

An Increased Plasma D-Dimer Levels During Different Stages of Normal and Complicated Pregnancies Among Women in Bisha, Saudi Arabia

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Introduction: Hypercoagulability is one of the most reported state among Pregnant women. During pregnancy, the concentrations of D-dimer increase in a trimester-dependent manner. The presence of gestational diabetes (GD) and gestational hypertension (GH) lead to further elevation in D-dimer levels. Pregnant women are at an increased risk of developing Venous thromboembolism (VTE), which can be fatal for both the mother and fetus. Elevated D-dimer levels during pregnancy could result in misdiagnosing other thrombotic diseases, emphasizing the need for further confirmatory testing for VTE. It is crucial to observe the plasma D-dimer concentrations among pregnant women at maternity and children's hospitals as it plays a role in guiding the anticoagulant treatments and minimizing the incidence of VTE among pregnant women.

Aim: The main objective of the current study was to detect the changes in the plasma D-dimer concentrations in healthy and complicated pregnancies across different gestational trimesters among women at the Maternity and Children's Hospital, Bisha, Saudi Arabia.

Methods: A cross-sectional study was conducted from March 2022 to March 2023, involving the analysis of plasma samples collected from 230 pregnant and non-pregnant women. Three samples were collected from each subject in each trimester. D-dimer measurement was conducted using an ACL Elite Pro Automated analyzer.

Results: The findings of this study show that D-dimer levels increased progressively throughout the pregnancy trimesters across all study groups. The increase was more noticeable among women with gestational diabetes (278.39 ± 29.808 ng/mL) and gestational hypertension (320.63 ± 12.157 ng/mL), suggesting that these complications influence D-dimer levels more significantly than healthy and multiple pregnancies. Notably, a positive correlation was found between age and D-dimer levels across all groups ($p < 0.05$), with the highest mean levels in the 41–48 age group.

Conclusion: D-dimer levels rise progressively throughout pregnancy and are significantly elevated in women with gestational diabetes and hypertension. These findings underscore the importance of interpreting D-dimer values in the context of gestational age and pregnancy complications. Additionally, maternal age influences D-dimer concentrations, emphasizing the need to interpret results within the context of age-related physiological changes during pregnancy.

Keywords: D-dimer, gestational diabetes, gestational hypertension

Introduction

The course of normal pregnancy is characterized by an enhanced activity of the coagulation system, resulting in recurrent thrombosis. Decreased levels of naturally occurring anticoagulants combined with increased pro-coagulation factors and the lower activity of fibrinolysis lead to frequent coagulation among pregnant women. The constant breakdown of these clots leads to an increase in Proteins known as D-dimer, a cross-linked fibrin degradation product.¹ During coagulation, thrombin generated by the coagulation cascade converts fibrinogen to fibrin polymers. This is further solidified by activated factor XIII, which cross-links the D domains of neighboring fibrin monomers. As plasmin acts on these cross-linked structures, D-dimer molecules are formed. Moreover, indigenous activation of the coagulation process leads to the release of D-dimer in negligible amounts. However, due to the maternal overstimulated coagulation systems, plasma D-dimer levels increase

