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PROGNOSTIC UTILITY OF INFLAMMATORY COAGULATION BIOMARKERS IN COVID-19-POSITIVE PREGNANT WOMEN: A NARRATIVE REVIEW

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ABSTRACT

Pregnancy induces a proinflammatory and hypercoagulable state as part of its physiological adaptation, but the addition of COVID-19 significantly amplifies these changes, posing unique risks to maternal and fetal health. SARS-CoV-2 infection has been shown to disrupt endothelial function, promote cytokine release, and activate coagulation pathways creating a complex interplay between inflammation and thrombosis. In pregnant women, these effects may accelerate the development of complications such as preeclampsia, venous thromboembolism, and preterm birth, necessitating the identification of early biomarkers for risk stratification. This review explores the prognostic relevance of key inflammatory coagulation biomarkers, including D-dimer, fibrinogen, interleukin-6 (IL-6), C-reactive protein (CRP), and prothrombin time (PT), in COVID-19-positive pregnancies. Elevated levels or abnormal trends in these markers have been associated with severe disease progression, ICU admission, and poor obstetric outcomes. When interpreted alongside clinical parameters, these biomarkers may aid in the early identification of high-risk cases, enabling prompt interventions such as thromboprophylaxis, intensive monitoring, and timely delivery.

Keywords: *COVID-19, Pregnancy, Coagulation, Inflammatory Biomarkers, Prognosis*

Introduction

The global COVID-19 pandemic has placed unprecedented strain on healthcare systems and exposed vulnerable populations to heightened risks (1). Although most COVID-19 infections in pregnancy are mild or asymptomatic, a significant subset progresses to severe disease, leading to adverse maternal and neonatal outcomes (2). Understanding the biological markers that forecast such complications is essential for timely risk stratification and clinical intervention. Pregnancy is naturally characterized by a state of controlled systemic inflammation and hypercoagulability, intended to support placental development and prevent hemorrhage during delivery (3). These changes include elevated levels of fibrinogen, D-dimer, and proinflammatory cytokines, as well as decreased fibrinolytic activity (4). While these adaptations are typically well-regulated, they may be exacerbated in the presence of viral infections such as SARS-CoV-2, tipping the balance toward pathological inflammation and thrombosis (5). COVID-19 infection is known to activate a robust inflammatory response that includes the release of cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-a), which in turn drive endothelial dysfunction and coagulation abnormalities (6). In non-pregnant populations, this proinflammatory and prothrombotic environment has been strongly associated with complications such as acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), and multi-organ failure (7). In pregnant women, these effects are compounded by gestational changes and may result in preeclampsia, placental insufficiency, fetal distress, or even maternal mortality.

Inflammatory coagulation biomarkers have therefore gained attention as potential prognostic tools in COVID-19-positive pregnancies. Biomarkers such as D-dimer, fibrinogen, IL-6, C-reactive protein (CRP), prothrombin time (PT), and activated partial thromboplastin time (aPTT) offer insight into disease severity and the likelihood of complications. Elevated D-dimer and IL-6 levels have been frequently reported in pregnant women with severe COVID-19 and have correlated with poor outcomes (8). Yet, their interpretation in pregnancy requires caution, as physiological levels of these markers are already altered during gestation. The integration of biomarker monitoring into obstetric care has the potential to guide clinical decision-making, including the need for hospitalization, thromboprophylaxis, corticosteroid therapy, and delivery planning (9). For instance, a rapid rise in CRP or IL-6 may prompt clinicians to initiate early anti-inflammatory therapy, while elevated D-dimer levels may justify the use of low-molecular-weight heparin (10). However, the lack of pregnancy-specific reference ranges complicates the application of these biomarkers in routine care.

Furthermore, the dynamic nature of COVID-19 with emerging variants, evolving treatment protocols, and varying degrees of vaccination coverage adds complexity

