

D-Dimer Level in Pregnancy with Covid-19 Infection : A Systematic Review



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Abstract— The outbreak of coronavirus disease 2019 (COVID-19), a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in December 2019 in Wuhan, Hubei province, spreading across China and then globally. The D-dimer concentrations of patients with COVID-19 in the third trimester were found relatively higher than those of uninfected pregnant women. This report aim to summarize the current evidence ofD-dimer level in pregnant and non-pregnant woman with and without Covid-19. On December 5, 2022, two databases including ScienceDirect and PubMed was searched to review and mine the latest published information about pregnancy, Covid-19, and D-dimer in the literature. After screening articles by removing duplicates and reading the abstract, 34 studies were considered to be relevant and included in this systematic review. Collected 23 about D-dimer level in pregnant woman with Covid-19 infection, 4 studies about D-dimer level in pregnant woman with Covid-19 infection vs pregnant woman without Covid-19 infection, and 7 studies about D-dimer level in pregnant woman with Covid-19 infection vs non-pregnant woman with Covid-19 infection. In view of fact that D-dimer level is high in pregnant patients, pregnant patient with covid-19 infection, and pregnant patient with severe symptomatic Covid-19 infection. D-dimer monitoring will be important in the clinical practice of pregnant woman with Covid-19 infection.

Keywords: D-Dimer, Covid-19, pregnancy, symptoms, pregnant, non-pregnant

1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19), a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in December 2019 in Wuhan, Hubei province, spreading across China and then globally [1,2,3]. This virus belongs to the β -Coronavirus family and is partially like the SARS-CoV and MERS-CoV coronaviruses, which have caused previous epidemics in China and the Middle East, respectively [2]. The World Health Organization (WHO) first declared a public health emergency of international concern on 30 January 2020 and then formally declared it a pandemic on 11 March 2020[2]. According to the WHO, it has affected over 196.55 million people worldwide, with more than 4.2 million deaths [2]. Pregnancy is characterized by altered immunity with predisposition to respiratory viral infections [4].

Previous studies reported that pregnant women infected with severe acute respiratory syndrome coronavirus (SARS-CoV) were more susceptible to severe adverse outcomes including maternal morbidity and death [4,5]. COVID-19 is usually mild in 81%, severe in 14%, and critical in 5% of nonpregnant patients, percentages which are similar (86%, 9%, and 5%, respectively) to pregnant women in early reports [6]. In physiological conditions such as pregnancy and pathological conditions such as cancer, inflammation and surgery the elevated level of D-dimer can be seen [7]. The D-dimer concentrations of patients with COVID-19 in the third trimester were found relatively higher than those of uninfected pregnant women [1].

The risk of developing SARS-CoV-2 infection in pregnant women is the same as in the general population [8]. This report aims to summarize the current evidence of D-dimer level in pregnant and non-pregnant women with and without COVID-19.

2. Method

On December 5, 2022, two databases including ScienceDirect and PubMed were searched to review and mine the latest published information about pregnancy, COVID-19, and D-dimer in the literature. The keywords used were “D-dimer” AND “COVID-19” AND “Pregnancy”. The criteria for inclusion were the texts written in English and the date of publication was between 2018 to 2022. The submissions accepted included original articles, brief reports, letters, and abstracts from the conference. The studies with inadequate data and contact letters to the editors were removed from the report.

The related documents were extracted in compliance with the criterion for inclusion and exclusion. Based on the study's objectives, the following data were collected: first author, region, sample size, age of studied patients, status pregnant or non-pregnant, and D-dimer levels.

3. Results

3.1 Search Results

From the beginning, we retrieved a total of 433 records through manual and electronic searches. The electronic search was performed through database search of Science Direct Elsevier and PubMed. Because of duplications in the records, 7 of them were removed from the retrievals. After the authors assessed the titles and abstracts of the records, the remaining 53 retrievals, 373 records were excluded for they were not relevant for this review in terms of outcome the study is interested. After screening articles, 34 studies were considered to be relevant and included in this systematic review.

