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Original article

Plasma D-Dimer Levels in Normal and Complicated Pregnancies

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Abstract
Pregnancy is associated with major physiological changes in the coagulation and fibrinolytic systems. These alterations produce a hypercoagulable state that helps protect against bleeding during placental separation but also complicates interpretation of D-dimer, a degradation product of cross-linked fibrin. To estimate plasma D-dimer levels in women with normal and complicated pregnancies and to evaluate their distribution according to gestational age and selected pregnancy-associated conditions. Thirty-seven pregnant women were included. Blood was collected into sodium citrate tubes, citrated plasma was obtained by centrifugation at 1500 × g for 15 minutes, and D-dimer was measured using a manual semi-quantitative latex agglutination assay (Helena Biosciences Europe, UK). Data were analyzed using SPSS version 16.0. The mean age was 31.62 ± 5.28 years. The overall mean D-dimer concentration was 1617.81 ± 1586.45 ng/mL (range, 121–7200). Mean D-dimer concentrations were 672.63 ± 532.84 ng/mL in the first trimester, 2660.27 ± 2038.41 ng/mL in the second trimester, and 1400.83 ± 1263.02 ng/mL in the third trimester. D-dimer was >500 ng/mL in 27 women (73%). The association between gestational trimester and categorized D-dimer level was not statistically significant (P=0.139). Elevated D-dimer levels were common in this study population and varied across gestational trimesters. Interpretation of D-dimer during pregnancy should consider physiological pregnancy-related changes, gestational age, and associated clinical conditions.
Keywords. D-Dimer, Pregnancy, Coagulation, Fibrinolysis, Venous Thromboembolism, Gestational Age.

Introduction

Pregnancy is accompanied by substantial anatomical, physiological, hematological, and hemostatic changes that enable maternal adaptation to the developing fetus. One of the most important adaptations is alteration of the coagulation and fibrinolytic systems. Pregnancy is generally considered a hypercoagulable and relatively hypofibrinolytic state, which helps protect the mother from excessive hemorrhage during placental separation and delivery [1–3]. Several coagulation factors, including factors VII, VIII, X, XII, fibrinogen, and von Willebrand factor, increase during pregnancy. In contrast, some physiological anticoagulant mechanisms are altered, particularly through reductions in free protein S levels.

Fibrinolytic activity is also reduced during pregnancy through increased concentrations of plasminogen activator inhibitors [5–18]. D-dimer is a fibrin degradation product generated during the breakdown of cross-linked fibrin. It reflects activation of both coagulation and fibrinolysis and is widely used in the diagnostic assessment of venous thromboembolism (VTE). In non-pregnant individuals with low clinical probability, a low D-dimer concentration has a high negative predictive value. However, interpretation during pregnancy is more difficult because D-dimer concentrations normally increase during gestation. Physiological elevation of D-dimer during pregnancy does not necessarily indicate thromboembolic disease. Conventional cut-off values used in non-pregnant populations may therefore have limited specificity in pregnant women. Gestational age, maternal characteristics, pregnancy-related complications, and other medical conditions may further influence D-dimer concentrations. This study was conducted to estimate plasma D-dimer levels in women with normal and complicated pregnancies and to examine their distribution according to gestational age and selected maternal clinical conditions.

Methods

Study Population

The study included 37 pregnant women with normal or complicated pregnancies. Women with a personal or family history of bleeding or thrombosis associated with increased D-dimer were excluded. Venous blood samples were collected by a qualified laboratory specialist into blue-top tubes containing sodium citrate. Citrated plasma was obtained after centrifugation at 1500 × g for 15 minutes. Testing was completed within 2 hours of blood collection.

Plasma D-dimer was measured using a Manual D-Dimer kit (Helena Biosciences Europe, UK), based on a semi-quantitative latex agglutination method. For qualitative testing, 20 µL of patient plasma and controls were placed on the test card, mixed with an equal amount of D-dimer latex reagent, and evaluated after 180–200 seconds. Visible agglutination was interpreted as positive; absence of agglutination was interpreted as negative. Positive samples were serially diluted (1:2, 1:4, and 1:8) for semi-quantitative estimation.

Statistical Analysis

Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS), version 26.0. Continuous variables were summarized using means and standard deviations, and categorical variables were presented as frequencies and percentages. A P-value <0.05 was considered statistically significant.