proportionally in a trimester-dependent manner, reaching its peak in the third trimester.^{2,3} To some extent, this state of hyperactive coagulation system is designed to prevent bleeding and miscarriages during Labor. Moreover, several conditions are associated with elevated D-dimer concentration. For instance, patients with recent surgery, kidney diseases, inflammation, trauma, cancer, coronary artery disease, and liver disease experience an increase in plasma D-dimer levels. However, this increase is more relevant to thrombotic diseases.⁴ Venous thromboembolism (VTE) is one of the most common coagulation disorders that affect pregnant women. Pregnant woman is more vulnerable to VTE in their first trimester.⁵ However, this risk increases during the postpartum period.^{5,6} This condition could be fatal to pregnant women therefore, early diagnosis and prevention are essential parts of monitoring pregnancies.⁷ D-dimer measurement is a valuable tool to observe hypercoagulability status during pregnancy. However, multiple changes could lead to misdiagnosing VTE. (Brown et al, 2003) have suggested adding compression ultrasonography to D-dimer measurement to confirm the diagnosis of VTE, enhancing the specificity of D-dimer measurement among pregnant women at risk of thrombotic diseases.⁸ Moreover, additional studies have described complications such as gestational diabetes (GD) and gestational hypertension (GH) as other reasons for elevated plasma D-dimer levels.⁹ Multiple pregnancies have also been linked to increased D-dimer levels.^{10,11} Nevertheless, these conditions are the most common complications associated with elevated plasma D-dimer during pregnancy. Additionally, fetal birth outcomes and failure of pregnancies conceived through in-vitro fertilizations have been linked to high plasma D-dimer concentrations by.^{12,13} Another study recommended monitoring D-dimer levels to manage anticoagulant therapeutic interventions for pregnant women who experience child loss due to antiphospholipid syndrome.¹⁴ A comprehensive evaluation of the clinical impact of high D-dimer concentrations during pregnancy is required to exclude suspected VTE. Understanding the specific role that D-dimer plays through different gestational periods is vital for implementing preventive measures for pregnant women at high risk of thrombotic diseases. Numerous international studies have explored D-dimer trends during pregnancy, yet local data from Saudi Arabia remain limited. Although some research has been conducted in other regions of the country, such as Riyadh and the Eastern Province,¹⁵ there is a scarcity of published data specifically from the southern region, including Bisha. This gap limits the ability to establish regionally appropriate reference ranges or to assess whether geographical, genetic, or sociodemographic differences influence D-dimer levels in pregnant women. Bisha region, characterized by a predominantly tribal population with distinct genetic and lifestyle patterns, may differ significantly from more urbanized or ethnically diverse regions in Saudi Arabia. These demographic differences could potentially influence hematological profiles, including coagulation parameters, thereby warranting targeted local research. Therefore, this study evaluated the D-dimer concentrations throughout different gestational trimesters among pregnant women admitted to the Maternity and Children's Hospital in Bisha, in the Northern Asir region of Saudi Arabia. Additionally, the impact of the presence or absence of multiple pregnancies and pregnancy-associated complications such as GD and GH on D-dimer levels was observed in this study.

Methodology

Study Design and Setting

A cross-sectional study was conducted between March 2022 to March 2023 at King Abdullah Hospital in Bisha, Saudi Arabia. The hospital is a tertiary referral center that provides healthcare services to a diverse population in Bisha region in the southern part of the Kingdom, including both urban and rural areas.

Study Population, Sample Size and Collection

The study included pregnant women attending the antenatal clinic, as well as a control group of healthy non-pregnant women of reproductive age. Pregnant participants were grouped into normal pregnancies, gestational hypertension, and gestational diabetes mellitus. All subjects voluntarily took part in this study and provided written informed consent after meeting the ethical standards for participation set forth by the study protocol. The study was conducted in accordance with the Declaration of Helsinki and after meeting the ethical standards set by Bisha University. Systematic random sampling was used to select participants from those attending the antenatal clinic during the study period. Inclusion criteria were singleton pregnancy, absence of known coagulation disorders, and agreement to participate in the study. Exclusion criteria included current use of anticoagulants, history of thrombotic disease, or chronic systemic illness. A total of 230 women aged between 18–48 years old. Most of the

Table 1 The Ages of Participants Evaluated for D-Dimer Levels in Maternity and Children's Hospitals in Bisha, Saudi Arabia

Age (in years)	18- 25	41
	26-40	146
	41- 48	43

Table 2 Numbers of Non-Pregnant Women, Healthy and Complicated Pregnancies, and Women with Multiple Pregnancies Among the Participants Assessed for D-Dimer

Normal non-pregnant woman	54
Healthy Pregnant woman	68
Multiple pregnancies	31
Pregnant woman with complications (Gestational diabetes (GD) and hypertension (GH))	GD: 50 GH: 27

participants^{15,16} were within the 26–40-year age group. Women aged 18–25 years accounted for 48 individuals, while 43 women were in the 41–48 years age group (Table 1).