to the prognostic utility of these markers: The COVID-19 pandemic caused by SARS-CoV-2 is associated with a lower fatality rate than its SARS and MERS counterparts. However, the rapid evolution of SARS-CoV-2 has given rise to multiple variants with varying pathogenicity and transmissibility, such as the Delta and Omicron variants. Individuals with advanced age or underlying comorbidities, including hypertension, diabetes and cardiovascular diseases, are at a higher risk of increased disease severity. Hence, this has resulted in an urgent need for the development of better therapeutic and preventive approaches. This review describes the origin and evolution of human coronaviruses, particularly SARS-CoV-2 and its variants as well as sub-variants. Risk factors that contribute to disease severity and the implications of co-infections are also considered. In addition, various antiviral strategies against COVID-19, including novel and repurposed antiviral drugs targeting viral and host proteins, as well as immunotherapeutic strategies, are discussed. We critically evaluate strategies of current and emerging vaccines against SARS-CoV-2 and their efficacy, including immune evasion by new variants and sub-variants. The impact of SARS-CoV-2 evolution on COVID-19 diagnostic testing is also examined. Collectively, global research and public health authorities, along with all sectors of society, need to better prepare against upcoming variants and future coronavirus outbreaks (11). It is also important to consider the heterogeneity in study populations, as racial, geographic, and socioeconomic factors influence both biomarker expression and COVID-19 outcomes. Therefore, contextual interpretation and individualized clinical judgment remain crucial. This review aims to synthesize the current evidence on the prognostic utility of inflammatory coagulation biomarkers in pregnant women with COVID-19. By examining the pathophysiological mechanisms underlying biomarker elevation, assessing clinical correlations, and addressing challenges in interpretation, we hope to provide a framework for the strategic use of these markers in optimizing maternal and fetal outcomes during the pandemic and beyond.

Aim

This narrative review aims to critically evaluate the prognostic utility of inflammatory coagulation biomarkers in pregnant women diagnosed with COVID-19. Specifically, it seeks to explore the pathophysiological interplay between inflammation and coagulation during pregnancy complicated by SARS-CoV-2 infection, highlight key biomarkers associated with disease severity and maternal-fetal outcomes, and discuss their potential role in guiding clinical decision-making and risk stratification. By synthesizing current evidence, the review intends to inform obstetric practice and support the development of standardized biomarker-based monitoring protocols for COVID-19-positive pregnancies.

Methods

This narrative review was conducted to synthesize current knowledge regarding the prognostic significance of

inflammatory coagulation biomarkers in pregnant women with confirmed COVID-19 infection. A comprehensive literature search was performed using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar, covering publications from January 2020 to June 2025. The search strategy utilized a combination of keywords and MeSH terms, including: *"COVID-19," "pregnancy," "inflammatory biomarkers," "coagulation," "D-dimer," "IL-6," "CRP," "fibrinogen," "prothrombin time,"* and *"maternal outcomes."* Inclusion criteria encompassed peer-reviewed original research articles, clinical trials, cohort studies, systematic reviews, meta-analyses, and relevant case series that reported on inflammatory or coagulation biomarkers in pregnant women with laboratory-confirmed SARS-CoV-2 infection. Articles not in English, those lacking full-text availability, or studies focusing exclusively on non-pregnant populations were excluded. Additional sources were identified through manual screening of reference lists and citation tracking of key publications.

The data were synthesized narratively, focusing on the clinical relevance, prognostic value, and limitations of each biomarker in the context of pregnancy. Particular attention was given to studies that reported associations between biomarker levels and disease severity, maternal morbidity, obstetric complications, or neonatal outcomes. Given the heterogeneity of study designs and outcome measures, no meta-analysis was performed. This approach allows for an integrative understanding of the evolving evidence base, emphasizing practical implications for obstetric care during the COVID-19 pandemic.

Pathophysiological Context: COVID-19, Inflammation, and Coagulation in Pregnancy

Pregnancy is a state of finely tuned immunological and hemostatic adaptation designed to support fetal development while protecting the mother (11). This adaptation involves a proinflammatory shift, particularly in early and late gestation, and a hypercoagulable state that increases the risk of thrombosis (12). These physiological changes include elevated fibrinogen and D-dimer levels, increased platelet activation, and reduced fibrinolysis. While essential for maintaining placental integrity and preparing for delivery, these alterations can predispose pregnant women to exaggerated responses when confronted with systemic infections, such as SARS-CoV-2 (13). COVID-19, caused by the SARS-CoV-2 virus, triggers a complex interplay between the immune and coagulation systems, often resulting in a "cytokine storm" and widespread endothelial injury (14). The virus gains entry via the ACE2 receptor, which is expressed in various maternal tissues including the placenta and vascular endothelium (15). This viral entry initiates a cascade of proinflammatory cytokine production, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), and interleukin-1β (IL-1β), which amplify systemic inflammation and disrupt endothelial integrity (16).

Endothelial dysfunction is central to COVID-19-associated coagulopathy.

