The Egyptian Journal of Hospital Medicine (January2023) Vol. 90 (2), Page 3266-3272

Study of Plasma D-Dimer Level in Normal Pregnancy and Complicated Pregnancy

Mohamed Mostafa Zaitoun, Tarek Mohammed Elbhiedy,
Ibtisam Issa Alarabi Jama*, Mohammed Ahmed Wasfy
Department of Obstetrics and Gynecology, Faculty of Medicine - Zagazig University, Egypt
***Corresponding author:** Ibtisam Issa Alarabi Jama, **Mobile:** (+20)01507027155, **E-mail**: ibtesamjama@gmail.com

ABSTRACT

Background: For further testing to rule out venous thromboembolism (VTE), pregnant women with high D-dimer levels are mandated to undergo further screening.

Objective: Early detection of complicated pregnancy through evaluation of D-dimer level.

Patients and methods: A total of 175 women were included in this case-control study and divided into 2 main groups: Group A "normal pregnancy": included 75 women who were subdivided into 3 equal groups (25 in each trimester) and group B "complicated pregnancy" that included 100 women all of them were in 3rd trimester of pregnancy who were subdivided into 4 equal groups (mild preeclampsia, severe preeclampsia, gestational diabetes mellitus and preterm rupture of membrane). D-dimer was assessed among all participants.

Results: D-dimer (DD) and fibrinogen levels were significantly increased with increasing of gestational age. Fibrinogen and white blood cells levels were statistically significantly higher among diabetic, preterm rupture of membrane (PROM) and patients with mild preeclampsia, while D-dimer, platelet and hemoglobin levels were not significantly different when compared to normal pregnancy cases. D-dimer, fibrinogen and white blood cells in our study were significantly increased in cases of severe preeclampsia when compared to normal ones. So, D-dimer was considered a highly sensitive and specific biomarker in diagnosis of sever preeclampsia as D-dimer >100 ng/ml had 88% accuracy in prediction of sever preeclampsia.

Conclusion: D-dimer was a highly sensitive and specific biomarker in diagnosis of severe preeclampsia only. D-dimer >100 ng/ml had 88% accuracy in prediction of sever preeclampsia.

Keywords: D-Dimer, Pregnancy, Complicated pregnancy.

INTRODUCTION

During pregnancy, coagulation factors tend to rise while natural anticoagulants tend to fall. Despite the significant drop in fibrinolysis during pregnancy, the progressive increase in D-dimer demonstrates that fibrinolysis is still an active process [(1)]. The ratio of plasminogen activators (tPA and uPA) to inhibitors (PAI-1/2) is critical to the regulation of fibrinolysis. The combination of pregnancy-induced hypercoagulability and hypofibrinolysis leads to an increase in intravascular thrombosis and coagulation disorder precipitates, among which D-dimer is a prominent example [(2)]. After a blood clot has been broken down by fibrinolysis, a small protein fragment called D-dimer (DD) is left in the blood [(3)].

Several researches looked into the possibility that abnormalities in the hemostatic system are linked to pregnancy-associated problems such as, gestational diabetes (GDM), premature rupture of membranes (PROM) and preeclampsia (PE). Preeclampsia's pathophysiology is poorly known, however it is thought to be multifaceted, analysing endothelial dysfunction and the intricate interplay between the inflammatory and coagulative pathways. There is currently no screening test for PE, despite the fact that the topic has received a great deal of attention. Given that blood clotting activation begins at an early stage in the progression of the disease [(4)].

Therefore, a rise in DD may begin before hypertension symptoms manifest. As a result, research into the potential diagnostic function of DD in preeclampsia and severe preeclampsia (SPE) is warranted. It is generally known that women with GDM have an increased risk of developing VTE during and after pregnancy [(5)]. Women with intrauterine haemorrhage are particularly vulnerable to preterm births, and thrombin's ability to trigger myometrial contractions is a key factor in the pathophysiology of these pregnancies [(6)].

Using the D-dimer test to diagnose pulmonary embolism (PE) during pregnancy has been disproven by a recent study [(7)]. The normal D-dimer values may be helpful in avoiding PE in pregnant and postpartum patients, according to a recent study by **Choi *et al.*** [(8)].

