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**Original Research Article**

# COVID-19 infection-associated coagulopathy and its association with adverse outcomes in Indian gravidas: a prospective analysis

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## ABSTRACT

**Background:** Objective of the study was the determination of trends of coagulation parameters and association between pregnant women with COVID-19 infection with adverse outcomes.
**Methods:** Design of the study was a prospective observational study. The study was conducted at the Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi. A total of 142 pregnant women with confirmed COVID-19 infection were recruited and studied prospectively between May 2020 and April 2021. Trends of coagulation parameters were compared in groups divided based on the adverse outcomes. 11 patients had adverse outcomes which included ICU admission or mortality. There were no adverse outcomes in the remaining 131 patients.
**Results:** The comparison of trends of coagulation parameters in both groups was studied. D-dimer and INR values were significantly higher, while fibrinogen level was significantly lower in COVID-19 subjects with adverse maternal outcomes than in those in which adverse maternal outcomes were not present ($p<0.05$). No significant difference was observed in other coagulation parameters like APTT.
**Conclusions:** Universal screening of coagulation parameters of all pregnant women with COVID-19 can be considered because of the association of adverse maternal outcomes with deranged D dimer and fibrinogen in our study.

**Keywords:** COVID-19, Pregnancy, Coagulopathy, D-dimer

## INTRODUCTION

The global pandemic caused by the novel coronavirus, officially named severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), which results in Coronavirus disease 2019 (COVID-19), originated in Wuhan, China, towards the end of 2019.[1] As of the current date, 09 October 2023, it has affected a staggering 696,314,799 individuals and tragically claimed the lives of 6,923,950 people, with daily increases in these numbers.

These viruses have the potential to impact various bodily systems, including the respiratory, intestinal, hepatic, and nervous systems, often resulting in severe outcomes such as acute respiratory distress syndrome (ARDS), multi-organ disease (MOD), and, in severe cases, fatality.[2-4] The inflammation associated with viral infection can predispose individuals to prothrombotic states.[5] Global literature affirms that infection rates during pregnancy do not significantly differ from those outside of pregnancy.

Research has demonstrated that coronavirus infections, such as MERS-CoV and SARS-CoV-1, can induce both systemic and intra-alveolar fibrin clots in animals and humans experiencing severe respiratory illness.[6] Preliminary reports on COVID-19 outcomes indicate that infected patients frequently exhibit thrombocytopenia (36.2%) and elevated D-dimer levels (46.4%). These rates escalate in patients with severe COVID-19 disease (57.7% and 59.6%, respectively). Excessive activation of the coagulation cascade and platelets can elucidate these occurrences. Viral infections prompt a systemic inflammatory response, disrupting the balance between procoagulant and anticoagulant homeostatic mechanisms.[7] Various pathogenetic mechanisms are implicated,

including endothelial dysfunction, elevation of von Willebrand factor, Toll-like receptor activation, and activation of the tissue-factor pathway.[7-9]

Given that pregnancy inherently presents a prothrombotic state, pregnant individuals might face an elevated risk of coagulopathic and/or thromboembolic complications due to COVID-19. Therefore, it is imperative to closely monitor coagulation parameters in pregnant individuals who test positive for SARS-CoV-2, as abnormalities in these parameters could serve as indicators of a more severe COVID-19 infection. This might necessitate proactive admission and contemplation of delivery to stabilize the maternal condition.

Regrettably, there is a paucity of data regarding coagulation studies in pregnant individuals with COVID-19 infection. To address this gap, our study set out to investigate coagulation parameters in pregnant women afflicted with COVID-19. Our study, conducted during the pandemic, adopted an observational approach and focused on liver coagulation parameters, analyzing them in detail to comprehend the association between coagulation derangement and COVID-19 infection.

## METHODS

Over one year (01 May 2020 to 30 April 2021), a descriptive-analytical observational study was conducted in the Department of Obstetrics and Gynaecology, Maulana Azad Medical College, and Associated Lok Nayak Hospital, New Delhi. All antenatal women admitted with a COVID infection were recruited irrespective of gestation period. Patients already on anticoagulation therapy and diagnosed with cases of liver disease and exposure to hepatotoxic drugs over the past three months were excluded. Routine clinical history like age, parity, socioeconomic status, and any associated risk factors such as diabetes mellitus, hypothyroidism, hypertension, and previous liver dysfunction was obtained. Relevant findings of the general and systemic examination were recorded. Baseline investigations were sent (complete haemogram, kidney function tests, serum electrolytes, coagulation profile (PT, INR, aPTT, fibrinogen, D-dimer), and liver function tests along with all antenatal investigations. Repeat coagulation profile were done on Day 1, day 4, and the day before discharge (7 or 14 days). Coagulation parameter trends were compared in groups based on the presence and absence of adverse outcomes. Adverse outcomes in the study included ICU admission and death. ICU admission criteria included study subjects who required mechanical ventilation or had a fraction of inspired oxygen ($FiO_2$) of at least 60% or more, shock identified by the use of vasopressor therapy, and elevated lactate levels (>2 mmol/l) despite adequate fluid resuscitation or failure of other organs. The results were analyzed using the Chi-square and Fisher's exact tests. A p value <0.05 was considered statistically significant. The anonymity and confidentiality of the participants were maintained throughout the study. Data was collected from the existing records of the patients available in the public domain.

