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D-Dimer Plasma Levels in Each Trimester of Diabetic Pregnant Women, A Case Control Study.

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Abstract

Background and objectives: Pregnancy increases D-dimer levels, making it a non-specific test for venous thromboembolism. This study compared D-dimer levels by trimester in healthy and diabetic pregnant women.

Methods: A case-controlled study was conducted from May 2022 to August 2023 at Gestational Diabetes Clinic/Maternity Teaching Hospital, Erbil City, Kurdistan Region, Iraq to compare D-dimer levels between two groups: 360 pregnant women diagnosed with diabetes (cases) and 360 normoglycemic pregnant women (controls). Blood samples were obtained once from each participant during a prenatal visit. Samples were collected from a vein and analyzed using a latex-based immunofluorescence assay on a Biozek DCR1000 machine to measure D-dimer concentration.

Results: D-dimer levels steadily increased throughout pregnancy in both groups, peaking in the third trimester. Notably, pregnant women with diabetes consistently had significantly higher D-dimer levels compared to controls across all trimesters ($p < 0.001$). Within the diabetic group, women with type 1 diabetes displayed the highest mean D-dimer concentration (1887.3 ng/ml), significantly higher than both type 2 diabetes (1518.0 ng/ml; $p = 0.036$) and gestational diabetes (1155.8 ng/ml; $p = 0.004$).

Conclusions: This study highlights a substantial rise in D-dimer levels throughout pregnancy, even in healthy women. Importantly, pregnant women with diabetes have considerably higher D-dimer levels compared to controls, with the highest observed in type 1 diabetes. These findings emphasize the need to consider diabetes when interpreting D-dimer levels for venous thromboembolism diagnosis in pregnancy.

Keywords: D-dimer, Diabetes, Pregnancy, Plasma level range,Venous thromboembolism

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Introduction

D-dimer is the breakdown product of cross-linked fibrin (by factor XIII). It illustrates the continuous activation of the hemostatic system.[1]Venous stasis, vascular endothelial injury, and hypercoagulability (Virchow's triad) are the three elements of venous thromboembolism .[1] Given that pregnancy consists of all three factors, the frequency of venous thromboembolism in pregnant women is 5.5–6 times greater than in other women of reproductive age .[2] This is an area of active research, with significant investigation occurring over the past 20 years.[3] The hemostatic reference intervals were derived using samples that were not pregnant; therefore they might not be applicable during pregnancy.[3] It is now widely known that D-dimer increases normally during pregnancy, maybe over the 0.5 g/ml cutoff used in non-pregnant women.[4.]According to reports, in the second and third trimesters of pregnancy, 78% and 99% to 100%, respectively, of pregnant women present with D-dimer levels higher than usual cut-off, this renders it a non-specific test in pregnancy. [5,6] Pregnancy-related D_dimer results that are positive are not always indicative of venous thromboembolism .[7] The D_dimer test's place in pregnancies is still up for debate. Even though normal levels are less likely to be detected in pregnancy, the European Society of Cardiology's recommendations for assessing D- dimer levels suggest that pulmonary embolism in pregnancy can be excluded, like for other patients with normal D-dimer levels.[8] However, excluding pulmonary embolism in pregnancy should not be done with the D-dimer, according to recommendations from the American Thoracic Society and Society of Cardiothoracic Radiology.[9] Several studies looked into the effects of diabetes on pregnancy-related problems. Pregnancies complicated by diabetes are associated with an increased risk of developing venous thromboembolism in both the pre- and postpartum periods .[10,11] In addition, compared to uncomplicated third trimester normoglycemic pregnancies, a considerable increase in the amount of D-dimer was observed during pregnancy complicated by diabetes.[12] Diabetic patients who have impaired glucose metabolism may experience vascular endothelial injury, which can trigger platelet activation, increased coagulation, fibrinolysis, and decreased anticoagulation function.[13] The study's goal was to compare the reference range for D.dimer test during each trimester of a healthy pregnancy to that of women with diabetes during pregnancy.