Previous studies that aimed to construct a reference interval for DD during pregnancy either used higher thresholds or the 2.5th and 97.5th percentiles, both of which were thought to increase specificity. During pregnancy, the traditional Virchow's triad of hypercoagulability, endothelial damage, and venous stasis caused by uterine compression all work together to increase the likelihood of thrombus formation. However, a more dramatic worsening of this hypercoagulable profile is described with regularly occurring diseases during pregnancy [(9)].

According to research by **Manol *et al.*** [(10)], an elevated D-dimer value in the third trimester of pregnancy is associated with the onset of preeclampsia. We therefore in this trial we aimed to determine and compare the plasma D-dimer level in normal pregnant

Received: 14/10/2022
Accepted: 17/12/2022

women and complicated pregnancies (Preeclampsia, preterm rupture of membrane, gestational diabetes).

PATIENTS AND METHODS

This case-control study was conducted at Obstetric Outpatient Clinic and Maternity Hospital, Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University Hospital.

Ethical approval: All participants provided their written informed consent, and the study was approved by the Zagazig University Medical Faculty Research Ethical Council "ZU-IRB #9726/24-8-2022". The Declaration of Helsinki, a code of conduct for medical research involving human participants, was followed throughout this investigation.

Inclusion criteria: Women aged 20-40 years old, with BMI < 40 kg/m^2, singleton viable pregnancy who were prime- and multiparous women with gestational age: Normal pregnant woman including women in 1st, 2nd and 3rd trimester. Complicated pregnant woman including women with mild and severe preeclampsia, gestational diabetes, and preterm rupture of membrane in 3rd trimester, were enrolled in the study.

Exclusion criteria: Women who had personal or family history of VTE, morbid obesity (BMI >40 kg/m^2), advanced maternal age (> 40 years), females who had suspected or confirmed deep vein thrombosis (DVT), previous recurrent spontaneous abortions or coagulation disorders as Von Willebrand disease, hemophilia, clotting factor deficiencies and hypercoagulable states or who received anti-coagulation prophylaxis or with current malignancy were excluded from the study.

All cases were divided into 2 main groups:

- **Group A "normal pregnancy":** included 75 women who were subdivided into 3 equal groups:
  - ✓ **A1:** included 25 women with normal pregnancy in 1st trimester.
  - ✓ **A2:** included 25 women with normal pregnancy in 2nd trimester.
  - ✓ **A3:** included 25 women with normal pregnancy in 3rd trimester.
- **Group B "complicated pregnancy":** included 100 women all of them were in 3rd trimester of pregnancy who were subdivided into 4 equal groups:
  - ✓ **B1:** included 25 women with **mild preeclampsia**. After the 20th week of pregnancy, a woman was considered to have mild preeclampsia if she received blood pressure readings on two occasions, each four hours apart, that were between 140 and 160 systolic and 90 and 110 diastolic, and if she also had proteinuria of 300 milligrams to 2 grams per 24 hours of urine, or a positive protein dipstick on at least two midstream urine samples taken six hours apart.
  - ✓ **B2:** included 25 women with **severe preeclampsia**. Blood pressure readings of 160 over 110 on two separate occasions, four hours apart, and proteinuria of more than 2 grams per 24 hours (as measured by a protein dipstick) in more than two midstream urine samples taken 6 hours apart were considered diagnostic of severe preeclampsia.
  - ✓ **B3:** included 25 women with **gestational diabetes mellitus**. A glucose intolerance of any severity diagnosed or diagnosed for the first-time during pregnancy is considered gestational diabetes mellitus (GDM). Gestational diabetes occurs in the later stages of pregnancy and is characterized by extreme insulin resistance caused by placental hormone release.
  - ✓ **B4:** included 25 women with **preterm rupture of membrane**. The term "premature rupture of membranes" refers to the rupturing of the amniotic sac before 37-week gestation.