## RESULTS

A total of 142 pregnant women with confirmed COVID-19 infection were recruited and studied prospectively between May 2020 and April 2021. The mean age of the study subjects was 27.31±4.41 years (Table 1). Trends of coagulation parameters were compared in groups divided based on the adverse outcomes. 11 patients had adverse outcomes which included ICU admission or mortality. There were no adverse outcomes in the remaining 131 patients. The comparison of trends of coagulation parameters in both groups was studied. D-dimer and INR values were found significantly higher, in COVID-19 subjects with adverse maternal outcomes than those study subjects in which no adverse maternal outcomes were present (p<0.05).

**Table 1: Sociodemographic profile of study subjects (n=142).**

| Variables | Frequency |
|---|---|
| **Age group (years)** | |
| 18-25 | 53 |
| 26-30 | 61 |
| 31-35 | 25 |
| >35 | 3 |
| Mean age | 27.31±4.41 |
| **Socioeconomic status** | |
| Upper middle | 30 |
| Middle | 57 |
| Lower middle | 55 |
| **Parity** | |
| Primi | 55 |
| Multi | 87 |
| **POG at admission (trimester)** | |
| 2nd | 2 |
| 3rd | 140 |

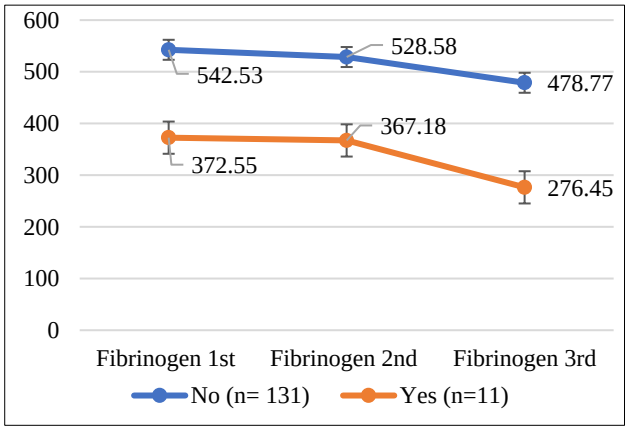


**Figure 1: Trend of fibrinogen level in COVID-19 subjects with and without adverse maternal outcome.**

Also fibrinogen level was significantly lower in patients with adverse outcomes compared to the ones who didn't have any adverse outcome. No significant difference was observed in other coagulation parameters like APTT.

Interestingly, an increasing trend was observed in D-dimer values while a decreasing trend was observed in fibrinogen values in the group with adverse maternal outcomes compared with the group with no adverse outcomes.

**Table 2: Trends of coagulation parameter and its association with adverse maternal outcome (n=11).**

| Parameters | Adverse maternal outcome | | P value |
|---|---|---|---|
| | No (n=131) | Yes (n=11) | |
| **INR** | | | |
| 1st | 0.848±0.140 | 1.055±0.497 | 0.36 |
| 2nd | 0.874±0.099 | 1.210±0.833 | 0.01 |
| 3rd | 0.924±0.173 | 1.424±1.190 | <0.01 |
| **D-Dimer** | | | |
| 1st | 658 (442-1075) | 1247 (1160-3266) | <0.01 |
| 2nd | 789 (457-1206) | 3436 (1490-5141) | <0.001 |
| 3rd | 764 (550-1346) | >5000 (867 to >5500) | <0.01 |
| **Fibrinogen (mg/dl)** | | | |
| Fibrinogen 1st | 542.53±156.78 | 372.55±124.79 | <0.01 |
| Fibrinogen 2nd | 528.58±160.70 | 367.18±185.47 | 0.01 |
| Fibrinogen 3rd | 478.77±181.38 | 276.45±139.55 | <0.01 |
| **APTT** | | | |
| 1st | 25.37±4.40 | 32.44±9.56 | 0.02 |
| 2nd | 29.58±7.64 | 37.93±14.79 | 0.15 |
| 3rd | 35.51±12.05 | 44.03±12.43 | 0.02 |