Patients and methods:

A case-control study was conducted from May 2022 to August 2023 at Gestational Diabetes Clinic/Maternity Teaching Hospital, Erbil City, Kurdistan Region, Iraq. The study involved a total of 720 women: 360 diabetic pregnant women and 360 normoglycemic pregnant women The Maternity Teaching Hospital offers a twice-weekly gestational diabetes clinic for pregnant women with or without pre-existing diabetes (type 1 or 2).The center confirmed gestational diabetes using WHO Diagnostic Criteria.[13.14]Women aged 18–40 years old with a BMI < 30 kg/m^2 and a singleton viable pregnancy with any parity throughout all trimesters of pregnancy, and who were willing to engage in the study were eligible for the control group. Pregnant women with pre-gestational and gestational diabetes, ages 18–40 years old, BMI < 30 kg/m^2, singleton viable pregnancy, any parity, any gestational age, and acceptance to participate in the research were the inclusion criteria for the case group. Women with a personal or family history of venous thromboembolism , obesity (BMI ≥ 30 kg/m^2), advanced maternal age (> 40 years), females who had suspected or confirmed deep vein thrombosis , previous

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recurrent spontaneous abortions or coagulation disorders such as hemophilia ,Von Willebrand disease, hypercoagulable states and clotting factor deficiencies , or who got anticoagulant prophylaxis, or who have a current malignancy, preeclampsia, preterm prelabour rupture of membranes, twin pregnancy, or recent COVID infection were excluded from the study. We aimed to find a difference in failure rates between two groups (cases and controls) with a high level of certainty (80% power) and a low chance of mistakenly rejecting a true null hypothesis (5% significance level). To achieve this, we calculated the ideal sample size for our case-control study, where each case is compared to one control subject. This calculation was based on a specific formula:

$$n = (Z_\alpha + Z_\beta)^2 * (p_1 - p_2)^2 / (p_1 * (1 - p_1) + p_2 * (1 - p_2))$$

* n is the sample size required.
* Z_α is the critical value of the standard normal distribution at the significance level α
* Z_β is the critical value of the standard normal distribution at power β.
* P_1 is the failure rate of control.
* P_2 is the failure rate of case.

In this case, Z_α is 1.96 (for a significance level of 0.05) and Z_β is 0.84 (for a power of 0.8). Prior data indicates that the failure rate of controls is 0.7 and the failure rate of the cases is 0.6. Substituting these values into the formula, we get: $n = (1.96 + 0.84)^2 * (0.7 - 0.6)^2 / (0.7 * (1 - 0.7) + 0.6 * (1 - 0.6)) = 360$.Therefore, we included 360 cases and 360 controls in the current study.The participants were separated into two groups: Group A, "normo-glycemic pregnant women," consisted of 360 women in their first, second, and third trimesters of pregnancy. Group B, "Diabetic Pregnant Women," consisted of 360 women who had diabetes during their first, second, and third trimesters of pregnancy. Blood was drawn once from each person involved in the study. The blood was taken from a vein and collected in a special blue tube containing a substance called sodium citrate (3.2%) to prevent clotting. A test called a latex-based immunofluorescence assay was used to measure the level of D-dimer in the blood. This measurement was done with a machine called the Biozek DCR1000. Out of all the people tested, 95% had a D-dimer level at or below 0.5 milligram per liter (mg/L), which is also equal to 500 nanograms per milliliter (ng/mL). To ensure ethical conduct, this study was approved by the Kurdistan Higher Council of Medical Specialties Research Protocol Ethics Committee on May 17, 2022 (reference number 1001). All women who agreed to participate (provided informed consent) did so in writing during the first interview. They were guaranteed confidentiality, meaning their information would be kept private and used only for research purposes. Throughout the study, we followed the ethical guidelines set forth by the Institutional Research Committee and the Declaration of Helsinki for research involving human subjects. Statistical analysis was performed using SPSS version 26. For categorical data (proportions) in two groups, the chi-square test assessed the presence of significant differences. For continuous data (means), the unpaired Student's t-test compared means between two groups. When comparing means among three or more groups, a one-way ANOVA test identified overall differences, followed by the LSD post-hoc test to pinpoint specific groups with significant variations. The Pearson correlation coefficient (r) evaluated the strength of the relationship between two variables. Throughout the analysis, a p-value less than 0.05 was considered statistically significant, indicating a low probability (less than 5%) that the observed differences occurred by chance.