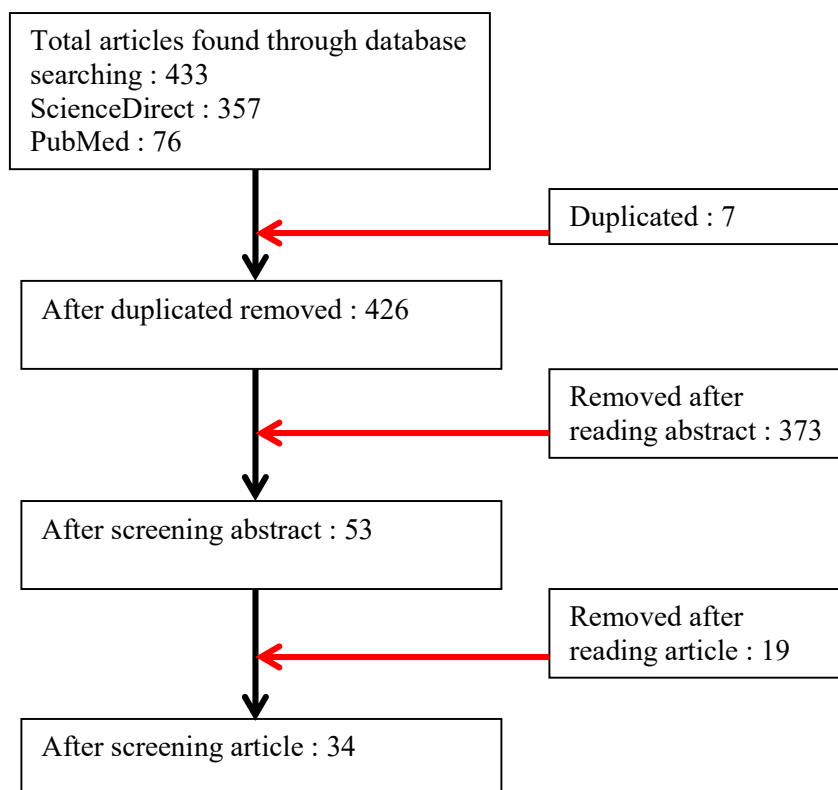


Figure 1. Flowchart for The Literature Search Performed on December 5, 2022

3.2 Description of Original Studies

Table 1 presents the descriptive summary of the characteristics of 34 studies. In this systematic review most of studies beraslalari China (n= 11), and others from Turkey (n=7), USA (n=5), Spanyol(n=4), India (n=1), Russia(n=1), UAE (n=1), Pakistan(n=1), Japan(n=1), Italy (n=1), and Boznia& Herzegovina(n=1). Collected 22 retrospective studies and 12 prospective studies. Collected 23 about d-dimer level in pregnant woman with covid-19 infection, 4 studies about d-dimer level in pregnant woman with covid-19 infection vs pregnant woman without covid-19 infection, and 7 studies about d-dimer level in pregnant woman with covid-19 infection vs non-pregnant woman with covid-19 infection. Unfortunately, most of studies showed D-dimer values in quantity (cut off 0,00 – 0,50 µg/mL), and others showed in quality. Most studies showed elevated D-Dimer level in pregnant woman with covid-19 infection.