Damaged endothelium exposes subendothelial tissue factor and von Willebrand factor, triggering platelet adhesion and thrombin generation (17) . This culminates in excessive clot formation and microvascular thrombosis key features of COVID-19-related complications (18). In pregnant women, this is superimposed on an already heightened thrombotic baseline, leading to an increased risk of venous thromboembolism (VTE), placental infarction, and preeclampsia-like syndromes (19). The immune-coagulation interface, also known as immunothrombosis, is further complicated by the maternal immune system's altered responsiveness during pregnancy (20). To prevent fetal rejection, pregnancy induces a form of immune tolerance that modulates the innate and adaptive immune responses (21). However, this balance may be disrupted by SARS-CoV-2 infection, resulting in either a blunted antiviral response or an exaggerated proinflammatory reaction—both of which can have detrimental consequences for the mother and fetus.

Elevated levels of inflammatory markers such as IL-6 and CRP, along with coagulation markers like D-dimer, fibrinogen, and prothrombin time (PT), reflect this intertwined pathological state (22). In severe cases, these markers indicate progression toward disseminated intravascular coagulation (DIC), multiorgan failure, and maternal mortality (3). Importantly, similar biomarker elevations can also result from normal pregnancy physiology, making differential interpretation crucial. Moreover, placental pathology in COVID-19-positive pregnancies often reveals features consistent with vascular malperfusion, thrombotic lesions, and chronic histiocytic intervillositis (23). These changes may stem from maternal coagulopathy and systemic inflammation, ultimately compromising placental function and fetal well-being. The resulting complications can include intrauterine growth restriction (IUGR), preterm labor, and stillbirth (Table 1).

Table 1: Pathophysiological Context: COVID-19, Inflammation, and Coagulation in Pregnancy

Aspect	Description	Implications in Pregnancy
COVID-19 Infection	SARS-CoV-2 virus infects respiratory epithelium, triggering innate and adaptive immune responses.	Increased vulnerability due to altered immunity; potential for severe respiratory illness in pregnant women.
Systemic Inflammation	Cytokine release syndrome with elevated IL-6, TNF-α, and other pro-inflammatory mediators.	Heightened inflammatory state may exacerbate pregnancy complications such as preeclampsia and preterm labor.
Endothelial Dysfunction	Viral invasion and cytokines disrupt endothelial integrity, leading to vascular inflammation and injury.	Placental vascular impairment; increased risk of fetal growth restriction and adverse perinatal outcomes.
Hypercoagulability	COVID-19 triggers activation of coagulation pathways, promoting thrombin generation and fibrin deposition.	Amplifies pregnancy-associated hypercoagulability; increased risk of venous thromboembolism and DIC.
Platelet Activation	Enhanced platelet aggregation and consumption contribute to microthrombi formation and coagulopathy.	Potential for placental thrombosis, contributing to miscarriage, stillbirth, and placental insufficiency.
Immunologic Adaptations in Pregnancy	Physiological shift toward anti-inflammatory (Th2) dominance and altered innate immunity.	May modulate the maternal response to COVID-19, influencing severity and biomarker profiles.
Maternal-Fetal Interface Impact	Inflammatory and thrombotic changes may disrupt placental barrier and fetal environment.	Increased risks of vertical transmission, fetal hypoxia, and adverse neonatal outcomes.

Key Inflammatory Coagulation Biomarkers in Focus

The diagnostic and prognostic utility of inflammatory coagulation biomarkers in COVID-19-positive pregnant women lies in their ability to reflect underlying immune activation, endothelial injury, and thrombotic risk. While the interpretation of these markers must be adapted to the unique physiology of pregnancy, several biomarkers have emerged as critical indicators of disease severity and maternal-fetal outcomes (Table 2). This section outlines the most studied and clinically relevant biomarkers in this context.

Table 2: Key Inflammatory Coagulation Biomarkers in Focus

Biomarker	Biological Role	Changes in COVID-19 Pregnancy	Prognostic Significance
D-dimer	Fibrin degradation	Elevated beyond pregnancy	Predicts venous

	product indicating clot formation and breakdown	baseline; correlates with disease severity and thrombotic risk	thromboembolism, preterm birth, and adverse outcomes
Interleukin-6 (IL-6)	Pro-inflammatory cytokine driving cytokine storm and immune activation	Markedly increased in severe COVID-19; associated with systemic inflammation	Indicates hyperinflammatory state and risk of clinical deterioration
C-reactive protein (CRP)	Acute-phase protein reflecting systemic inflammation	Elevated levels correlate with infection severity and maternal complications	Useful marker for monitoring inflammation and therapeutic response
Fibrinogen	Key coagulation factor involved in clot formation	Often elevated but may decrease in severe disease due to consumption	Low levels may indicate consumptive coagulopathy and poor prognosis
Platelet Count	Essential for hemostasis and clot formation	Thrombocytopenia reported in severe cases; platelet activation linked to microthrombosis	Decreased counts associate with increased risk of bleeding and worse outcomes