According to inclusion and exclusion criteria, patients were subjected to:

a) Complete history taking of clinical importance including: Personal history, present history (main complaint): as mild and severe preeclampsia, gestational diabetes, preterm rupture of membrane, also menstrual history: day of last menstrual period and regularity. Obstetric history: gravidity, parity, previous miscarriages or obstetric complications, outcomes and gestational age by confirmed 1st day of last menstrual period or documented 1st trimester ultrasound scan and contraceptive history were taken.

b) Complete clinical examination:

- ***General examination*:** pay close attention to your vitals (blood pressure, pulse rate, temperature), BMI, and overall complexion.
- ***Local examination*:** Utilizing a clean Cusco speculum PPROM can be diagnosed with a vaginal examination, as the presence of amniotic fluid leaking from the cervical canal or collecting in the vaginal fornix is pathognomonic. If there is no obvious sign of amniotic fluid, the lady may be advised to perform a Valsalva maneuver or cough to cause fluid to seep from the cervix. The cervix and vagina will be examined with a sterile speculum on patients who are not in active labor.

c) Antenatal ultrasound examination.

d) Investigation: On the day of admission, patients undergo a battery of tests including measurement of serum D-dimer concentration and fibrinogen levels, as well as a complete blood count and blood biochemistry.

- **D-dimer:** A trained laboratory professional collected the blood in a blue-top tube containing sodium citrate anticoagulant. 15-minute centrifugation at 1500 X g yielded citrated plasma. A semi-quantitative latex agglutination assay, the Manual D-dimer kit (Helena Biosciences Europe, UK) was used to determine plasma D-dimer concentration. Two hours after the blood was drawn, testing was finished at the hospital lab.

Study outcome:

- Analysis of D-dimer levels in healthy pregnant women and those with complications.
- Analyzing the difference in D-dimer plasma concentrations between uncomplicated and difficult pregnancies.

Statistical Analysis

Data were analyzed using SPSS 21 (Statistical Package for the Social Services) (SPSS). The findings were displayed using both tabular and graphical formats. Results were displayed using standard statistical measures such as means, medians, standard deviations, and confidence intervals. The accuracy of the data was demonstrated with the help of statistics. The student's t test (T) was utilized. Pearson Chi-Square and Chi-Square for Linear Trend were used to analyse the quantitatively diverse data (X^2). In this case, a significant P value ≤ 0.05. We utilised Wilcoxon's Signed Rank test for matched samples because our data did not follow a normal distribution. Multiple comparisons of sets of category variables were made using the McNemar test. P value ≤ 0.05 was considered significant.

RESULTS

The studied groups were comparable as regards age, parity and BMI. While the Gestational age was significantly lower among the preterm rupture of membrane (PROM) (Table 1).

Table (1): Demographic and obstetric characters of normal pregnancy and complicated pregnancy

Variable		1st Trimester N=25	2nd Trimester N=25	3rd Trimester N=25	P.value
Age: (years)	Mean ± SD Range	27.5±4.8 18-40	26±3.7 22-33	27.4±3.9 21-40	0.37
Parity: N (%)	Primi N (%) Multi N (%)	7 (28.0) 18 (72.0)	10 (40.0) 15 (600)	6 (24.0) 19 (76.0)	0.4
Gestational age (weeks)	Mean ± SD Range	10.3±2.0 7-14	25-8±1.2 24-28	35±1.2 32-37	**<0.001**
BMI	Mean ± SD Range	23.8±2.3 20-30	25±2.9 21-31	25.2±2.1 22-30	0.09

Complicated pregnancy						
Variable		**DM N=25**	**SPET N=25**	**PROM N=25**	**M.PET N=25**	**P.value**
Age: (years)	Mean ± SD Range	25.6±7 17-43	25.4±6.6 18-47	273±6.2 18-40	26.2±7.1 17-43	0.7
Parity: N (%)	Primi N (%) Multi N (%)	10 (40) 15 (60)	8 (32) 17 (68)	7 (28) 18 (72)	5 (20) 20 (80)	0.47
Gestational age (weeks)	Mean ± SD Range	34.1±1.9 31-37	35±2.3 30-39	33.3±2.1 28-36	35.1±2.1 29-39	**0. 01***
BMI	Mean ± SD Range	24.7±3.1 20-35	24.6±2.7 21-31	24.9±2.2 21-30	24.6±2.7 20-31	0.9

Gestational diabetes (DM), sever preeclampsia (SPET), Preterm rupture of membrane (PROM), mild preeclampsia (M-PET)

In normal pregnancy, D-dimer was significantly increased in 3rd trimesters, while the fibrinogen, platelet, hemoglobin and white blood cell were not statistically significant (P>0.05). In complicated pregnancy, D-dimer was significantly higher in sever preeclampsia (SPET), when compared to other groups. While the fibrinogen, platelet, hemoglobin and white blood cell were not statistically significant (P>0.05) (Table 2).