Table 1. Descriptive Summary of The Characteristics of 34 Studies

Study	Study Region	Method	Sample Size (n)	Gestational Age	D-Dimer
Jingjiao Zhou et al	China	Retrospective study	16 Pregnant women with covid 19	3 rd trimester	Elevated in Pregnant women with

					covid 3,32 mg/dl (2,18-4,21) Healthy pregnant women : 1,70 (1,07-2,60)
Atakan Tanacan et al	Turkey	Prospective case control	180 (90 pregnancy with covid-19 ; 90 normal pregnancy)	1 st – 3 rd trimester	Elevated in pregnant women with covid-19 : 1.2 mcg/ml (1.1) Pregnant women without Covid-19 : 0.6 (0.5)
Itziar Carrasco et al	Spain	Prospective observational	105 pregnant women with Covid-19	2 nd – 3 rd trimester	Elevated D-Dimer (ng/mL) 637 No pneumonia 864 Pneumonia 493 There were no thromboembolic complications
Ali eman et al	Turkey	Retrospective comparative	19 pregnant women with Covid-19 in ICU	3 rd trimester	D-Dimer (0-500 Ug FEU/L) Increased levels of D-Dimer values in 15 patients (78.9%) Pregnant women died : 845 Discharged

					from ICU : 738
Stephanie A. Fisher et al	USA	Retrospective cohort	175 pregnant women with Covid-19	1 st – 3 rd trimester	100% elevated D-Dimer in pregnant women with asymptomatic Covid-19 95.7% elevated D-Dimer in symptomatic 93.6% elevated D-Dimer in mild to moderate symptoms 100% elevated D-Dimer in severe to critical symptoms
Andrea Lombardi et al	Italy	Retrospective cohort	62 pregnant women with Covid-19	3 rd trimester	D-Dimer (µg/L) 1727 (1069–3328)
Yajuan Zhong et al	China	Retrospective	36 pregnant women with covid-19 36 healthy pregnant women as a control	5 weeks – 41 weeks 69.4% 3 rd trimester	Compared with pregnant women without Covid-19, pregnant women with Covid-19 had increased levels of D-Dimer
Komal Sundeep Hazari et al	UAE	Case control	79 pregnant with Covid-19 85 non-pregnant	1 st – 3 rd trimester	D-dimer were significantly higher in

			with Covid-19		pregnant women than in non-pregnant women D-dimer [32 (50.8%) vs 3(6%)] ; p < 0.001
Mohammad Sohaib Asghar et al	Pakistan	Single Centered Retrospective	131 Covid-19 positive 60 pregnant 71 non-pregnant	Mean 31 weeks	D-Dimer >0.50 mcg/mL Pregnant : 3.97 Nonpregnant : 7.40 D-Dimer was lower in pregnant patients as compared to non-pregnant females
Kadir Burak Ozer et al	Turkey	Retrospective cross-sectional	34 patients with Covid-19 : 15 pregnant with Covid-19 19 non-pregnant with Covid-19	11-40 weeks	The mean value of the D- dimer of the Pregnant woman with Covid-19 was of 962 523.644 ng/ml (minimum: 540 ng/ml; maximum: 2,560 ng/ml), and, regarding the Non-pregnant women, it was of

					3,732.1 6,605.985 ng/ml (minimum: 200 ng/ml; maximum: 30,000 ng/ml). This difference was found to be statistically significant ($p < 0.05$).
Gordana Grgic et al	Bosnia and Herzegovina	Retrospective	61 pregnant with Covid-19 : 32 symptomatic 29 asymptomatic	All trimester	D-dimer ($p = 0.00124$), Symptomatic 2.8 Asymptomatic 2.58
Shuang Xu et al	China	Retrospective	64 patients with Covid-19: 34 pregnant women with Covid-19 30 nonpregnant with Covid-19	All trimester	D-dimer of pregnant women ($1.37 \pm 1.11 \mu\text{g/mL}$) were higher ($P = .001$ and $P = .003$) than that of nonpregnant women ($3.46 \pm 0.73 \text{ g/L}$ and $1.79 \pm 2.91 \mu\text{g/mL}$, respectively).
Chunchen Wu et al	China	Retrospective	8 pregnant women with Covid-19	3 rd trimester	D-Dimer levels during prepartum were normal, but increased significantly