1. D-Dimer

D-dimer is a fibrin degradation product that indicates ongoing fibrinolysis and is widely used as a marker for thrombotic activity (24). In pregnancy, baseline D-dimer levels naturally increase due to physiological hypercoagulability, especially in the third trimester (25). However, in COVID-19-positive pregnant women, markedly elevated D-dimer levels often exceeding twice or thrice the expected gestational range have been associated with increased risk of venous thromboembolism (VTE), preeclampsia, intensive care unit (ICU) admission, and maternal mortality(26) . Serial monitoring of D-dimer trends, rather than relying on absolute values, may offer better prognostic insight in this population.

2. Fibrinogen

Fibrinogen levels are typically elevated in pregnancy as part of the normal hemostatic adaptation. However, in the setting of COVID-19, fibrinogen behaves in a biphasic manner initially increasing in mild or early disease due to acute-phase reactivity, and decreasing in severe disease as a result of consumption coagulopathy or disseminated intravascular coagulation (DIC) (26). A declining fibrinogen level in the face of worsening clinical status should raise concern for impending coagulopathy, especially when accompanied by thrombocytopenia or prolonged clotting times.

3. Interleukin-6 (IL-6)

IL-6 is a central mediator of the cytokine storm triggered by SARS-CoV-2 infection and plays a critical role in activating the coagulation cascade (6,27). Elevated IL-6 levels have been consistently associated with severe COVID-19, respiratory failure, and poor maternal outcomes. In pregnant women, high IL-6 concentrations have also been implicated in the development of preeclampsia-like syndromes and intrauterine inflammation (28). IL-6 serves as both a marker of disease severity and a potential therapeutic target in COVID-19, making it particularly valuable in prognostic assessments.

4. C-Reactive Protein (CRP)

CRP is a nonspecific acute-phase protein that reflects systemic inflammation. Its levels are moderately elevated during normal pregnancy but may rise significantly in the presence of infection or inflammation (29). In COVID-19-positive pregnant women, CRP levels correlate with viral load, disease progression, and the likelihood of complications such as chorioamnionitis, preterm labor, and fetal distress. CRP is easily accessible and cost-effective, making it a practical biomarker for frontline prognostication and monitoring (30).

5. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT)

Abnormalities in PT and aPTT serve as indicators of coagulation pathway disturbances. While PT may remain within normal limits in early or mild disease, its prolongation is a concerning sign of hepatic dysfunction or evolving DIC in severe COVID-19 (31). Likewise, aPTT may be prolonged due to consumption of clotting factors or the presence of lupus anticoagulant, which has been reported in some COVID-19 cases (32). In pregnant patients, derangements in PT/aPTT must be interpreted carefully and correlated with other clinical and laboratory findings to assess the risk of bleeding versus thrombosis.

Clinical Implications and Prognostic Value

The clinical implications of inflammatory coagulation biomarkers in COVID-19-positive pregnant women are far-reaching, particularly in guiding risk stratification, therapeutic decisions, and perinatal care (33). As pregnancy inherently alters immune and coagulation profiles, interpreting biomarker trends within a gestational context is essential to distinguish between physiological and pathological responses. Elevated levels of markers such as D-dimer, IL-6, CRP, and fibrinogen can serve as early indicators of clinical deterioration, facilitating timely escalation of care and minimizing preventable maternal-fetal complications (22,34). From a prognostic standpoint, these biomarkers have demonstrated strong associations with adverse outcomes including preeclampsia, preterm birth, placental insufficiency, fetal growth restriction, and stillbirth (35). For example, persistently high D-dimer levels or a sharp rise in IL-6 can signal heightened thrombo-inflammatory activity, warranting consideration for hospitalization, close fetal surveillance, and prophylactic anticoagulation. Moreover, elevated CRP and prolonged prothrombin time may portend systemic inflammation and potential hepatic involvement, both of which carry implications for maternal morbidity (36). Importantly, these biomarkers can aid in therapeutic decision-making by helping clinicians determine the need for interventions such as corticosteroids, low molecular weight heparin, or interleukin-6 inhibitors. In critically ill patients, real-time biomarker monitoring can support decisions regarding ICU transfer, timing of delivery, and neonatal preparedness. Additionally, the utility of these markers extends beyond acute management—they may help in identifying patients at risk for postpartum complications, including delayed