Table (2): Lab parameters for normal pregnancy, and in complicated pregnancy

Variable		1st N=25	2nd N=25	3rd N=25	P. value
D. Dimer (mg/L)	Mean ± SD	75.5±17.6	76.7±18.01	114±26.3	0.02*
Fibrinogen (mg/dL)	Mean ± SD	1.7±0.25	1.01±0.23	1.99±0.48	0.22
Platelet (PLT) (mcL)	Mean ± SD	180±42.31	190.1±46.2	196.6±48.1	0.64
Hemoglobin (HB) (g/dL)	Mean ± SD	10.6±0.9	10.5±0.76	10.6±0.6	0.86
White blood cell (WBC) (cells/µL)	Mean ± SD	7.6±1.7	7.9±1.8	7.65±1.7	0.91

Complicated pregnancy						
Variable		**DM N=25**	**SPET N=25**	**PROM N=25**	**M.PET N=25**	**P.value**
D. Dimer (mg/L)	Mean ± SD	107.9±25.10	208.6±51.1	132.6±30.21	106.4±24.7	**<0.001***
Fibrinogen (mg/dL)	Mean ± SD	2.7±0.5	2.9±0.5	2.76±0.5	2.86±0.6	0.67
Platelet (PLT) (mcL)	Mean ± SD	239.7±58.12	196.6±47.1	232.2±52.1	230±55.1	0. 45
Hemoglobin (HB) (g/dL)	Mean ± SD	10.3±2.3	11.2±1.8	10.4±2.3	11±1.0	0.27
White blood cell (WBC) (cells/µL)	Mean ± SD	10.5±2.11	12.3±2.8	10.7±2.3	10.8±2.4	0.62

Gestational diabetes (DM), sever preeclampsia (SPET), Preterm rupture of membrane (PROM), mild preeclampsia (M-PET).

Fibrinogen and white blood cells were statistically higher among diabetics when compared to normal pregnancy, while D-dimer, platelet and hemoglobin were not significant (Table 3).

Table (3): Comparison between normal pregnancy in (3rd trimester) and gestational diabetes (DM) as regards lab parameters.

Variable	NP	DM	P. value
D. Dimer	100± 23.3	71±16.6	0.28
Fibrinogen	1.99± 0.48	2.7±0.5	**<0.001***
Platelet (PLT)	196.6±47.7	239.7±58.12	0. 057
Hemoglobin (HB)	10.6±0.6	10.3±2.3	0.73
White blood cell (WBC)	7.65±1.7	10.5±2.11	0.02*

D-dimer, fibrinogen and white blood cell were significantly higher among sever preeclampsia (SPET) when compared to normal pregnancy, while platelet and hemoglobin were not significant (Table 4).

Table (4): Comparison between normal pregnancy in (3rd trimester) and sever preeclampsia (SPET) as regards lab parameters.

Variable	NP	SPET	P. value
D. Dimer	100 ± 24.1	164 ± 40.2	**<0.001****
Fibrinogen	1.99 ± 0.47	2.9±0.5	**<0.001****
Platelet (PLT)	196.6±46.2	196.6±46.3	0. 86
Hemoglobin (HB)	10.6±0.6	11.2±1.8	0.3
White blood cell (WBC)	7.65±1.6	12.3±2.6	0.002*

Fibrinogen and white blood cells were significantly higher among PROM when compared to normal pregnancy, while D-dimer, platelet and hemoglobin where not significant (Table 5).

Table (5): Comparison between normal pregnancy in (3rd trimester) and preterm rupture of membrane (PROM) as regards lab parameters.

Variable	NP	PROM	P. value
D. Dimer	100± 24.2	71±15.7	**0.4**
Fibrinogen	1.99 ± 0.41	2.76±0.5	**<0.001****
Platelet (PLT)	196.6±45.7	232.2±56.2	0.1
Hemoglobin (HB)	10.6±0.6	10.4±2.3	0.8
white blood cell (WBC)	7.65±1.5	10.7±1.9	0.006*

Fibrinogen and white blood cells were significantly higher among mild preeclampsia (M-PET) when compared to normal pregnancy, while D-dimer, platelet and hemoglobin were not significant (Table 6).