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Results

A total of 37 pregnant women were included in the study. The mean age was 31.62 ± 5.28 years, with an age range of 22–42 years. Regarding age distribution, 8 women (21.6%) were aged ≤25 years, 19 (51.4%) were aged 26–35 years, and 10 (27.0%) were aged 36–40 years. Seventeen participants (45.9%) were classified as obese, while 20 (54.1%) were not obese. The mean number of children was 2.27 ± 1.52 (Table 1).

Table (1): Participant Characteristics of the Studied Pregnant Women

Characteristic	No. (%) / Mean ± SD
Age, years	**31.62 ± 5.28**
Age ≤25 years	8 (21.6%)
Age 26–35 years	19 (51.4%)
Age 36–40 years	10 (27.0%)
Obesity: Yes	17 (45.9%)
Obesity: No	20 (54.1%)
Number of children	**2.27 ± 1.52**
First trimester	8 (21.6%)
Second trimester	11 (29.7%)
Third trimester	18 (48.6%)

The overall mean plasma D-dimer concentration was 1617.81 ± 1586.45 ng/mL, with values ranging from 121 to 7200 ng/mL. The highest mean D-dimer concentration was observed among women in the second trimester (2660.27 ± 2038.41 ng/mL), followed by those in the third trimester (1400.83 ± 1263.02 ng/mL) and first trimester (672.63 ± 532.84 ng/mL), as shown in Table (2).

Table (2): Mean Plasma D-Dimer Concentrations According to Gestational Trimester

Trimester	Mean D-dimer (ng/mL)	SD
First trimester	672.63	532.842
Second trimester	2660.27	2038.411
Third trimester	1400.83	1263.015

D-dimer concentrations exceeded 500 ng/mL in 27 women (73.0%), whereas 10 women (27.0%) had concentrations below 500 ng/mL. The distribution of categorized D-dimer concentrations did not differ significantly across gestational trimesters ($P = 0.139$), as presented in Table (3).

Table (3): Distribution of Categorized D-Dimer Concentrations According to Gestational Trimester

Gestational trimester	D-dimer <500 ng/mL	D-dimer >500 ng/mL
First trimester	4	4
Second trimester	1	10
Third trimester	5	13

Several clinical conditions were reported among the study participants, including COVID-19, thyroid disease, pulmonary embolism (PE), hypertension, deep venous thrombosis (DVT), and diabetes mellitus (DM). COVID-19 was the most frequently reported condition, affecting 22 women (59.5%). Diabetes mellitus was reported in 6 women (16.2%), thyroid disease in 5 (13.5%), pulmonary embolism and hypertension in 4 women each (10.8%), and deep venous thrombosis in 3 women (8.1%), as shown in Table (4).

Table (4): Distribution of the Studied Pregnant Women According to Associated Clinical Conditions

Condition	Frequency	Percent
COVID-19	22	59.5%
Thyroid disease	5	13.5%
Pulmonary embolism	4	10.8%
Hypertension	4	10.8%
Deep venous thrombosis	3	8.1%
Diabetes mellitus	6	16.2%

Among women with COVID-19, 17 (77.3%) had D-dimer concentrations >500 ng/mL, while 5 (22.7%) had concentrations <500 ng/mL. Among women without COVID-19, 10 (66.7%) had D-dimer concentrations >500 ng/mL and 5 (33.3%) had

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concentrations <500 ng/mL. No statistically significant association was found between COVID-19 status and categorized D-dimer concentration (*P* = 0.708), as presented in Table (5).

Table (5): Association Between COVID-19 Status and Categorized D-Dimer Concentration

COVID-19 status	D-dimer <500 ng/mL	D-dimer >500 ng/mL	Total
COVID-19: Yes	5 (22.7%)	17 (77.3%)	22 (100%)
COVID-19: No	5 (33.3%)	10 (66.7%)	15 (100%)
Total	**10 (27.0%)**	**27 (73.0%)**	**37 (100%)**

P = 0.708

Discussion

The present study evaluated plasma D-dimer concentrations among women with normal and complicated pregnancies and demonstrated that elevated D-dimer levels were common. Overall, 73% of the participants had D-dimer concentrations above 500 ng/mL, with an overall mean concentration of 1617.81 ± 1586.45 ng/mL. These findings support the well-established concept that pregnancy is associated with progressive activation of the coagulation and fibrinolytic systems, resulting in physiological increases in circulating D-dimer. Consequently, interpretation of D-dimer during pregnancy using the conventional reference threshold applied to non-pregnant individuals may lead to a high proportion of apparently abnormal results. The high frequency of D-dimer values above 500 ng/mL observed in the present study is consistent with recent studies demonstrating that D-dimer concentrations increase substantially during normal pregnancy. Fu et al. [25], in a large study including 1,972 pregnant women, reported increasing D-dimer concentrations with advancing gestational age and emphasized the need for gestational age-specific reference intervals.