					in four patients
Yulan Wang et al	China	Retrospective	27 pregnant with Covid-19	3 rd trimester	<p>Pregnant women : 16/27 (59%) <3 mcg/mL 5/27 (19%) 3 and 5 mcg/mL 6/27 (22%) >5 mcg/mL</p> <p>Pregnant non covid-19 : 24/27 (89%) <3 mcg/mL 3/27 (11%) 3 and 5 mcg/mL</p> <p>The D-Dimer concentrations of patients with Covid-19 in the 3rd trimester were found relatively higher than those of uninfected women, indicated an increased risk of thromboembolic disease.</p>
Zozan Guleken et al	Turkey	Experimental	37 pregnant with Covid-19	2 nd – 3 rd trimester	<p>D-Dimer : 0,00 – 0,50 µg/mL</p> <p>2nd trimester asymptomatic : 1.54</p> <p>3rd trimester</p>

					<p>asymptomatic : 2.93 2nd trimester with severe Covid-19 symptoms : 37.70 D-dimer levels were higher than the reference level. There was an increase of D-Dimer in the 3rd trimester group compared with the 2nd trimester group. But the 2nd trimester group with severe Covid-19 symptoms has the highest D-Dimer value.</p>
Eda UreyenOzdemi r et al	Turkey	Prospective study	100 pregnant women with Covid-19	3 rd trimester	<p>Mild symptoms : 1.6 Moderate symptoms : 2.3 Severe symptoms : 2.5 Pregnant women with severe Covis-19 symptoms</p>

					have the highest levels of D-Dimer
Esra Can et al	Turkey	Prospective case-control study	46 pregnant women with Covid-19: Non severe group : 25 Severe group : 21	Mean 29 weeks	Mean D-Dimer level : 1.8 Non severe group : 1.7 µg/ml Severe group : 2.2 µg/ml The D-Dimer value was significantly associated with the disease severity.
Mahesh Asalkar et al	India	Cross-sectional study	9 pregnant woman with Covid-19	1 st - 3 rd trimester	D-Dimer was raised in 7 cases (78%) of maternal mortality with the values >3 times the upper limit of D-Dimer seen in 67% cases. D-Dimer range : 465-30,700 ng/mL (normal range 130-1700 ng/mL)
XiaoMing Gong et al	China	Retrospective study	10 pregnant women with Covid-19	3 rd trimester	D-Dimer levels were increased in 8 patients (range 507 –

					2141 ng/mL)
Dongmei Cao et al	China	Retrospective study	10 pregnant women with Covid-19	3 rd trimester	D-dimer $\mu\text{g/mL}$ median : 2.294, range (0.93-6.48)
Zhiqiang Wang et al	China	Retrospective study	72 women with Covid-19: 30 pregnant with Covid-19 42 non-pregnant with Covid-19	3 rd trimester	D-Dimer normal range : 0-1 $\mu\text{g/mL}$ Pregnant women : 2.5 $\mu\text{g/mL}$ Non-pregnant : 0.3 $\mu\text{g/mL}$
Lijie Wei et al	China	Retrospective study	43 women with Covid-19: 17 pregnant with Covid-19 26 nonpregnant with Covid-19	1 st – 3 rd trimester	D-Dimer in pregnant women : 2.1 $\mu\text{g/mL}$ Nonpregnant : 0.3 $\mu\text{g/mL}$ 92% (11/12) of pregnant women were observed with an elevated D-dimer level, which was significantly higher than nonpregnant women (2.1 vs 0.3 $\mu\text{g/mL}$, $P < .001$;
Erica M. Lokken et al	USA	Retrospective study	46 pregnant women with Covid-19	1 st – 3 rd trimester	a markedly, elevated D-dimer was detected in 1 of 5 patients