Table (6): Comparison between normal pregnancy in (3rd trimester) and mild preeclampsia (M-PET) as regards lab parameters.

Variable	NP	M-PET	P. value
D. Dimer	100± 23.3	71±16.6	0.74
Fibrinogen	1.99 ± 0.42	2.86±0.6	**<0.001****
Platelet (PLT)	196.6±44.7	230±56.1	0.1
Hemoglobin (HB)	10.6±0.6	11±1.0	0.2
white blood cell (WBC)	7.65±1.4	10.8±2.1	**0.006***

There was significant +ve correlation between gestational age, D-dimer and fibrinogen (Table 7).

Table (7): Correlation between gestational age (weeks) and D-dimer & Fibrinogen

	r	p
D. Dimer	0.23	**<0.001****
Fibrinogen	0.48	**<0.001****

D-dimer was highly sensitive and specific in diagnosis of sever preeclampsia (S.PET), D-dimer >100 had 88% accuracy in prediction of sever preeclampsia (S.PET) (Table 8).

Table (8): Validity of D-dimer in diagnosis of sever preeclampsia (S.PET)

Variable	SPE	NG	Sensitivity	specificity	PV		Accuracy
					+ve	-ve	
Cut off 100 D. Dimer							
>100	24	5	96.0 %	80.0 %	82.8 %	95.2 %	88.0 %
≤ 100	1	20					

DISCUSSION

Pregnancy causes a slow but steady shift in the body's hemostatic mechanisms, with hypercoagulability peaking in the third trimester and gradually fading in the postpartum period **(11).** They are of no clinical significance and should be viewed as a protective mechanism for the developing fetus to prevent excessive bleeding during labor and delivery **(12)**.

Our study reported that D-dimer and fibrinogen levels were significantly increased with increasing gestational age.

Preeclamptic patients and healthy pregnant women without preeclampsia were compared to respect to their mean plasma D-dimer levels, **Shams and colleagues (13)** established a goal of determining the average plasma D-dimer levels in pregnant women. They agree with us that there was a strong correlation between preeclampsia and plasma D-dimer levels during the third trimester. Preeclamptic patients had a higher mean plasma D-dimer level compared to normotensive pregnant women. A cross-sectional study with 154 pregnant women was conducted. An independent sample t-test was used to evaluate the differences in mean plasma D-dimer levels between patients with preeclampsia and those without the condition. The mean plasma D-dimer concentration was 1.020.07 ng/ml in preeclamptic patients and 0.180.04 ng/ml in healthy controls (p0.00) **(13)**.

Similar results were reported in 2017 through a study done in Sudan, Africa, which found that preeclamptics had significantly higher plasma fibrinogen (p=0.00) and D-dimer levels compared to normotensive pregnant women (p=0.00) **(14).** But **Catarino *et al.* (15)** investigated a small number of

pregnant women and found no statistically significant difference in mean D-dimer level between those with preeclampsia and those with normotensive blood pressure. This disparity could be due to the fact that some researchers prefer to detect D-dimer in the mother's blood rather than in the umbilical cord.

In each trimester of pregnancy, **Siennicka and his colleagues** [16] sought to establish reference values for D-dimers and fibrinogen concentrations. Similar to our findings, they found that physiological processes accounted for the elevations in D-dimer and fibrinogen levels seen during pregnancy. Seventy-one pregnant women participated in the study. Intravenous blood was taken at 11–14, 20–22, and 30–31 weeks of pregnancy. Fibrinogen levels were determined by a coagulation method, whereas D-dimer levels were evaluated by an enzyme-linked fluorescence assay. D-dimer and fibrinogen levels both increased noticeably throughout pregnancy (p= 0:0001). Further, in the second trimester of pregnancy, D-dimers were positively correlated with fibrinogen (r = 0.475; p 0.001). **Rodríguez-Peña and Ibáñez-Pinilla** [17] discovered a correlation between high D-dimer levels and the severity of pre-eclampsia. They also found a link between elevated D-dimer levels and the severity of preeclampsia, lending credence to the idea that the activation of fibrinolysis and the coagulation system is a key physiopathologic component of the disease. The case group had significantly higher D-dimer levels than the control group (19.3 percent vs. 2.3 percent)**.**

Murphy and coworkers [18] used the Auto-Dimer assay to determine a gestation-specific reference range for D-dimer in normal, pregnant women carrying single infants. In their cross-sectional study, they utilised simultaneous-quantile regression to construct a model of normal D-dimer concentration vs gestational week, with median, 5th percentile, and 95th percentile values running from week 6 to week 42. They confirmed our findings that D-dimer levels increase progressively in all pregnancies [18].