Results:

Two groups of pregnant women were included in the study, group A women who

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were not diabetic (control) (n = 360), and group B women who were diabetic (case) (n = 360). The mean age (SD) of the whole sample was 30.4 (7.4) years, the median was 30 years, and the age range was 18–45 years. The largest proportion of women (41.4%) were aged 25–34 years, but there was no significant difference between the two groups in the age distribution (p = 0.196), or in means (p = 0.060). Around half (48.3%) of the women were multiparous, and 23.3% were grand multiparous, but the difference was also not significant between the groups (p = 0.302). More than half (52.8%) of the diabetic women were in the third trimester, compared with 25% of the control group (p < 0.001) as shown in Table (1).

Table (1): Basic characteristics of mothers.

	Diabetes	Control	Total	
	No. (%)	No. (%)	No. (%)	P*
Age				
< 25	106 (29.4)	85 (23.6)	191 (26.5)	
25-34	145 (40.3)	153 (42.5)	298 (41.4)	
≥ 35	109 (30.3)	122 (33.9)	231 (32.1)	0.196*
Mean (SD)	29.9 (7.5)	30.9 (7.2)		0.060**
Parity				
Nulliparous	57 (15.8)	40 (11.1)	97 (13.5)	
Primiparous	54 (15.0)	53 (14.7)	107 (14.9)	
Multiparous	167 (46.4)	181 (50.3)	348 (48.3)	
Grand multiparous	82 (22.8)	86 (23.9)	168 (23.3)	0.302*
Gestational age				
First trimester	41 (11.4)	123 (34.2)	164 (22.8)	
Second trimester	129 (35.8)	147 (40.8)	276 (38.3)	
Third trimester	190 (52.8)	90 (25.0)	280 (38.9)	< 0.001*
Total	360 (100.0)	360 (100.0)	720 (100.0)	

* By the Chi square test. ** by the unpaired t test.

Details of the descriptive statistics of the D-dimer of cases and controls are presented in table (2). It is evident in the mentioned table and in Figure (1) that there's a clear upward trend in D-dimer mean for both diabetic and normoglycemic pregnant women as pregnancy progresses. The highest number of means is observed in the third trimester for both groups in each trimester; diabetic women consistently have a higher number of D-dimer mean compared to normoglycemic pregnant women. This disparity is most pronounced in the third trimester (p < 0.001). The standard deviation (SD) of D-dimer in diabetics was 1114.3 ng/ml, compared with 552.9 ng/ml in the control group (p < 0.001) as mentioned in Table (2).