690 Venous blood samples (5 mL) were collected from the antecubital vein using standard phlebotomy techniques during each gestational trimester (first trimester; conception to 12 weeks; second trimester – 13 to 27 weeks; and third trimester – 28 to 40 weeks). Samples were drawn into 3.2% sodium citrate anticoagulant tubes for coagulation analysis. Immediately after collection, the tubes were gently inverted to ensure proper mixing, labeled, and transported on ice to the chemistry laboratory at the Maternity and Children's Hospital Laboratory Department. Plasma was separated by centrifugation at 3000 rpm for 15 minutes and stored at –80°C until D-dimer analysis.

Parity Assessment

Parity was recorded for each pregnant participant and categorized as primigravida or multigravida. This variable was later analyzed to explore its association with D-dimer levels. The study groups involved 54 non-pregnant and 177 pregnant women. Among the pregnant participants, there were 68 healthy pregnancies, 31 had multiple pregnancies, and 77 pregnancies had complications, with 50 women with gestational diabetes (GD) and 27 with gestational hypertension (GH) (Table 2).

D-Dimer Measurements

The blood samples were mixed and centrifuged for 15 min at 2000×g, and then Plasma was separated. Following the manufacturer's protocol, D-dimer levels for each sample were measured using an ACL Elite Pro Automated analyzer (Werfen, US). This analyzer measures D-dimer through the principle of Latex enhanced turbidimetric immunoassay, reporting results in Nanograms per milliliter (ng/mL) for each sample.

Statistics and Data Analyses

For each variable, D-dimer concentrations were entered into Microsoft Excel, where the mean and the standard deviations were calculated. Prism GraphPad was used to create graphical representations of D-dimer levels, and

statistical differences between all groups were assessed using *t*-test and one-way ANOVA with a significance level of $p < 0.05$ and a 95% confidence interval.

Results

D-Dimer in Non-Pregnancy State VS Normal Pregnancy

Initially, the current study evaluated D-dimer levels in both non-pregnant and women with healthy pregnancies to determine that D-dimer is elevated in pregnancy regardless of the presence or absence of pregnancy-associated complications. 54 non-pregnant women were recruited for this study to serve as a control group. D-dimer concentration was measured for both non-pregnant and healthy pregnant women. The results show that D-dimer levels are significantly higher in healthy pregnant women (approximately 307 ng/mL) compared to non-pregnant women (approximately 201 ng/mL), suggesting that D-dimer levels increase during healthy pregnancies compared to non-pregnant states (Figure 1).

Comparative Analysis of D-Dimer Levels in Healthy Pregnancies and Complicated Pregnancies Across Trimesters

This study also compared D-dimer levels across all three trimesters among women with healthy pregnancies and those with complicated pregnancies. Blood samples were analyzed to evaluate D-dimer levels in healthy pregnant women and pregnant women with multiple pregnancies, gestational diabetes, and gestational hypertension during different gestational periods. The levels of D-dimer for the 68 healthy pregnant women have demonstrated that the average levels increased significantly from 256.62 ng/mL in the first trimester to 276.61 ng/mL in the third trimester, indicating a significant rise in D-dimer levels from the first to the third trimester in healthy pregnancies (Figure 2A). For the 31 pregnant women with multiple pregnancies, D-dimer levels showed a significant increase from an average of 273.83 ng/mL in the first trimester to 293.44 ng/mL in the third trimester, indicating a substantial rise in D-dimer levels throughout pregnancy (Figure 2B). Among the 50 pregnant women with gestational diabetes, D-dimer levels significantly increased from an average of