Hale and coworkers [19] focused on the early and late stages of pregnancy when they took measurements of fibrinogen (Fib), D-dimer, plasminogen activator type-1 (PAI-1), and tissue type plasminogen activator (T-Pa). Despite our finding that fibrinogen levels rise early in pregnancy, they found that fibrinolysis rises late in pregnancy, which they attributed to the procoagulant environment of pregnancy. When comparing the results of the pre-pregnancy evaluation to those of the early pregnancy evaluation, only fb showed a significant change. D-dimer, PAI-1, and T-Pa all increased in the third trimester of pregnancy compared to pre-pregnancy and early pregnancy levels (p .001). Different techniques of measuring fibrinogen and D-dimer levels, as well as potential differences in sample size, could account for the observed discrepancy**.**

We also reported that **fibrinogen** and **white blood cells levels** were statistically significantly higher among **diabetic**, **preterm rupture of membrane (PROM)** and patients with **mild preeclampsia** while D-dimer, platelet and hemoglobin levels were not significantly different when compared to normal pregnancy cases. On the other hand, D-dimer, fibrinogen and white blood cells in our study were significantly increased in cases of severe preeclampsia compared to normal ones. So, D-dimer was considered a highly sensitive and specific biomarker in diagnosis of sever preeclampsia as D-dimer >100 ng/ml had 88% accuracy in prediction of sever preeclampsia

The purpose of **Khawaja and coworkers** (20) study was to determine whether or not elevated d-dimer levels were associated with pre-eclampsia. Thirty people were preeclamptic, whereas the other 30 were considered to have normal blood pressure. They found similar results to ours, with 14 (46.67%) of the case group (pre-eclampsia) having elevated d-dimer levels compared to only 4 (13.33%) of the control group (normotensive). The correlation between pre-eclampsia and elevated d-dimer levels (>0.5 g/ml) was statistically significant (p = 0.005), and the odds ratio was 5.69**.**

Baboolall *et al.* [2] conducted a retrospective observational cohort study to compare the prevalence of D-dimer levels in third trimester healthy pregnancies to those complicated by mild PE, severe PE, gestational diabetes mellitus (GDM), premature rupture of membranes (PROM), and preterm premature rupture of membranes. The researchers also aimed to determine whether or not DD is useful for diagnosing moderate or severe PE. They found a substantial link between the length of the mother's pregnancy and DD, attributing 42.9% of the variance in DD to this factor. Receiver operating characteristic (ROC) curves were created, and an AUC of 0.828 was found, which suggests that this particular distribution can be used to predict cases of severe preeclampsia.

Reviewing the literature, plasma D-dimer was studied by **de Barros Pinheiro and coworkers** [21] to determine its diagnostic utility in hypertensive and normotensive pregnant women. There was a grand total of 194 papers located. This meta-analysis corroborated our findings that higher plasma D-dimer levels in the third trimester of pregnancy are related with preeclampsia [21].

The current study's strengths may be traced back to the thoroughness with which all follow-up data were recorded, all relevant data were included in the analysis, and all clinical assessment and evaluation of study outcomes were performed by the same group of experts.

Coagulation parameter comparisons were not as accurate in this study since not all cases were studied in the same trimester. Also, the reliability of the results was limited by the study's small sample size.

CONCLUSION

D-dimer was a highly sensitive and specific biomarker in diagnosis of severe preeclampsia only. D-

dimer >100 ng/ml had 88% accuracy in prediction of sever preeclampsia. In addition, fibrinogen and white blood cells levels were statistically significant higher among patients with mild/severe preeclampsia, diabetic and preterm rupture of membrane (PROM).