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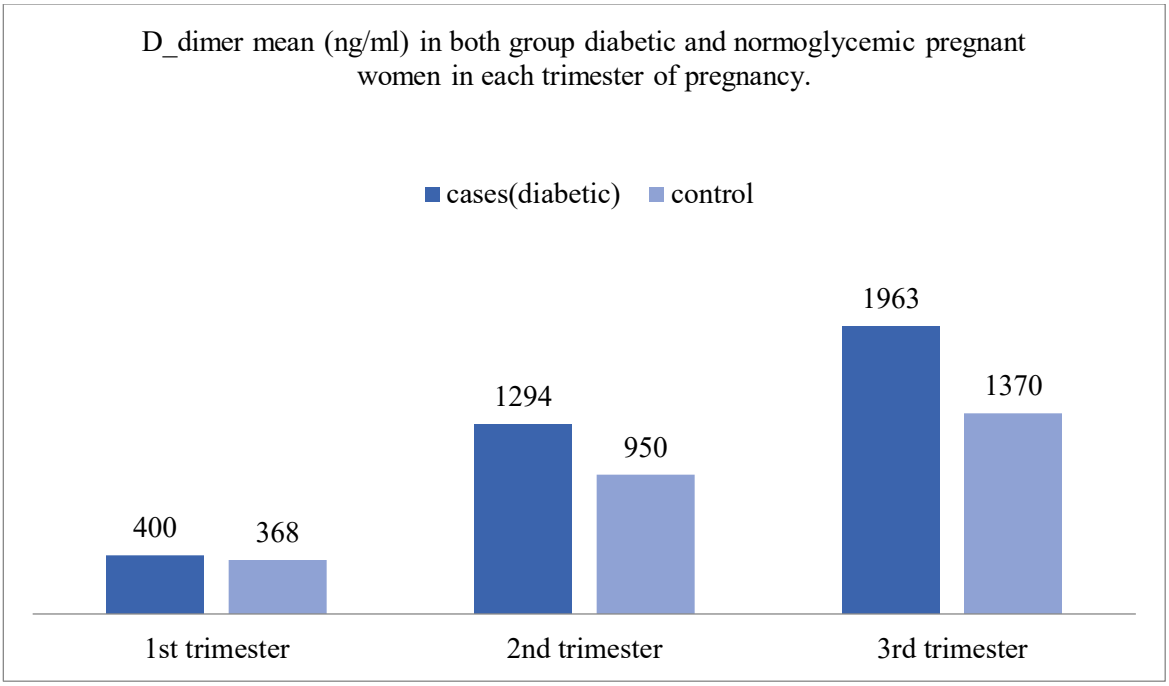

Figure (1): Mean of D-dimer of diabetic and normoglycemic pregnant women.

Table (2): Descriptive statistics of D-dimer (ng/ml) in study groups.

	Diabetes (n = 360)	Control (n = 360)
Mean	1532.9	835.6
SD	1114.3	552.9
Median	996.0	696.0
Minimum	167.0	150.0
Maximum	4500.0	2856.0
95% CI		
Lower bound	1417.5	778.3
Upper bound	1648.4	892.9
Percentiles		
5th	286.7	172.1
25th	626.3	322.0
50th	996.0	696.0
75th	2474.0	1328.3
95th	3565.3	1764.3

Table (3) shows that the highest mean of D-dimer among diabetics was among women with type 1 diabetes (1887.3 ng/ml), which was significantly (p = 0.036) higher than that of women with type 2 diabetes (1518.0 ng/ml), and it was also significantly (p = 0.004) higher than that of gestational diabetes (1155.8 ng/ml). No significant (p = 0.080) difference was detected between the means of type 2 and gestational diabetes.

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Table (3): Means of D-dimer of diabetic pregnant women by type of diabetes.

95% Confidence Interval											
DM††	N	Mean of D-dimer	SD	SE	Lower Bound	Upper Bound	Min	Max	P*	G†	P**
Type 1	46	1887.3	1418.0	209.1	1466.2	2308.4	276	4500		1X2	0.036
Type 2	282	1518.0	1094.7	65.2	1389.6	1646.3	167	4132	0.015	1X3	0.004
GDM	32	1155.8	511.8	90.5	971.2	1340.3	480	2260		2X3	0.080
Total	360	1532.9	1114.3	58.7	1417.5	1648.4	167	4500			

*By ANOVA. **by LSD. † G: Comparing types of diabetes.
DM: diabetes; GDM: gestational diabetes mellitus.

It is evident in Table (4) that the longer the pregnancy, the higher the D-dimer level ($p < 0.001$). The means of D-dimer of the first, second, and third trimesters were 390.0 ng/ml, 1261.2 ng/ml, and 1963.9 ng/ml, respectively.

Table (4): Means of D-dimer of diabetic pregnant women by trimester of pregnancy.

95% Confidence Interval									
Trimester	N	Mean of D-dimer	SD	SE	Lower Bound	Upper Bound	Min.	Max.	P*
First	41	390.9	140.3	21.9	346.6	435.1	167.0	673.0	
Second	129	1261.2	918.8	80.9	1101.1	1421.3	275.0	3566.0	< 0.001
Third	190	1963.9	1123.6	81.5	1803.1	2124.7	280.0	4500.0	
Total	360	1532.9	1114.3	58.7	1417.5	1648.4	167.0	4500.0	

*By ANOVA test.