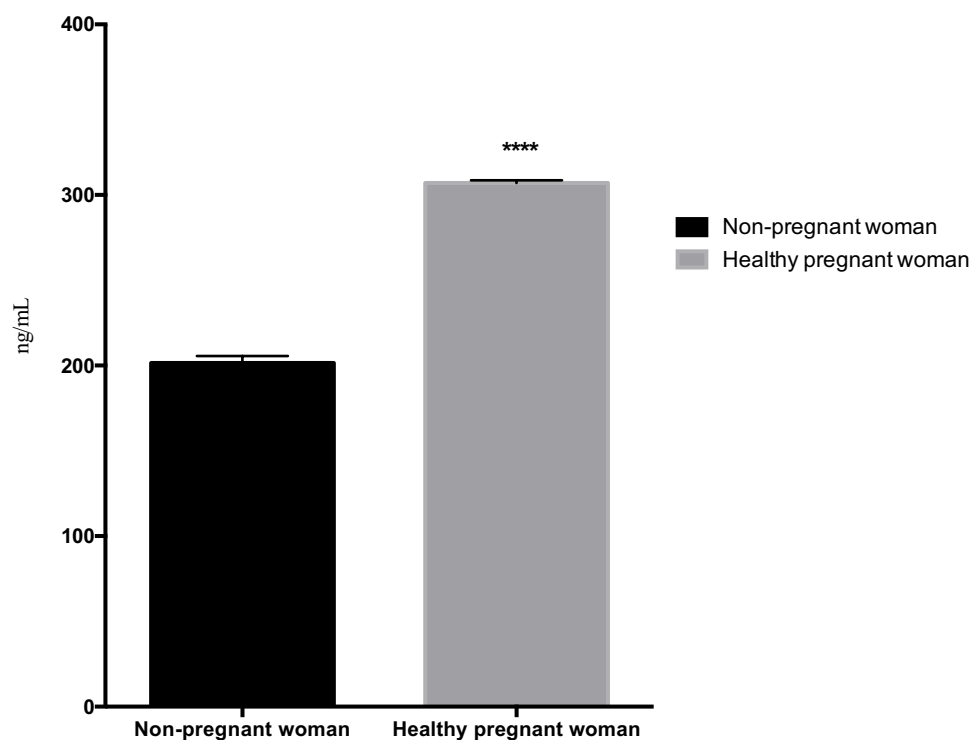


Figure 1 D-dimer concentrations among non-pregnant compared to women with healthy pregnancies. (**** $p < 0.0001$ using *t*-test).