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

REFERENCES

1. **Moiz B (2017):** A review of hemostasis in normal pregnancy and puerperium. Natl J Heal Sci., 2: 123–7.
2. **Baboolall U, Zha Y, Gong X *et al.* (2019):** Variations of plasma D-dimer level at various points of normal pregnancy and its trends in complicated pregnancies: a retrospective observational cohort study. Medicine, 98 (23): e15903. doi: 10.1097/MD.0000000000015903.
3. **Riley R, Gilbert A, Dalton J *et al.* (2016):** Widely used types and clinical applications of D-dimer assay. Lab Med., 47: 90–102.
4. **Dusse L, Rios D, Pinheiro M *et al.* (2011):** Pre-eclampsia: Relationship between coagulation, fibrinolysis and inflammation. Clin Chim Acta., 412: 17–21.
5. **Jacobsen A, Skjeldestad F, Sandset P (2008):** Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium-a register-based case-control study. Am J Obstet Gynecol., 198: 1–7.
6. **Keren-Politansky A, Breizman T, Brenner B *et al.* (2014):** The coagulation profile of preterm delivery. Thromb Res., 133: 585–9.
7. **Goodacre S, Horspool K, Nelson-Piercy C *et al.* (2018):** The DiPEP study: an observational study of the diagnostic accuracy of clinical assessment, D-dimer and chest X-ray for suspected pulmonary embolism in pregnancy and postpartum. BJOG., 26 (3): 383-392.
8. **Choi H, Krishnamoorthy D (2018):** The diagnostic utility of D-dimer and other clinical variables in pregnant and post-partum patients with suspected acute pulmonary embolism. Int J Emerg Med., 11 (1): 10. doi: 10.1186/s12245-018-0169-8.
9. **Gorar S, Alioglu B, Ademoglu E *et al.* (2016):** Is there a tendency for thrombosis in gestational diabetes mellitus? J Lab Physicians, 8: 101–5.
10. **Manolov V, Marinov B, Masseva A *et al.* (2014):** Plasma D-dimer levels in preeclampsia. Akusherstvo i ginekologiia, 53: 15–18.
11. **Honigberg M, Givertz M (2019):** Peripartum cardiomyopathy. BMJ., 364: k5287. doi: 10.1136/bmj.k5287.
12. **Kourlaba G, Relakis J, Kontodimas S *et al.* (2016):** A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. International Journal of Gynecology & Obstetrics, 132 (1): 4-10.
13. **Shams N, Taimoor A, Nazir A *et al.* (2022):** Comparison of d-dimer levels in preeclampsia and normal pregnancy. Pakistan Journal of Physiology, 18 (1): 20-22.
14. **Abdelgadir S, Gaufri N (2017)** Estimation of Plasma D-Dimer Levels in Sudanese Women with Preeclampsia. Open Access Library Journal, 4: 1-6.
15. **Catarino C, Rebelo I, Belo L *et al.* (2008):** Relationship between maternal and cord blood hemostatic disturbances in preeclampatic pregnancies. Thromb Res., 123: 219–24.
16. **Siennicka A, Kłysz M, Chełstowski K *et al.* (2020):** Reference values of D-Dimers and fibrinogen in the course of physiological pregnancy: the potential impact of selected risk factors—a pilot study. BioMed Research International, 20: 3192350. https://doi.org/10.1155/2020/3192350.
17. **Rodríguez-Peña Y, Ibáñez-Pinilla M (2020):** Elevated levels of D-dimer tested by immunoturbidimetry are associated with the extent of severity of pre-eclampsia. International Journal of Gynecology & Obstetrics, 150 (2): 241-247.
18. **Murphy N, Broadhurst D, Khashan A *et al.* (2015):** Gestation-specific D-dimer reference ranges: a cross-sectional study. BJOG: An International Journal of Obstetrics & Gynaecology, 122 (3): 395-400.
19. **Hale S, Sobel B, Benvenuto A *et al.* (2012):** Coagulation and fibrinolytic system protein profiles in women with normal pregnancies and pregnancies complicated by hypertension. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 2 (2): 152-157.
20. **Khawaja U, Amin O, Afghan S *et al.* (2019):** Association Between Pre-Eclampsia and High D-Dimer Levels. Journal of the Society of Obstetricians and Gynaecologists of Pakistan, 9 (4): 200-203.
21. **de Barros Pinheiro M, Junqueira D, Coelho F *et al.* (2012):** D-dimer in preeclampsia: systematic review and meta-analysis. Clinica Chimica Acta., 414: 166-170.