Evaluation of Hypercoagulability State in Uncomplicated Pregnancy post Covid-19 Vaccination through Trimester-Specific Evaluation of Fibrin Degradation Products

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Abstract

Background: Pregnancy inherently enhances the body's propensity for coagulation, while the COVID-19 vaccinations additionally modify immune response systems that affect haemostasis. Observations of pregnancy-associated elevations in FDPs suggest that information regarding FDP fluctuations during the trimester following COVID-19 vaccination is scarce. The objective of the study is to examine the correlation between COVID-19 immunisations administered throughout various pregnancy trimesters and FDP levels in normal pregnancies, while also contrasting these results with those of non-pregnant adult women. **Methods:** The study had 160 female volunteers categorised into four groups: first, second, and third trimester pregnant women, along with non-pregnant controls, each group containing forty subjects. Participants were classified into two groups according to their COVID-19 immunisation status: vaccinated and unvaccinated. FDP concentrations were evaluated via a commercial immunoturbidimetric technique. The study employed non-parametric statistical techniques, specifically the Kruskal-Wallis and Mann-Whitney U tests, in conjunction with Spearman's correlation analysis, with a p-value of less than 0.05 denoting statistical significance. **Results:** FDP levels recorded during pregnancy demonstrated a steady increase, with vaccinated individuals exhibiting higher FDP readings compared to unvaccinated controls ($p < 0.001$). All readings documented throughout gestation were within the typical physiological parameters. No thrombotic events were observed. A strong statistically significant link was seen between COVID-19 vaccination and elevated FDP values ($\rho = 0.714$, $p < 0.001$). **Conclusion:** Pregnant people vaccinated against COVID-19 exhibit modest yet physiologically adequate elevations in FDP levels, especially during the later stages of gestation. This study underscores the necessity for pregnancy-specific reference ranges to prevent the misdiagnosis of coagulation disorders in expectant mothers.

Keywords: Fibrin Degradation Products, Pregnancy, COVID-19 Vaccination, Coagulation, Hypercoagulability, Trimester Analysis, Maternal Safety, D-dimer.

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Introduction

Hemostasis During Pregnancy

Pregnancy causes a complex modification in the maternal haemostatic system.[1] This encompasses the physiological adjustments required to address homeostatic obstacles during delivery.[1] During the initial trimester, pregnancy correlates with elevated levels of various coagulation factors, such as fibrinogen (factor I), factor VII, factor VIII, factor IX, and factor X.[2,3] Moreover, there is a reduction in anticoagulant proteins such as protein S and a decline in fibrinolytic activity. These intricate modifications modify the haemostatic equilibrium towards a prothrombotic or hypercoagulable condition, hence markedly elevating the risk of venous thromboembolism (VTE) throughout pregnancy and the postpartum phase.[4] The incidence of venous thromboembolism (VTE) in pregnant women is approximated to be quintuple that of non-pregnant women within the same age cohort.[5]

This physiological hypercoagulability serves as a protective mechanism that prevents excessive haemorrhage during labour and the postpartum phase. The medical assessment of thrombosis situations during pregnancy presents significant hurdles that complicate the interpretation of coagulation marker test results. Comprehensive study is required to delineate the typical coagulation marker patterns throughout various trimesters, which will aid in differentiating normal pregnancy changes from pathological disorders such as disseminated intravascular coagulation, preeclampsia, and placental abruption.[6]

Fibrin Degradation Products Formation During Coagulation Process

The disintegration of fibrin clots yields residual molecules known as fibrin degradation products (FDPs). Following the formation of fibrin by thrombin's cleavage of fibrinogen, the fibrinolytic pathway degrades the fibrin, yielding fibrin degradation products (FDPs) that subsequently enter the bloodstream.[7] D-dimer is the most widely utilised clinical marker derived from FDPs exists as D-dimer.[8] D-dimer serves as a marker for both fibrinolysis and coagulation activation, reflecting the ongoing turnover of fibrin.[8]