All the differences between the two means of the three trimesters were significant ($p < 0.001$), as estimated by the LSD post-hoc test.A positive and significant correlation was detected between D-dimer and weeks of gestation ($r = 0.631$, $p < 0.001$) as presented in Figure (2) in diabetic pregnant women.

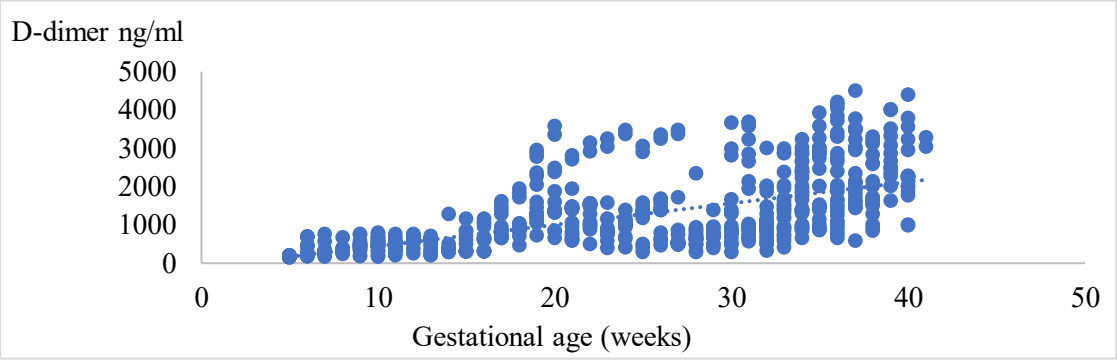

Figure (2): Correlation between D-dimer and gestational age in diabetic pregnant women**.** A positive and significant correlation was detected between D-dimer and weeks of gestation. ($r = 0.853$, $p < 0.001$), as presented in Figure (3)**,** in normoglycemic pregnant women.

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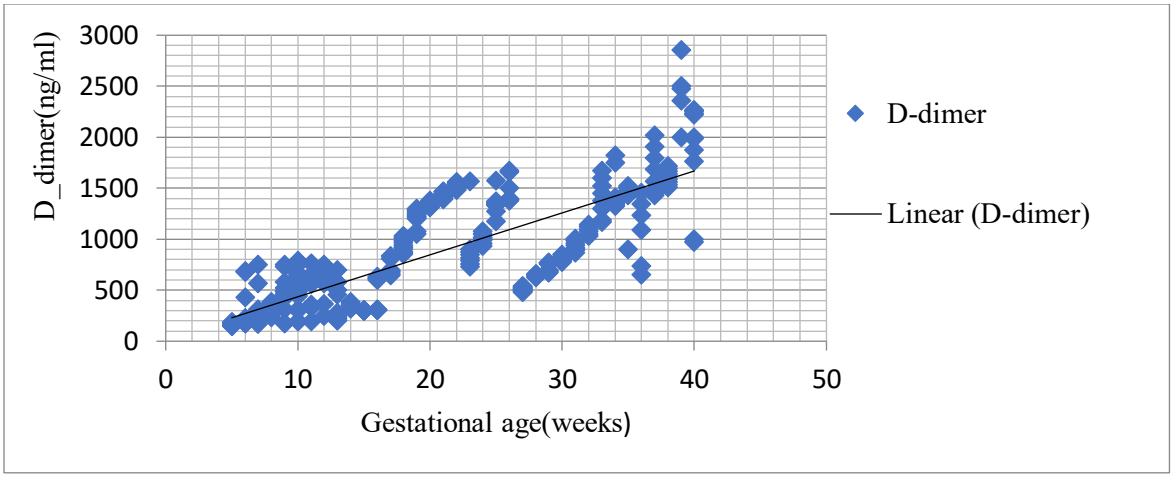

Figure (3): Correlation between D-dimer and gestational age in normoglycemic pregnant women.

