women with PE. With increasing age of pregnant mother, the mean dimer number did not increase in both groups of pregnant women with and without PE. Also, with increasing number of pregnancies (gravida), the mean of dimer did not increase in pregnant women with and without PE. Finally, concomitant use of D-dimer and Wells' criteria can help us to diagnose or rule out pulmonary thromboembolism and minimize the risk of pregnant women being exposed to X-rays. However, due to the biological diversity of the dimer of each woman during normal pregnancy, repeated measurements of the dimer in the evaluation of thromboembolic pregnancy do not have clinical utility.

## Acknowledgments

This study was the result of the dissertation thesis registered in Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran and financially supported by the Vice-Chancellor for Research of the AJUMS, Ahvaz, Iran.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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