D-dimer exists at very low levels when the body maintains its normal state. Nevertheless, D-dimer levels together with other FDPs dramatically increase when coagulation rates become elevated because of pregnancy, surgery, inflammation, trauma, or thromboembolic disease.[9] During pregnancy, D-dimer levels increase as gestational age advances but typically exceed the non-pregnancy diagnostic criteria.[10] The elevated risk for coagulation stems from improved fibrinolysis together with enhanced thrombin activity.[8] The clinical assessment of D-dimer remains challenging because similar elevations occur both during normal pregnancy periods and in pathological conditions such as VTE or preeclampsia.[4]

FDPs as Biomarkers of Coagulation Activation

FDPs serves as an established biomarker for recognizing and tracking thrombotic situations.[8] It is a diagnostic tool for deep VTE as well as pulmonary embolism and disseminated intravascular coagulation. Elevated FDPs in obstetric practice function as early indicators for abnormal coagulation states and three adverse pregnancy conditions: intrauterine growth restriction, placental abruption, and preeclampsia.[3,4,6]

Research studies demonstrate that FDPs tend to rise after the first trimester, since their median values increase from 0.5 µg/mL during the first trimester to greater than 1.5 µg/mL during the third trimester.[11-13] Whereas, the recent laboratory standards for reference values exhibit disagreements between facilities, yet medical guidelines urge healthcare providers to exercise caution when relying on D-dimer tests to exclude VTE during pregnancy unless accompanied by clinical assessment and imaging findings.[14]

The assessment of FDPs helps to monitor coagulation pathway activation. The combination of elevated levels correlates with systemic inflammation and endothelial dysfunction and immune activation and these processes help explain both typical and irregular pregnancy transformations.[15]

Effect of COVID-19 Vaccination on Coagulation

The COVID-19 pandemic required prompt and rapid vaccination development and mass distribution to reduce the prevalence of the virus to reduce disease problems. Therefore, vaccine, including mRNA vaccines (Pfizer-BioNTech and Moderna) and adenoviral vector-based vaccines (AstraZeneca and Johnson & Johnson), which health authorities distributed worldwide, also to expectant mothers.[16] Post-licensure surveillance studies now demonstrated the safety along with effectiveness of COVID-19 vaccines for pregnant women although trials excluded this population during the initial stages.[17]

Reports of unusual fibrin clots occurring after receiving adenoviral vector-based vaccines initially was worrying about vaccine-induced thrombotic thrombocytopenia (VITT).[18] The development of platelet-activating antibodies against platelet factor 4 (PF4) leads to thrombosis combined with thrombocytopenia, defining the condition known as VITT.[18] The extremely small number of recorded cases triggered scientists to evaluate how COVID-19 vaccines affect blood clotting systems.[19] Studies evaluated that COVID-19 vaccines could lead to brief coagulation issues, which might cause increased levels of FDPs. Post-vaccination assessments show FDPs elevations mostly after the first dosage but research indicates this happens because of immune system inflammatory responses which do not signify actual thrombosis development.[19] The mRNA vaccines exert minimal influence on blood coagulation functions while demonstrating no additional threat for pregnant women to suffer thrombotic issues.[20]

The physiologic condition of pregnancy maintains

its own built-in risk to trigger blood clots although it remains distinct from other states. The literature about the relationship between COVID-19 vaccination and FDP biomarkers is required to conduct risk assessments and provide vaccine counseling and clinical management to patients.

The FDP levels increase during pregnancy, there is a lack of trimester-specific data post-COVID-19 vaccination. Most current studies report FDP values in the general population or non-pregnant adults, with limited data stratified by pregnancy status or gestational age. Moreover, comparative analyses of FDP levels in vaccinated pregnant women versus non-pregnant counterparts are scarce. Such data are essential to accurately contextualize FDP elevations, which could lead to unnecessary interventions or misdiagnosis of thrombotic conditions. The present study aims to evaluate trimester-specific FDP levels in uncomplicated pregnancies following COVID-19 vaccination and comparing them to those in age-matched non-pregnant vaccinated women.