To assess the statistical significance of correlation coefficients (like r = 0.6 and r = 0.8) using a chi-squared test. This method involves calculating a chi-squared statistic based on the sample size (n) and the correlation coefficient (r). In our case, with a sample size of 720, the chi-squared statistic for r = 0.6 would be 262.44. With one degree of freedom (Df = 1), consulting a chi-squared table with this statistic (262.44) reveals a p-value much lower than 0.05 (typically denoted as alpha). Since the p-value is less than our chosen significance level (alpha), we can conclude that a correlation coefficient of 0.6 is statistically significant. Repeating this process for r = 0.8 would likely yield an even stronger level of significance. Therefore, this analysis suggests a statistically significant relationship between the two variables for both correlation coefficients. Interpretation: The correlation coefficient of r = 0.6 indicates a moderately positive correlation between the two variables. The correlation coefficient of r = 0.8 indicates a strong positive correlation between the two variables.

Discussion:

Pregnancy causes a slow but steady shift in hemostatic mechanisms, with hypercoagulability peaking in the third trimester and gradually fading in the postpartum period.[1]They are of no clinical significance and are reviewed as a protective mechanism to prevent excessive bleeding during labour and delivery.[4]A study by Sweeting et al. found a link between rapid increases in D-dimer levels during pregnancy and a higher risk of complications. These complications can include gestational diabetes, placenta previa , macrosomia and increased postpartum hemorrhage.[13] The incidence rate of diabetes shows an upward trend annually.[14] According to a study by Zhu, Yibing, et al., pregnant women's GDM may be predicted by the D-dimer measurement.[12]The results of this study were the means of D-dimer in the first, second, and third trimesters of normoglycemic pregnancies were 368.3 ng/mL, 950.3 ng/mL, and 1370.9 ng/mL, respectively, which is similar to reports by Siennicka et al. Predictably, the pregnant women's D-dimer concentrations grew gradually and statistically considerably, peaking in the third trimester of pregnancy.[14]According to a previous study, there is a correlation between D-dimer level and diabetes.[15] Corroborating findings by Chen et al. (pp. 394-400), our study revealed a significant difference in serum D-dimer levels between diabetic and

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normal blood glucose groups throughout pregnancy. Diabetic women consistently exhibited higher D-dimer levels in each trimester.[15] A prior study by Gregg et al has demonstrated that D-dimer is higher in diabetic pregnancy throughout the three trimesters of pregnancy.[16] Means of D-dimer in the first, second, and third trimesters of diabetic pregnancies were 390.9 ng/mL, 1261.2 ng/mL, and 1963.9 ng/mL, respectively. In our study, it was evident that the mean D-dimer of diabetics was 1532.9 ng/ml, compared with 835.6 ng/ml in the control group ($p < 0.001$). This is the first study to compare and encompass three forms of diabetes in pregnancy. In this study, women with type 1 diabetes had the highest mean D-dimer of diabetics (1887.3 ng/ml), which was considerably ($p = 0.036$) higher than women with type 2 diabetes (1518.0 ng/ml) and significantly ($p = 0.004$) higher than women with gestational diabetes (1155.8 ng/ml). This study was not without its drawbacks. To begin with, incomplete clinical data and selection bias may arise from prospective data gathering. Furthermore, this study did not include a long-term postpartum follow-up of the participants, making it impossible to determine the long-term incidence rates of metabolic syndromes such as diabetes mellitus and hypertension. Postpartum follow-up will be conducted in the future in order to investigate the variations in serum D-dimer levels during pregnancy and postpartum as well as the effects of postpartum glycolipid metabolism. Moreover, D-dimer concentration was only measured at prenatal visits rather than before the condition started. Consequently, a larger cohort is needed to validate these findings.

Conclusions:

Our study confirmed that D-dimer levels increase consistently during pregnancy, even among women without health issues, reaching their highest point in the third trimester. Notably, pregnant women with diabetes exhibited notably higher D-dimer levels throughout pregnancy compared to healthy women, with the most elevated levels observed in those with type 1 diabetes, followed by type 2 and gestational diabetes. These findings can improve the interpretation of D-dimer levels for diagnosing venous thromboembolism in pregnant women with diabetes.

Conflicts of interest:

None.

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