					(20%) in which the test was ordered (case 25, 4.08 ng/mL) (>4.0 µg/mL)
Augusto Pereira et al	Spain	Retrospective study	60 pregnant women with Covid-19	1 st – 3 rd trimester	D dimer median >1.9 µg/mL,, range 0.4-7.8
Roman G. Shmakov	Russia	Cohort/prospective study	66 pregnant women with Covid-19	2 nd – 3 rd trimester	D-dimer, ng/L 1361 (822–2045)
Rebecca A. M.	USA	Cohort/prospective study	64 pregnant women with Covid-19	2 nd – 3 rd trimester	D-dimer (100-1500 ng/mL) 1325.63388.5
Nan Yu	China	Retrospective study	7 pregnant women with Covid-19	3 rd trimester	D-dimer was above the normal range in all patients.
Shoichi Magawa	Japan		Pregnant women with Covid-19: Before group (delta) (n = 77) After group (omicron) (n = 50)	3 rd trimester	D-dimer levels (µg/mL), 2.55 2.10 versus 2.16 1.77 (p = 0.427).
Xu Qiancheng	China	Retrospective study	28 pregnant women with Covid-19, 54 non-pregnant women with Covid-19		Pregnant : 2.80 (1.36–4.29) Non-pregnant : 0.26 (0.13–0.42)
Olga Grechukhina	USA	Retrospective study	141 pregnant women with Covid-19	1 st – 3 rd trimester	D-dimer 5-10 mg/L

Elias Ortiz Molina	Spain	Retrospective study	20 pregnant women with Covid-19	3 rd trimester	D-dimer 2.04 µg/mL (SD = 3.36)
Erica M. Lokken,	USA	Retrospective study	24 pregnant women with Covid-19	2 nd – 3 rd trimester	29.4% (5 of 17) had an elevated D-dimer, 1.5 (0.2e4.5)
Nuray Yazihan	Turkey	Cohort/prospective study	96 healthy pregnant women, 90 pregnant women with COVID19	2 nd – 3 rd trimester	D-Dimer mg/L covid: 2.289 health : 0.7647
Marta Defez-Martin	Spain	Cohort/prospective study	153 pregnant women with COVID-19	2 nd – 3 rd trimester	elevated D-dimer in up to 46.4%

3.3 D-dimer in Pregnant Woman with Covid-19 Infection

There are 24 studies showed D-dimer level in pregnant woman with covid-19 infection. In prospective observational study by Itziar Carrasco et al, showed 105 pregnant women with increase values of D-Dimer (median : 637, range 438 – 1325 ng/mL) [9]. The infection can be asymptomatic in carriers or the virus can cause symptoms in infected individuals such as fever, dry cough, and dyspnea, but in severe symptoms of COVID-19 infection can cause acute respiratory distress syndrome (ARDS) and even death [7]. Although D-dimer is increase in pregnant woman with covid-19 infection, but in others studies there are different result of D-dimer between asymptomatic and symptomatic pregnant woman with covid-19 infection, where D-dimer in asymptomatic pregnant woman with covid-19 infection is higher [8,10]. In contrast, Zozan Guleken et al make 3 groups of pregnant woman with covid-19 infection into asymptomatic 2nd trimester, asymptomatic 3rd trimester, and symptomatic 2nd trimester and their D-dimer levels are 1.54, 2.93, and 37.70 µg/mL, respectively. Although D-dimer level in asymptomatic 3rd trimester pregnant woman is higher than asymptomatic 2nd trimester, D-dimer level of symptomatic 3rd trimester is the highest [11]. There are two studies which divided symptomatic pregnant woman with covid-19 infection into two groups, non-severe and severe symptomatic, and group of severe symptoms has higher d-dimer level [12,13]. Several studies have demonstrated poor prognosis for coagulopathy in patients with severe COVID-19 [7].