Methodology

Study Design Population and Grouping

A cross-sectional study at Al Azhar University Hospitals will be conducted from June 2024 to March 2025, with a population of n=160 women divided evenly into four groups: first trimester (n=40), second trimester (n=40), third trimester (n=40), and non- pregnant controls (n=40). The individuals were paired by age and recruited in succession. At the time of FDP assessment, the immunisation status of the patients was documented, revealing that 120 were vaccinated (75%) and 40 were unvaccinated (25%). All immunised individuals completed the whole vaccination regimen prior to becoming pregnant. The exclusion criteria comprised chronic illnesses, autoimmune diseases, known coagulopathies, anticoagulant usage, or other infections.

Ethical Approval and Consent

Ethical approval was secured from the Al Azhar Faculty of Medicine Ethics Committee, and all subjects provided signed informed consent prior to data collection.

Data Collection and Variables

FDP concentrations were quantified with an automated immunoturbidimetric technique. The principal outcome was the concentration of FDP. The COVID-19 vaccination status was encoded as a binary variable (Yes = 1, No = 0), whereas pregnancy status was classified as an ordinal variable (1 = first trimester, 2 = second trimester, 3 = third trimester, and 4 = non-pregnant).

Data Handling and Statistical Analysis

Data were collected and analysed with the Statistical Package for Social Sciences (SPSS Version 26). The normality of the major variables was evaluated utilising the Shapiro-Wilk and Kolmogorov-Smirnov tests, in conjunction with Q-Q plots and boxplots. Non-parametric procedures were employed due to the absence of normal distribution of FDPs, utilising the Kruskal-Wallis test for trimester comparisons, the Mann-Whitney U test for inter-group vaccination comparisons, and Spearman's rho correlation to evaluate connections among variables. Statistical significance was established at $p < 0.05$, and confidence intervals (CI) were computed at 95%.

Results

Immunoturbidimetric Assay

Sample Characteristics and Completeness

All 160 participants submitted comprehensive data without any omissions. The population was uniformly distributed throughout four gestational groups. One hundred twenty individuals (75%) reported receiving the COVID-19 vaccine.

Descriptive Statistics of FDPs and Covariates

The average FDP level was 1.31 ± 0.078, with a range of 0.01 to 5.20 and an interquartile range (IQR) of 1.47. The 95% confidence interval for the mean FDP ranged from 1.15 to 1.46. Significantly, severe FDP levels ≥ 4.2 were recorded in certain third-trimester subjects, albeit in the absence of clinical indications of thrombosis.

The mean COVID-19 vaccination status (binary) was 0.75 ± 0.434, with a 95% confidence interval of 1 to 0.25. The mean pregnancy status (ordinal, 1–4) was 2.50 ± 1.122, with a 95% confidence interval ranging from 1.25 to 4.

Table 1: Descriptive Statistics of FDPs and COVID Vaccination.

	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles 25th
FDPs	160	1.3059	.98140	.01	5.20	.4250
Covid vaccination	160	.75	.434	0	1	.25
Status	160	2.50	1.122	1	4	1.25

Distribution and Normality

Normality testing indicated substantial variance for all variables ($p < 0.001$). Q-Q plots and stem-and-leaf diagrams indicated a right-skewed distribution for FDPs, predominantly concentrated between 1.0 and 2.0. High outliers (>4.0) were infrequent but anticipated due to late gestation physiology. As shown in Figure 1.

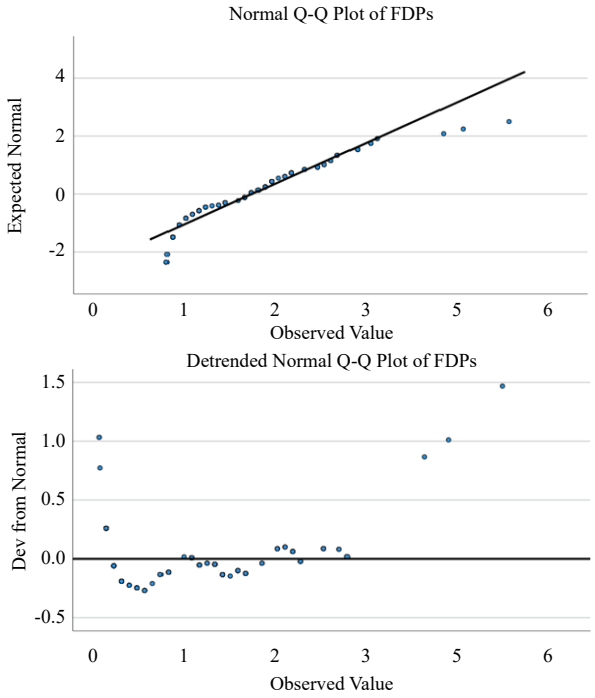

Figure 1: Normal and De trended Normal Q-Q plots of FDPs.