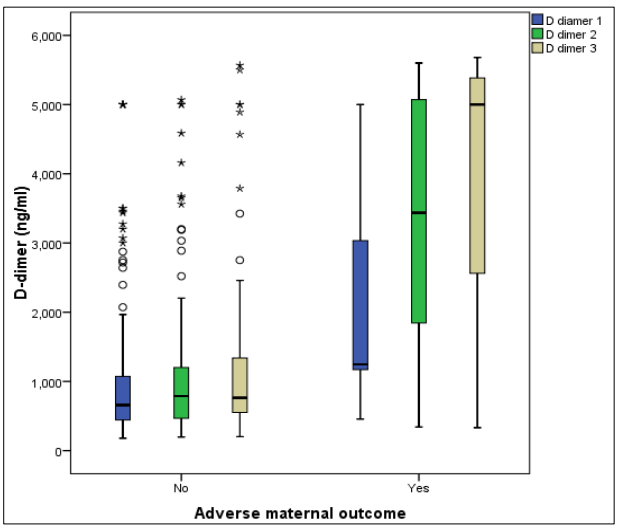


**Figure 2: Trend of D dimer level in COVID-19 subjects with and without adverse maternal outcome.**

## DISCUSSION

In obstetric patients, interpretation of coagulation tests and possible abnormality is even more challenging as pregnancy-induced coagulation changes confound them. Pregnancy and COVID-19 can both lead to an increase in blood coagulation within the body.[13] In normal pregnancy, fibrinogen concentration and D-dimer values increase, and both activated partial thromboplastin time (APTT) and prothrombin time are shorter due to the increase of the plasma concentration of most coagulation factors. With COVID-19 infection, additional coagulation changes may occur, which may mirror the disease severity. An increase in D-dimer concentrations has been observed and prolongation of both APTT and PT, the latter leading to an increase in international normalized ratio (INR) values. Because pregnancy-induced increases in coagulation factors confound these changes, laboratory results may not initially appear to be abnormal (i.e., falsely high as compared to non-pregnant values) Preliminary reports on COVID-19 pandemic outcomes have shown that infected patients may have elevated D-dimer (46.4%) while these rates are even higher in patients with severe COVID-19 disease (57.7% and 59.6%, respectively). Elevated D-dimer levels might correlate with an unfavorable outcome in COVID-19.[14] Nevertheless, there has been limited exploration of this aspect in pregnant individuals."

Elevated D-dimer can be explained by the excessive activation of the coagulation cascade. In our study, D dimers were significantly elevated in patients with adverse outcomes. Viral infections elicit the systemic inflammatory response and cause an imbalance between procoagulant and anticoagulant homeostatic mechanisms.[6] Multiple pathogenetic mechanisms are involved, including endothelial dysfunction, von Willebrand factor elevation, Toll-like receptor activation, and tissue-factor pathway activation.[6-8] Furthermore, during the H1N1 viral pneumonia outbreak, previous work demonstrated that elevations in d-dimer levels suggest an increased risk of thrombosis.[10] These investigations in SARS-CoV-2-positive pregnant women are vital, as their derangement may signal a more severe COVID-19 infection and may warrant pre-emptive admission and consideration of delivery to achieve maternal stabilization.

To date, there is scarce data to report on COVID-19 accurately- associated coagulation changes in obstetric patients and identify possible mechanisms for the observed alterations. In these cases, coagulation factor concentrations are often abnormally low (less than 100% and often in the range of 40–60%), and changes seem to occur in both "intrinsic" and "extrinsic" pathways. In the rare cases in which circulating anticoagulant antibodies were assessed, they were not found in the plasma of these pregnant women. In a report on three non-pregnant patients with severe COVID-19 infection, a primary coagulopathic state was observed with thrombocytopenia, lengthened TT, and highly increased D-dimer concentrations.[11] Taken together, data obtained in

pregnant and non-pregnant patients suggest that the underlying pathophysiology resulting in abnormal laboratory values is likely related to a (compensated) state of intravascular coagulation (DIC).

Hypercoagulability increases morbidity by increasing thromboembolic events, which may occur both during and after pregnancy. In a systematic review by Juliette Servante et al for case reports and a series of pregnant women between September 2019 and June 2020 with a diagnosis of COVID-19.[12] Information on coagulopathy based on abnormal coagulation test results or clinical evidence of DIC, and arterial or venous thrombosis, was extracted using a standard form. One thousand sixty-three women met the inclusion criteria, of which three (0.28, 95% CI 0.0 to 0.6) had arterial and/or venous thrombosis, seven (0.66, 95% CI 0.17 to 1.1) had DIC, and a further three (0.28, 95% CI 0.0 to 0.6) had coagulopathy without meeting the definition of DIC. Five hundred and thirty-seven women (56%) had been reported as having given birth and 426 (40%) as having an ongoing pregnancy. There were 17 (1.6, 95% CI 0.85 to 2.3) maternal deaths in which DIC was reported as a factor in two.