3.4 D-dimer in Pregnant Woman with Covid-19 Infection with Pregnant Woman without Any Defined Risk Factor

There are four studies which compared D-dimer of pregnant woman with covid-19 infection with pregnant woman without any defined risk factor as control group [14,17]. In the first study, by Atakan Tanacan et al, a prospective case-control study of 90 pregnant woman with covid-19 infection and 90 pregnant woman without any defined risk factor with D-dimer levels of 2.1 and 0.6 mcg/mL, respectively [15]. Similarly, by Zhong et al, in retrospective study, conducted on 36 pregnant women with covid-19 and 36 healthy pregnant women, pregnant women with Covid-19 had higher D-dimer level [16]. In last study of 90 pregnant women with COVID-19 and 96 healthy pregnant women have level of D-dimer 2.289 and 0.7647 mg/L, respectively [17].

3.5 D-dimer in Pregnant Woman with Covid-19 Infection with Non-Pregnant Woman with Covid-19 Infection

There are 7 studies showed D-dimer level in pregnant woman with covid-19 infection with non-pregnant woman with covid-19 infection [3,5,18-22]. Retrospective study by Zhiqiang Wang et al, 30 pregnant woman with covid-19 infection has higher D-dimer level than 42 non-pregnant woman with Covid-19 infection, 2.5 and 0.3 µg/mL, respectively [3]. Similarly, there are three studies in China where D-dimer level in pregnant woman with covid-19 infection is higher than non-pregnant woman with covid-19 infection [5,18,22]. In contrast, there are three studies with different result, where non-pregnant woman with covid-19 infection has higher D-dimer level [19-21].

4. Discussion

Pregnancy is associated with numerous physiological changes that affect the functioning of almost every organ system, including changes in hemostasis [23]. The consequence of high procoagulation activity is increased fibrin turnover, as indicated by increasing concentrations of D-Dimers (D-D), recognized as the most sensitive markers of secondary fibrinolytic activation, with successive trimester [24]. It is often emphasized in the medical literature that D-Dimer concentrations, which are products of the action of plasmin on stabilized fibrin, and fibrinogen (Fb), are increased in pregnant women compared to nonpregnant women, and their increase progresses with the stage of pregnancy [23]. They should be considered an adaptive mechanism protecting a pregnant woman against delivery hemorrhage and generally do not have any clinical implications.

The result of this study, as expected, four studies showed elevated D-dimer level in healthy pregnancy [14-17]. In the case of D-Dimers, the concentrations for the entire group of pregnant women fell within the following ranges: first trimester 167-721 ng/mL, second trimester 298-1653 ng/mL, and third trimester 483-2256 ng/mL, uses a cut-off value of <500 ng/mL for non-pregnancy [24]. It is worth emphasizing that elevated levels of D-Dimer may appear both in normal pregnancy and in complicated pregnancy [23].

Following the outbreak of the COVID-19 pandemic, Several studies have been conducted to study the association between initial D-dimer measurements and disease severity and outcome [26]. In this study, all studies showed that there are elevated D-dimer level in pregnant woman with covid-

19 infection (cut-off value of <500 ng/mL) [3,5,7, 9-22, 26-40]. A study done by Zhang et. al. in China including 343 patients concluded that D-dimer could be an early useful marker for predicting in-hospital mortality in patients. They found the optimal cutoff point for D-dimer to be 2 $\mu\text{g/ml}$ [41]. A similar study in India found the optimal cutoff value for admission D-dimer to predict hospital mortality to be 1.44 $\mu\text{g/ml}$, whereas the optimal value for highest D-dimer measurement during hospital stay for predicting hospital mortality was 2.01 $\mu\text{g/ml}$ [42]. In contrast, the optimal cutoff value for admission D-dimer for predicting mortality has not been agreed upon in the current literature [25].

5. Conclusion

D-dimer measurements in a laboratory test needed for evaluation of pregnant patients with covid-19 infection. In view of fact that D-dimer level is high in pregnant patients, pregnant patient with covid-19 infection, and pregnan patient with severe symptomatic Covid-19 infection. D-dimer monitoring will be important in the clinical practice of pregnant woman with Covid-19 infection.

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