Trimester Comparison of FDP Levels

The Kruskal-Wallis test indicated substantial variations in FDP levels among gestational stages (H = 98.554, df = 3, $p < 0.001$). The mean rank FDP values increased between trimesters: first trimester (74.71), second trimester (110.09), third trimester (113.76), and non-pregnant (23.44), as illustrated in Table 2, Figure 2, and Figure 3. The data validate a gestational-age dependent increase in FDP levels, consistent with established physiological hypercoagulability during pregnancy.

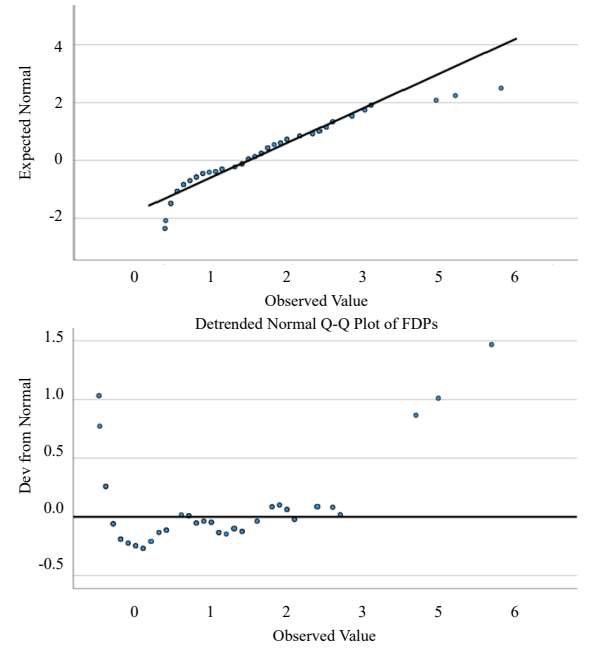

Figure 2: Normal and Detrended normal Q-Q plot of FDPs.

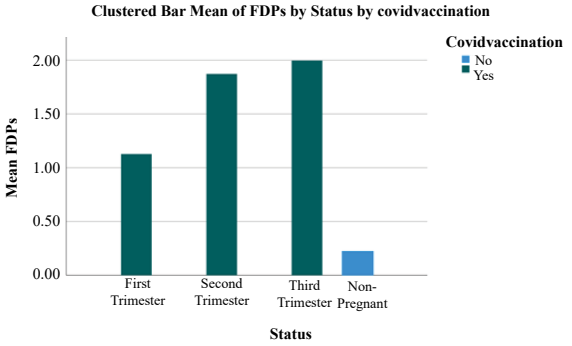

Figure 3: Clustered Bar Mean of FDPs by Status by COVID Vaccination.

Table 2: The Four Groups (ranks) of FDPs and COVID Vaccination.

Ranks			
	Status	N	Mean Rank
FDPs	First Trimester	40	74.71
	Second Trimester	40	110.09
	Third Trimester	40	113.76
	Non-Pregnant	40	23.44
	Total	160	
Covid vaccination	First Trimester	40	100.50
	Second Trimester	40	100.50
	Third Trimester	40	100.50
	Non-Pregnant	40	20.50
	Total	160	

Effect of COVID-19 Vaccination on FDPs

The Mann-Whitney U test indicated significantly elevated FDP levels in vaccinated individuals (U = 117.5, Z = -9.009, $p < 0.001$), as illustrated in Table 3 and Figure 4. Vaccinated women exhibited a mean FDP rank of 99.52, whereas unvaccinated women had a rank of 23.44, signifying a substantial post-vaccination increase that remained within anticipated physiological limits.