Similarly, Xu et al. [26] demonstrated marked physiological changes in D-dimer throughout pregnancy and puerperium and established pregnancy-specific reference limits that were substantially higher than the conventional 0.5 mg/L threshold. These findings support the present observation that a large proportion of pregnant women may have D-dimer concentrations above 500 ng/mL in the absence of confirmed thromboembolic disease. D-dimer concentrations in the present study also differed according to gestational trimester. Mean concentrations were 672.63 ± 532.84 ng/mL in the first trimester, 2660.27 ± 2038.41 ng/mL in the second trimester, and 1400.83 ± 1263.02 ng/mL in the third trimester. Although the highest numerical concentration was observed during the second trimester, the association between gestational trimester and categorized D-dimer concentration was not statistically significant (P=0.139). The relatively low mean concentration during the first trimester agrees with recent evidence showing that D-dimer concentrations are generally lower during early pregnancy than during later gestation [25–27]. However, the observation that the second trimester had a higher mean D-dimer concentration than the third trimester differs from the general pattern described in several recent studies. Fu et al. [25] reported an overall increase in D-dimer with advancing gestational age.

Dai et al. [27] similarly demonstrated higher D-dimer concentrations during the third trimester compared with earlier pregnancy and established trimester-specific reference intervals. Xu et al. [26] also reported progressively increasing upper reference limits from the first through the third trimester. Thus, while the present study agrees with previous studies regarding the overall elevation of D-dimer during pregnancy, the trimester pattern differs because the highest mean was observed in the second rather than the third trimester. Several factors may explain this difference. First, the present study included only 37 participants, with unequal numbers in the three gestational groups: 8 women in the first trimester, 11 in the second trimester, and 18 in the third trimester. Therefore, a small number of participants with markedly elevated D-dimer concentrations could substantially influence the calculated mean, particularly in the second-trimester group. In addition, the study included both normal and complicated pregnancies. Maternal disorders such as COVID-19, pulmonary embolism, deep venous thrombosis, hypertension, diabetes mellitus, thyroid disease, and obesity may influence coagulation activation independently of gestational age. Methodological differences are also important because D-dimer concentrations vary according to the analytical method, reagent, instrument, population characteristics, and units of measurement. Recent studies therefore emphasize the importance of establishing assay- and population-specific pregnancy reference intervals [25,27,28]. The absence of a statistically significant association between trimester and D-dimer concentrations categorized using the 500 ng/mL threshold may also be explained by the limited value of this conventional cut-off during pregnancy.

Because physiological D-dimer concentrations frequently exceed 500 ng/mL as pregnancy progresses, dichotomizing pregnant women into values above or below this threshold may reduce the ability to detect meaningful gestational differences. Liu et al. [28], using trimester-specific coagulation reference intervals in singleton and twin pregnancies, emphasized that pregnancy-specific ranges are more appropriate for evaluating coagulation abnormalities and their relationship with pregnancy complications. Therefore, the lack of statistical significance in the present study should not be interpreted as evidence that gestational age does not affect D-dimer concentration. The findings also have important implications for the evaluation of venous thromboembolism during pregnancy. Pregnancy itself is associated with an increased risk of venous thromboembolism, while physiological elevation of D-dimer reduces the specificity of the test when a fixed non-pregnant threshold is used. Recent evidence supports the use of D-dimer as part of structured diagnostic strategies rather than as an isolated investigation. Stals et al. [29], in a systematic review and individual-patient-data meta-analysis, reported that D-dimer-based diagnostic approaches can contribute to safely excluding pulmonary embolism in selected pregnant women when incorporated into appropriate clinical algorithms. Similarly, Makowska et al. [30]

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emphasized that D-dimer results during pregnancy should be interpreted together with clinical probability and validated pregnancy-adapted diagnostic approaches. COVID-19 was the most frequently reported associated clinical condition in the present population, occurring in 22 women (59.5%).