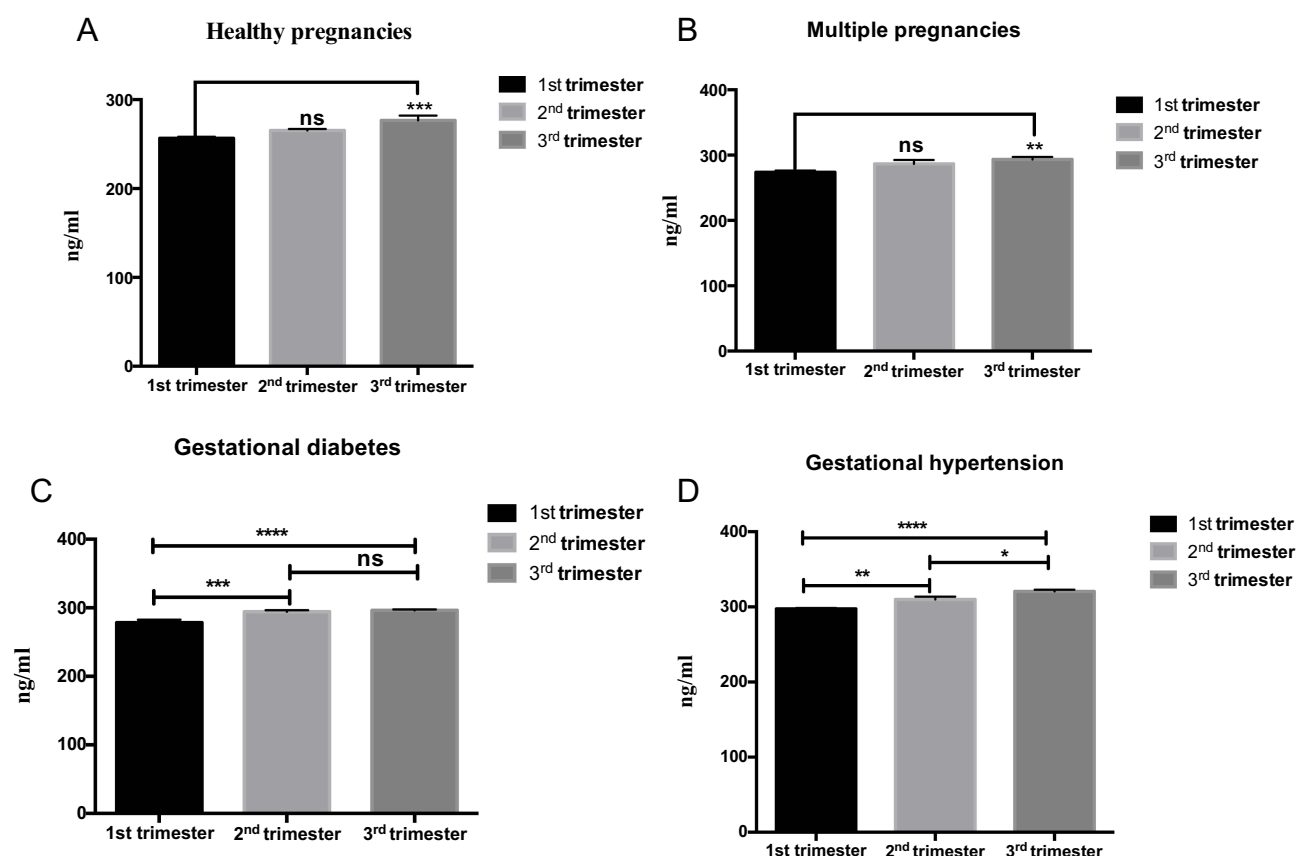


Figure 2 D-dimer values among women with various pregnancy conditions across all trimesters. The changes in D-dimer concentrations (ng/mL) across the three trimesters of pregnancy in four different groups of women: (A) healthy pregnancies (N=68), (B) multiple pregnancies (N=31), (C) gestational diabetes (N=50), and (D) gestational hypertension (N=27). D-dimer values are presented as mean $\pm$ standard error of the mean (SEM), and statistical significance was assessed using one-way ANOVA. In healthy pregnancies, D-dimer levels rose significantly from the first trimester (256.62 ± 13.201 ng/mL) to the third trimester (276.61 ± 45.065 ng/mL) (*** $p = 0.0003$). Similarly, women with multiple pregnancies exhibited an increase from 273.83 ± 14.16 ng/mL in the first trimester to 293.44 ± 20.842 ng/mL in the third trimester (* $p = 0.0061$). For women with gestational diabetes, D-dimer levels increased significantly from 278.39 ± 29.808 ng/mL in the first trimester to 296.17 ± 11.6213 ng/mL in the third trimester (*** $p = 0.0015$, **** $p < 0.0001$ between trimesters). The most elevated D-dimer levels were observed in the gestational hypertension group, with values rising from 297.31 ± 7.5365 ng/mL in the first trimester to 320.63 ± 12.157 ng/mL in the third trimester, showing significant differences across all trimesters (* $p = 0.0125$, ** $p = 0.0014$, **** $p < 0.0001$). These findings indicate a trimester-dependent increase in D-dimer levels, with variations across pregnancy conditions.

278.39 ng/mL in the first trimester to 296.17 ng/mL in the third trimester, indicating a notable rise throughout pregnancy (Figure 2C). In the 27 pregnant women with gestational hypertension, D-dimer levels showed a significant increase from an average of 297.31 ng/mL in the first trimester to 320.63 ng/mL in the third trimester, indicating a notable rise in D-dimer levels throughout pregnancy (Figure 2D).

Age-Related Variation in D-Dimer Levels Among Pregnant and Non-Pregnant Women

The mean D-dimer levels were compared across three age categories (18–25, 26–40, and 41–48 years) for both pregnant women (cases) and non-pregnant women (controls) to evaluate the potential influence of maternal age on D-dimer levels. In the case group, the mean D-dimer level was highest in the 41–48 age group (1780.5 ± 222.7 ng/mL), followed by the 26–40 age group (1564.3 ± 180.2 ng/mL), and the 18–25 age group (1423.7 ± 145.6 ng/mL). Similarly, in the control group, the D-dimer levels also increased with age, with the 41–48 age group showing a mean of 558.2 ± 97.4 ng/mL, followed by 478.6 ± 85.9 ng/mL in the 26–40 age group and 415.3 ± 74.1 ng/mL in the 18–25 age group.