Table 3: Mann-Whitney U test: FDPs level in Vaccinated Participants.

	Covid Vaccination	N	Mean Rank	Sum of Ranks
FDPs	No	40	23.44	937.50
	Yes	120	99.52	11942.50
	Total	160		

Correlation Analysis

The Spearman's rho analysis (Table 4) indicated a robust positive connection between FDPs and immunisation ($\rho = 0.714$, $p < 0.001$). A moderate negative connection exists between FDPs and pregnancy status ($\rho = -0.364$, $p < 0.001$). An intense inverse association exists between vaccination and the pregnancy group ($\rho = -0.775$, $p < 0.001$), primarily attributable to non-pregnant controls exhibiting reduced immunisation rates. The data indicate that vaccination correlates with slight increases in FDP, particularly noticeable during mid- and late-pregnancy, although remaining within physiological limits.

Table 4: Spearman's Correlation of FDPs and COVID Vaccination Correlations.

			FDPs	Covid vaccination	Status
Spearman's rho	FDPs	Correlation Coefficient	1.000	.714**	-.364**
		Sig. (2-tailed)	.	.000	.000
		N	160	160	160
	Covid vaccination	Correlation Coefficient	.714**	1.000	-.775**
		Sig. (2-tailed)	.000	.	.000
		N	160	160	160
	Status	Correlation Coefficient	-.364**	-.775**	1.000
		Sig. (2-tailed)	.000	.000	.
		N	160	160	160

Discussion

The current study's findings demonstrate that FDP levels vary during different pregnancy stages in women who have been vaccinated against COVID-19, even though this topic has been previously examined in published medical research. Moreover, the results indicate that FDP levels increase during pregnancy, irrespective of the woman's vaccination status regarding COVID-19. This research significantly enhances our understanding and provides evidence-based insights into coagulation markers in pregnant individuals who have received vaccinations.

Thrombotic disorders lead to an elevation in fibrin degradation products (FDPs) due to the breakdown of fibrin clots. During pregnancy, especially in the third trimester, there is a natural rise in FDP levels that surpasses the normal thresholds observed in non-pregnant individuals. Research indicated that 64% of women with preeclampsia exhibited increased FDP levels (>5 µg/mL), while healthy non-pregnant women consistently kept their FDP levels below this threshold.[21] Whereas a study showed positive FDP (≥ 10 µg/dL) and D-dimer (≥ 2 µg/dL), the levels were extremely high due to streptococcal infections during pregnancy.[22] Another study showed that the FDP reference interval for first-time delivery was <9.28 mg/L, whereas multipregnant women's level was <10.52 mg/L (ages 18–34) and <11.72 mg/L (ages 35–45), underscoring the importance of considering maternal age and parity when interpreting FDP levels in late pregnancy.[23] The studies conducted indicate that the value of FDP molecules is positively correlated with the number of pregnancies and the age of the individual. Additionally, the challenge posed by laboratory detection errors is significant for healthcare providers. As a result, the current research aims to furnish vital information for the development of reference tests for FDPs that are based on pregnancy stages, thereby improving clinical diagnosis and minimizing patient distress.

It is reported that a pregnant women become more likely to form blood clots because their bodies increase procoagulant factors but suppress fibrinolysis while markers including D-dimer and FDPs reach elevated levels.[6] It is due to significant homeostatic alteration during pregnancy second and third trimesters to maintain blood control at birth. The measured FDP levels rose progressively from the first to the third trimester independently of vaccination status. A temporary increase in D-dimer levels occurred after vaccine administration and then returned to normal.[24] In vaccinated participants, the current study showed a detection of increased FDPs while no actual clinical abnormalities were detected. A study demonstrated that mRNA COVID-19 vaccines maintained safe clinical conditions for pregnant women by not causing more thrombotic complications.[19] The activation of the immune system due to the vaccine led to transient modifications in hemostatic balance, but no enduring harmful laboratory results were found, highlighting the need for future studies on immunity during pregnancy.