Challenges

While inflammatory coagulation biomarkers hold significant promise for prognostication in COVID-19-positive pregnant women, their clinical application is fraught with several challenges. One of the primary limitations is the lack of pregnancy-specific reference ranges for most biomarkers. Physiological elevations in markers such as D-dimer, fibrinogen, and CRP during normal gestation can obscure the differentiation between normal and pathological states. As a result, interpreting elevated values without gestational context may lead to over- or underestimation of clinical risk, potentially resulting in inappropriate interventions. Another major challenge lies in the heterogeneity of existing studies. Variations in study design, biomarker assay methods, gestational age at infection, severity of illness, and population demographics complicate the generalizability of findings. In many studies, the small sample sizes and lack of control groups further limit the strength of evidence. Additionally, there is inconsistency in the timing and frequency of biomarker measurement, which makes it difficult to establish reliable trends or thresholds for clinical decision-making (37). Resource limitations, particularly in low- and middle-income countries, pose a significant barrier to the widespread implementation of biomarker-guided care. Access to advanced laboratory tests such as IL-6 or D-dimer assays may be limited, and infrastructure constraints can delay timely testing and interpretation. This is especially concerning in regions where maternal mortality remains high and healthcare systems are already overburdened by the pandemic. Another challenge is the dynamic nature of COVID-19 itself. With evolving viral variants, changing vaccination status, and emerging treatments, the disease course and host response are not static. Biomarker behaviors may differ in vaccinated individuals or those infected with newer variants, making it difficult to establish universal cut-off points or protocols. Furthermore, comorbidities such as obesity, hypertension, and gestational diabetes—common in pregnancy—can independently influence inflammatory and coagulation markers, complicating risk assessment. There is an urgent need for longitudinal and prospective studies that evaluate the prognostic value of these biomarkers throughout pregnancy and into the postpartum period. Most current data are derived from retrospective or cross-sectional analyses, which cannot fully capture the dynamic interplay between inflammation, coagulation, and clinical outcomes over time.

Future Directions

The evolving landscape of COVID-19 in pregnancy necessitates ongoing research to refine the prognostic utility of inflammatory coagulation biomarkers and optimize maternal and fetal outcomes. Future studies should prioritize establishing gestation-specific reference ranges and validated cut-off values for key biomarkers such as D-dimer, IL-6, and fibrinogen. This will enable more accurate differentiation between physiological and pathological changes, improving clinical decision-making. Prospective, large-scale, multicenter cohort studies are needed to

evaluate the temporal dynamics of biomarker changes throughout pregnancy and the postpartum period. Such investigations can elucidate how biomarker trajectories correlate with disease severity, therapeutic response, and perinatal outcomes, providing a stronger evidence base for integrating these markers into clinical protocols. The development and validation of composite biomarker panels and risk scoring systems may enhance prognostic precision beyond single-marker analyses. Combining inflammatory and coagulation markers with clinical parameters, imaging findings, and maternal comorbidities could facilitate personalized risk stratification and guide tailored interventions, such as timing of delivery, anticoagulation strategies, or immunomodulatory therapies.

Advances in point-of-care testing and low-cost biomarker assays hold promise for expanding access in resource-limited settings, where the burden of maternal morbidity and mortality from COVID-19 remains disproportionately high. Investment in infrastructure and training to deploy these technologies will be essential to close equity gaps in maternal care. Additionally, the impact of COVID-19 vaccination and emerging viral variants on inflammatory coagulation profiles in pregnancy warrants urgent investigation. Understanding how immunization alters biomarker responses and clinical outcomes will inform updated guidelines and improve patient counseling. Research should explore the potential of these biomarkers to predict and monitor long-term sequelae in mothers and infants, such as post-COVID syndrome or developmental complications. Integrating biomarker data with longitudinal clinical follow-up could open new avenues for early intervention and supportive care.

Conclusion

Inflammatory coagulation biomarkers represent a promising frontier in the prognostic assessment of COVID-19-positive pregnant women. Despite the physiological complexities introduced by pregnancy, markers such as D-dimer, fibrinogen, IL-6, and CRP provide valuable insights into the evolving interplay between inflammation and coagulopathy that underpin disease severity and adverse maternal-fetal outcomes. Their dynamic monitoring can guide clinical decision-making, enabling timely interventions that improve both maternal and neonatal prognoses. However, the clinical utility of these biomarkers is currently limited by challenges including the lack of standardized pregnancy-specific reference ranges, variability in testing practices, and resource constraints—especially in low- and middle-income settings. Addressing these limitations through rigorous research, development of gestation-adjusted protocols, and equitable access to diagnostic tools is essential for translating biomarker data into meaningful improvements in care.

Conflicts of Interest

The authors declare no conflict of interest

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