Statistical analysis using one-way ANOVA revealed a significant difference in D-dimer levels between the age groups in both the case and control groups ($p < 0.001$). These findings further reinforce the influence of age on D-dimer levels, in addition to pregnancy status (Figure 3).

Comparison of D-dimer Levels by Age Group

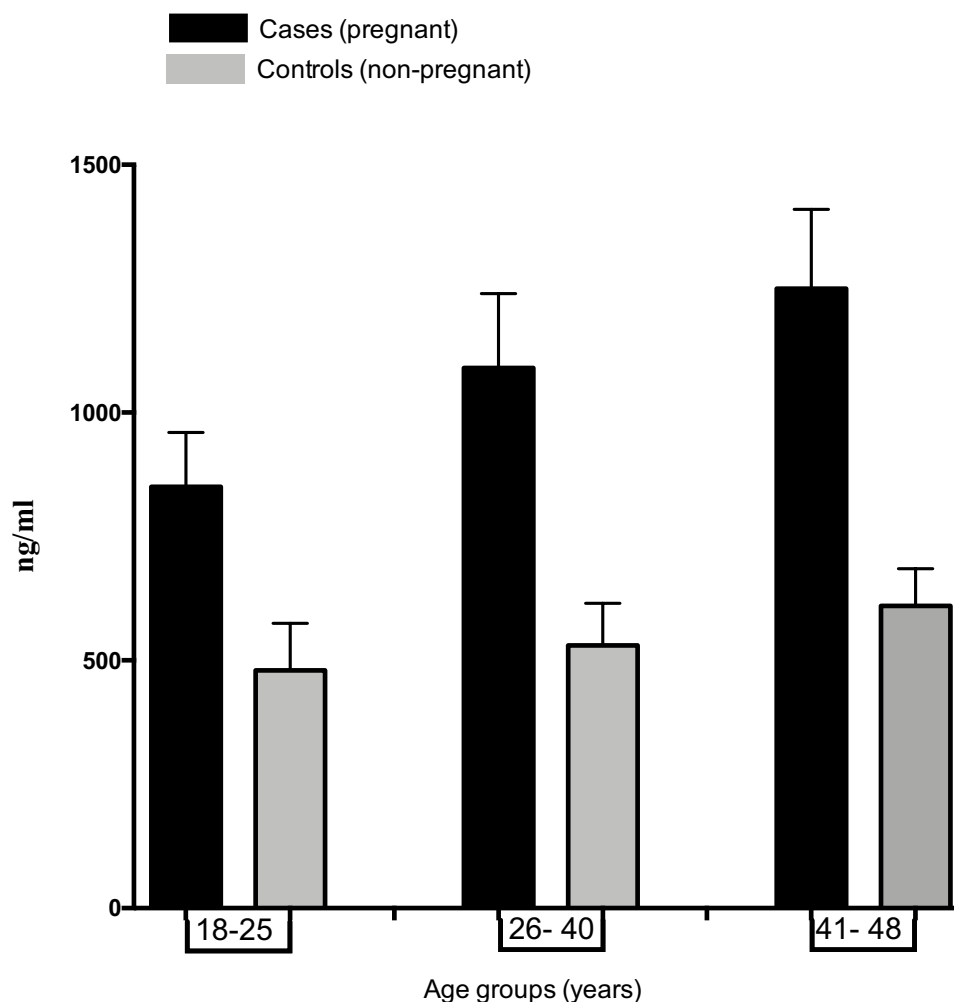


Figure 3 Comparison of mean D-dimer levels (ng/mL) across different age groups (18–25, 26–40, 41–48 years) among pregnant women (cases) and non-pregnant women (controls). The grouped bar chart demonstrates a significant progressive increase in D-dimer levels with age in both groups, with consistently higher levels observed among pregnant women. Error bars represent standard deviation. **** $p < 0.0001$ using one-way ANOVA).