Among women with COVID-19, 17 (77.3%) had D-dimer concentrations above 500 ng/mL compared with 10 (66.7%) among women without COVID-19. Nevertheless, no statistically significant association between COVID-19 status and categorized D-dimer level was identified. This differs to some extent from the findings of Paixão et al. [31], who studied pregnant women with and without SARS-CoV-2 infection and found significantly higher D-dimer concentrations among women with COVID-19, particularly among patients requiring intensive care. They suggested that D-dimer may have prognostic value in pregnant women with COVID-19. The difference between the present study and Paixão et al. [31] may be related to sample size, severity of COVID-19 infection, timing of blood collection, gestational age distribution, and differences in analytical methodology. The present study contained only 37 women and did not stratify COVID-19 cases according to disease severity. Consequently, the statistical power to detect an association between COVID-19 and elevated D-dimer was limited. Furthermore, the use of a simple cut-off of 500 ng/mL may have obscured a potential relationship because D-dimer frequently exceeds this concentration during normal pregnancy.

Recent population-level evidence also supports a relationship between COVID-19 and thrombotic risk during pregnancy. Örtqvist et al. [32], in a large population-based study from Sweden and Norway, reported increased venous thromboembolism risk following COVID-19 during pregnancy and the postpartum period, with the greatest relative risk occurring shortly after infection. These findings reinforce the importance of considering COVID-19 as an additional thrombotic risk factor during pregnancy, although elevated D-dimer alone cannot establish the diagnosis of venous thromboembolism. Other pregnancy-associated complications may also contribute to increased D-dimer concentrations. The present study included participants with hypertension, diabetes mellitus, pulmonary embolism, and deep venous thrombosis. Recent evidence indicates that abnormal activation of coagulation and fibrinolysis is particularly relevant in hypertensive pregnancy disorders.

A 2025 systematic review and meta-analysis by Alemayehu et al. [33] demonstrated higher D-dimer concentrations among women with preeclampsia compared with normotensive pregnant women. Therefore, variation in the prevalence and severity of pregnancy complications within the present study population may partly account for the wide distribution of D-dimer values and the large standard deviations observed. Maternal age and obesity may represent additional contributing factors. The mean maternal age in this study was 31.62 ± 5.28 years, while 45.9% of participants were classified as obese. Although the source data suggested a possible increase in D-dimer with maternal age, sufficient inferential statistical analysis was not available to establish an independent association. Therefore, conclusions regarding the effects of age or obesity on D-dimer concentration cannot be made from the present data. Larger studies using multivariable analysis would be required to distinguish the independent effects of gestational age, maternal characteristics, COVID-19, and other pregnancy complications. An important feature of the present findings is the considerable variability in D-dimer concentrations, with an overall range of 121–7200 ng/mL and large standard deviations within individual trimesters. Such variability emphasizes that a single universal D-dimer threshold is unlikely to provide optimal discrimination during pregnancy. Recent studies have consistently recommended pregnancy- or trimester-specific reference intervals [25–28]. However, these reference ranges may differ among populations and analytical systems, highlighting the need for locally validated intervals using standardized quantitative D-dimer assays.

Several limitations should be considered when interpreting these results. The small sample size limits statistical power and the reliability of subgroup comparisons. The unequal distribution of participants across gestational trimesters may also have influenced the observed trimester means. Furthermore, D-dimer was determined using a semi-quantitative latex agglutination method rather than a fully quantitative high-sensitivity assay. The inclusion of women with several different clinical conditions introduces additional heterogeneity, while the limited number of participants prevented appropriate multivariable adjustment for potential confounding factors. These limitations may partly explain differences between the present findings and larger recent studies. Despite these limitations, the study demonstrates that elevated D-dimer concentrations are common during pregnancy and highlights the limitations of applying the conventional 500 ng/mL threshold without considering gestational age and maternal clinical status. The overall findings are broadly consistent with recent studies showing physiological elevation of D-dimer during pregnancy, although the observation of the highest mean concentration in the second trimester differs from the progressive third-trimester increase reported in larger populations. These differences emphasize the need for larger prospective studies in the local population using standardized quantitative assays, trimester-specific reference intervals, and adequate adjustment for maternal characteristics and pregnancy-associated complications.

Conclusion

Elevated plasma D-dimer concentrations were common among the pregnant women included in this study, with 73% having values above 500 ng/mL. D-dimer concentrations varied across gestational trimesters and were numerically highest during the second trimester, but the association between trimester and categorized D-dimer concentration was not statistically significant. These findings support careful interpretation of D-dimer during pregnancy in the context of gestational age, physiological pregnancy-related changes, maternal characteristics, and associated clinical conditions. Larger prospective studies using validated quantitative D-dimer assays are recommended.

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Ethical considerations
Permission to carry out the study was obtained from the Libyan National Committee for Biosafety and Bioethics

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