"Individuals diagnosed with COVID-19 are advised to receive thromboembolic prophylaxis due to the coagulopathy induced by the disease".[15] Prophylaxis becomes especially crucial since pregnancy alone can induce coagulation. This aspect should be taken into account in conjunction with the patient's condition".[16] As per the guidelines from the American Society of Hematology, individuals with elevated D-dimer levels who have COVID-19 should be provided with anticoagulant treatment.[17] "Numerous studies indicate that D-dimer levels are elevated in pregnant women with COVID-19, yet distinguishing this increase can be challenging due to the natural elevation of D-dimer during pregnancy.[18-19] "In a case-control study conducted by Hazari et al, it was noted that D-dimer levels were elevated in pregnant individuals with COVID-19, with a comparison made against COVID-19 patients who were not pregnant".[20]

Also, there is no literature comparing trends of parameters in COVID-19-infected gravidas with adverse outcomes.

## CONCLUSION

Pregnancy in itself increases the thromboembolic risk, which is even greater during the postpartum period. Due to additional coagulation changes induced by COVID-19 infection. Hence monitoring coagulation parameters is of utmost importance in COVID-infected gravidas for better prediction of outcomes and subsequent management.

Here, we highlight trends of coagulation parameters and a possible link between maternal COVID-19 infection and rapid maternal deterioration with progressive coagulopathy.

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## REFERENCES

1. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
2. Johns Hopkins University. Johns Hopkins University Coronavirus Resource Center. Available at: https://coronavirus.jhu.edu/map.html. Accessed on 23 April 2020.
3. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet. 2003;361(9366):1319-25.
4. Kupferschmidt K. Researchers scramble to understand camel connection to MERS[J]. Science. 2013;341(6147):702.
5. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019[J]. N Engl J Med. 2020;382(8):727-33.
6. Giannis D, Ziogas IA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol. 2020;127:104362.
7. Subramaniam S, Scharrer I. Procoagulant activity during viral infections. Front Biosci (Landmark Ed). 2018;23:1060-81.
8. Van Gorp EC, Suharti C, Ten Cate H, Dolmans WM, van der Meer JW, Ten Cate JW, et al. Infectious diseases and coagulation disorders. J Infect Dis. 1999;180(1):176-86.
9. Key NS, Vercellotti GM, Winkelmann JC, Moldow CF, Goodman JL, Esmon NL, et al. Infection of vascular endothelial cells with herpes simplex virus enhances tissue factor activity and reduces thrombomodulin expression. Proc Natl Acad Sci. 1990;87:7095-9.
10. Wang ZF, Su F, Lin XJ, Dai B, Kong LF, Zhao HW, et al. Serum D-dimer changes and prognostic implication in 2009 novel influenza A(H1N1). Thromb Res. 2011;127(3):198-201.
11. Vlachodimitropoulou Koumoutsea E, Vivanti AJ, Shehata N, Benachi A, Le Gouez A, Desconclois C, et al. COVID-19 and acute coagulopathy in pregnancy. J Thromb Haemost. 2020;18(7):1648-52.
12. Servante J, Swallow G, Thornton JG, Myers B, Munireddy S, Malinowski AK, et al. Haemostatic and thrombo-embolic complications in pregnant women with COVID-19: a systematic review and critical analysis. BMC Pregnancy Childbirth. 2021;21(1):108.

13. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol. 2020;13(11):1265-75.
14. Long H, Nie L, Xiang X, Li H, Zhang X, Fu X, et al. D-Dimer and prothrombin time are the significant ındicators of severe COVID-19 and poor prognosis. Biomed Res Int. 2020;6159720.
15. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033-40.
16. Di Renzo GC, Giardina I. Coronavirus disease 2019 in pregnancy: consider thromboembolic disorders and thromboprophylaxis. Am J Obstet Gynecol. 2020;223(1):135.
17. Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv. 2021;5(3):872-88.
18. Pereira A, Cruz-Melguizo S, Adrien M, Fuentes L, Marin E, Perez-Medina T. Clinical course of coronavirus disease-2019 in pregnancy. Acta Obstet Gynecol Scand. 2020;99(7):839-47.
19. Shmakov RG, Prikhodko A, Polushkina E, Shmakova E, Pyregov A, Bychenko V, et al. Clinical course of novel COVID-19 infection in pregnant women. J Matern Fetal Neonatal Med. 2020;35(23):4431-7.
20. Hazari KS, Abdeldayem R, Paulose L, Kurien N, Almahloul Z, Mohammad H, et al. Covid-19 infection in pregnant women in dubai: a case-control study. BMC Pregnancy Childbirth. 2021;21(1):658.

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