Discussion

Pregnancy is well-recognized as a naturally occurring hypercoagulable state, which is primarily an adaptive physiological mechanism aimed at minimizing bleeding during delivery. This state is characterized by increased levels of procoagulant factors such as fibrinogen, factor VII, VIII, and X, along with reduced fibrinolytic activity and a decrease in certain anticoagulant proteins.^{14,15} One of the markers that reflects this prothrombotic shift is the plasma D-dimer concentration. This study determined to evaluate the increase in D-dimer concentrations during all the trimesters of normal and complicated pregnancies among Saudi women as this increase does not always indicate the presence of thrombotic diseases. Other factors that could play a role in elevating the levels of D-dimer during pregnancies, such as multiple gestations, gestational diabetes, and gestational hypertension, were also evaluated in this study. During a normal pregnancy, the risk of developing different thrombotic diseases rises as mothers develop multiple hemostatic changes, leading to a change in the levels of D-dimer. This represents a significant maternal health risk that could lead to hospitalization and pregnancy loss.¹⁶ The current study supports the body of literature that suggests that the D-dimer levels increase across the pregnancy trimesters.^{17–19} The present study revealed that the incidence of high D-dimer is prevalent among pregnant women in the Maternity and Children's Hospital in Bisha, Kingdom of Saudi Arabia. Our

study compared D-dimer levels in non-pregnant and healthy pregnant women and found that D-dimer levels are significantly higher in healthy pregnancies than in non-pregnant states.

Additionally, D-dimer levels were measured across all trimesters in women with healthy pregnancies and complicated pregnancies (multiple gestations, gestational diabetes, and gestational hypertension). In all cases, D-dimer levels increased significantly from the first to the third trimester, with the highest point of increase observed with gestational hypertension. The present study confirmed that the d-dimer levels in pregnant women are significantly elevated compared to healthy pregnancy. Multiple studies have described similar findings where D-dimer concentration is elevated because of pregnancy.^{20,21} This fact prompted other studies to suggest the need for making a higher cut-off value of D-dimer only for pregnancy to enhance the specificity of D-dimer measurement as a diagnostic tool for VTE, which is a prevalent condition during pregnancy.^{22–24} D-dimer was found to be elevated among 9 out of 10 pregnant women who suffered from VTE at a concentration much higher than the highest point in each gestational trimester.²⁵ Cesarean birth was also reported to contribute to the elevation of D-dimer levels at a higher concentration when compared to VTE patients without pregnancy.²⁶ The findings of our study, alongside these results, suggest that women during pregnancy tend to have higher D-dimer levels that could reduce the specificity of D-dimer measurement for a pregnant woman who suffers from VTE. Another study suggested that imaging techniques such as ultrasonography will enhance the diagnosis of coagulopathies during pregnancy.²⁷ The current study described a trimesters-dependent increase in D-dimer levels among pregnant women with healthy pregnancies and multiple gestations. This confirms the findings of previous studies that have described that the concentration of D-dimer is elevated during gestation, indicating a hyperactive coagulation system combined with Increased fibrinolysis. This could result from the formation of the placenta and the release of fibrin from sedentary blood aggregations at the lower part of the body because of the increased uterus size across trimesters.^{28,29}

Another critical factor considered in this study was the number of times a woman had been pregnant. Research has shown that multiple pregnancies may be linked to a higher risk of cardiovascular disorders, potentially due to a history of childbirth that can elevate blood glucose and lipid levels.³⁰ One study found that having 6 or more pregnancies was associated with an increased risk of cardiovascular issues.³⁰ Thus, this study considered multiple pregnancies a potential cause of elevated D-dimer levels. (Kim et al, 2017) reported that 90% of women with multiple pregnancies had higher D-dimer levels, compared to only 10% who had normal levels. This suggests that elevated D-dimer levels may also be related to the number of pregnancies, indicating that multiple pregnancies could be a significant risk factor for future pregnancies. This finding aligns with our study, where we have shown that women with multiple pregnancies exhibited a substantial rise in D-dimer levels throughout pregnancy.