The current results showed difference in mRNA vaccinated patient. The previous studies reported that the mRNA-based COVID-19 vaccines prove highly safe for the general population and pregnant individuals.[25] In contrast, a study showed that it highly effective during pregnancy.[26] Studies show that post-vaccination a temporary rise occurs in coagulation marker levels.[27] In this context, a study showed that healthy adults developed minor increases in D-dimer levels because their immune system reacted after vaccination.[23] A study showed that coagulation markers briefly elevated but not accompanied by clinical thrombosis events.[28] The research by Liang et al. demonstrated that vaccination did not lead to noteworthy changes in coagulation marker results including D-dimer in healthy non-pregnant individuals.[29] The conflicting data results may stem from dissimilar population traits as well as variations in sampling timing following vaccines together with the fact that their study participants did not experience pregnancy-related alterations in hemostatic functions. The discussion about vaccine and pregnancy effects on coagulation becomes more complex because this study showed that pregnancy independently produces profile changes, which vaccination tends to augment lightly yet produces no concerning clinical symptoms.

The results of this research align with previous observations indicating that vaccinated pregnant women showed notably higher levels of FDP, although these increases remained within the expected physiological ranges for late pregnancy. Notably, none of the participants experienced any clinically significant thrombotic events, which underscores the hematological safety of vaccination during pregnancy. Additionally, this study supports the prevailing recommendations from prominent health organizations, such as the American College of Obstetricians and

Gynecologists (ACOG) and the World Health Organization (WHO), both of which endorse COVID-19 vaccination for pregnant individuals. By confirming the lack of thrombotic incidents and the presence of physiological FDP increases, our findings advocate for the continued use of the vaccine while promoting careful consideration of laboratory results in clinical settings.

Limitations

The cross-sectional research methodology precludes the measurement of fluctuations in FDP levels that transpire before and after immunisation within the same individuals. The analysis omitted distinct categories related to vaccine type, dosage, and post-vaccination interval, despite the potential for these factors to influence FDP data. The study exclusively focused on low-risk pregnancies, so omitting physiological alterations associated with problematic pregnancies, such as preeclampsia and thrombophilia. Our analysis excludes measures of D-dimer and platelet count in conjunction with fibrinogen, which could have offered a more comprehensive assessment of the patient's coagulation state. The specific vaccine type and dosage were not indicated; however, the completion history of the Covid-19 immunisation doses was documented irrespective of the vaccine type or dosage.

Conclusion

This study analyses FDP concentrations during pregnancy trimesters in vaccinated women, comparing them with non-pregnant individuals. The research indicates that biological alterations in FDPs transpire during pregnancy and demonstrates slight significant increases in measurements from vaccinated individuals. Moreover, the findings indicated that the observed changes did not reflect clinical levels of thrombosis while being within the medical guidelines for pregnant patients. Research indicates the safe administration of mRNA COVID-19 vaccines during pregnancy, which bolsters universal immunisation initiatives; nonetheless, it necessitates obstetric practitioners to comprehend the usual coagulation alterations that occur during pregnancy. The study has built a framework to support risk-aware healthcare decisions while highlighting the necessity for data unique to pregnancy-related illnesses to inform global immunisation strategies.

Future Perspectives

Multicenter studies are necessary to examine FDP alongside alterations in coagulation indicators from pregnancy to immunisation and postpartum recovery. The research findings might achieve more application by examining high-risk obstetric patients in conjunction with both vaccine kinds and dosage level assessments. Investigating cellular and molecular immunologic profiling might assist scientists in comprehending how immunisations alter pregnancy-associated coagulation activity at the cellular level. Progressive research must develop and validate precise reference ranges for FDPs and D-dimer across each trimester of pregnancy.

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Authors' Contributions

All authors contributed to the study, encompassing study conception and design, data collection, analysis and interpretation of results, draft manuscript, reviewed and approved the final version of the manuscript.

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Statement of Ethics

The study was conducted according to ethical standards, including clearance from the local health authorities. The patient's records were kept confidential, and all the procedures followed the institutional and national ethical guidelines.

Conflict of Interest

The authors declare no conflict of interest.

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