Moreover, gestational diabetes GD is a common pregnancy complication that poses health risks to both the mother and fetus.³¹ GD has been linked to an increased blood coagulation rate by.³¹ They suggested that gestational diabetes can lead to blood clotting due to enhanced platelet activation, elevated coagulation factors such as fibrinogen production, and decreased fibrinolytic activity.³² Our study investigated the levels of D-dimer among pregnant women with GD, revealing a significant increase across all trimesters except for the 2nd and the 3rd, as the difference was not statistically significant. Another study explored the potential association between elevated D-dimer levels and gestational diabetes GD; their findings describe that most of the women with GD showed high D-dimer concentrations.³³ They noted a positive relationship between third-trimester D-dimer levels and GD, but these differences were not statistically significant. However, these findings suggest that GD may influence D-dimer concentrations during pregnancy.^{34,35}

This study also investigated the levels of D- dimer in pregnancies with gestational hypertension GH. D-dimer levels significantly increased among all women with GH in our study, showing a consistent rise throughout pregnancy and higher values than in other study groups. Several other studies have described similar findings. In agreement with our research, (Soma-Pillay et al, 2016) found that most of their study population had an elevated D-dimer concentration. A higher proportion of women with severe GH had elevated D-dimer levels compared to those with non-severe GH.³⁶ Another study described that approximately half of their evaluated subjects had D-dimer concentrations above the standard limit. Patients with severe GH were presented with higher D-dimer levels compared to those with non-severe GH.³⁷ In women with severe GH, elevated D-dimer levels result from increased fibrin production, consistent with the GH pathophysiology. This process also includes the formation of microthrombi and excessive fibrin deposition, which can

cause reduced blood flow to organs and the placenta. Furthermore, women with GH demonstrate a heightened hypercoagulable state and inflammatory response compared to those who have healthy pregnancies.³⁸ The current study also revealed a progressive increase in D-dimer levels with advancing age in both pregnant and non-pregnant women, with significantly higher values observed in pregnant participants across all age groups. These findings align with previous reports indicating that D-dimer levels naturally rise with age, even in healthy individuals, likely due to age-related changes in coagulation and fibrinolytic activity.^{39,40} During pregnancy, this physiologic elevation is further amplified due to increased thrombin generation and reduced fibrinolytic activity, processes that intensify with maternal age.⁴¹ The highest D-dimer levels were seen in the 41–48 age group, a demographic increasingly represented in modern obstetrics due to delayed childbearing. These age-related variations underscore the importance of considering maternal age when interpreting D-dimer levels during pregnancy to avoid misdiagnosis of thromboembolic events or underestimation of coagulation risks.¹⁹ Moreover, the age-specific reference ranges could enhance the clinical utility of D-dimer in obstetric care, especially in high-risk populations.

Study Limitations

The study did not assess other coagulation parameters such as fibrinogen, PT, and APTT, which could have provided a more comprehensive view of the coagulation status. Additionally, unmeasured confounding factors—such as obesity, smoking, and subclinical conditions—may have influenced D-dimer levels and should be considered in future research.

Conclusion

Our study found that high D-dimer levels are common among pregnant women at the Maternity and Children's Hospital in Bisha, Saudi Arabia. D-dimer levels were significantly higher in healthy pregnancies compared to non-pregnant women. Across all trimesters, D-dimer levels increased significantly, with the highest levels observed in pregnancies complicated by gestational diabetes and gestational hypertension. Additionally, the study revealed a progressive increase in D-dimer levels with advancing maternal age in both normal and complicated pregnancies, suggesting age-related physiological changes may influence coagulation markers. Gradual changes in the hemostatic system are typical in a normal pregnancy. The specificity of the D-dimer test decreases significantly during pregnancy due to the ordinary hypercoagulability state. Factors such as recurrent thrombosis contribute to elevated levels of various clotting and fibrinolysis proteins and increased D-dimer concentrations. Pregnant women with a history of hypertension and diabetes should receive more guidelines to manage the natural increase in D-dimer levels during pregnancy. This can help prevent complications related to elevated D-dimer levels.

Data Sharing Statement

The authors confirm that the data that support the findings of this study is available within the article.

Ethics Declarations

The university of bisha ethics committee reviewed and approved the ethical criteria of this study.

Acknowledgments

1. The author is thankful to the Deanship of Graduate Studies and Scientific Research at the University of Bisha for supporting this work through the Fast-Track Research Support Program.

Disclosure

The author declares no conflicts of interest in this work.

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