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Review Article

Pathophysiology of COVID-19 in Pregnancy: A Critical Review

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ABSTRACT

COVID-19 infection during pregnancy presents a complex clinical scenario with potential implications for both maternal and neonatal health. This literature review examines the pathophysiological mechanisms underlying COVID-19 in pregnancy and its effects on the developing foetus and neonate. The infection is known to impact placenta, potentially leading to abnormalities in foetal development. Maternal immune responses, including cytokine storm and endothelial activation, contribute to the systemic inflammation observed in severe cases, which may result in adverse pregnancy outcomes such as preterm birth, preeclampsia and fetal growth restriction. Additionally, there is a risk of vertical transmission of the infection, although it appears to be rare. Neonates born to mothers with COVID-19 may experience respiratory complications and require NICU admission. Furthermore, the long-term consequences of COVID-19 infection during pregnancy on neonatal health and development, including the risk of multisystem inflammatory syndrome in child, are areas of ongoing research and requires further investigation. Understanding pathophysiology of these conditions during pregnancy is crucial for developing effective management strategies and improving maternal and neonatal outcomes. Present literature review aims to provide a comprehensive overview of the reported pathophysiological mechanisms of COVID-19 infection in pregnant women and their foetus, highlighting the need for continued research and surveillance to address the gaps in knowledge and inform clinical practice.

Key words: COVID-19, Inflammation, Vascular change, Thrombosis, Pregnancy.

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INTRODUCTION

The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has significantly impacted global health, with pregnant women and children emerging as vulnerable populations. Pregnant women undergo unique physiological changes that can alter their immune response and increase susceptibility to respiratory infections, including COVID-19.[1-4] Similarly, although children report less severe disease as compared to adults, they can still experience significant morbidity and mortality, especially when in presence of underlying health conditions. The pathophysiological mechanisms of COVID-19 infection in pregnant women and children primarily involve inflammation, vascular changes and thrombosis, which can lead to both short-term and long-term effects.[5]

COVID-19 triggers an inflammatory response characterized by the release of pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-alpha). This cytokine storm can result in tissue damage and organ dysfunction, particularly affecting the lungs and other vital organs.[6] In pregnant women, this inflammation can contribute to pregnancy complications, such as preterm birth and preeclampsia, while in children, it can lead to Multisystem Inflammatory Syndrome (MIS-C), a severe and potentially life-threatening condition.[7] COVID-19 also causes endothelial dysfunction and vascular inflammation, leading to impaired blood flow and an increased risk of thrombosis.[8] Pregnant women are already at an increased risk of venous thromboembolism due to changes in coagulation factors during pregnancy and COVID-19 can further exacerbate this risk.[9] Furthermore, COVID-19 is associated with a hypercoagulable state, increasing the risk of thrombosis in both pregnant women and children.[10] Thrombotic events can occur in the placenta, leading to placental insufficiency and fetal growth restriction.[11] In children, thrombosis can result in severe complications, such as stroke or myocardial infarction.[12]

Understanding these mechanisms is crucial for managing COVID-19 in pregnant women and children and minimizing its impact on maternal and fetal health. This literature review aims to delve into the pathophysiological mechanisms involving inflammation, vascular changes and thrombosis, elucidating

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their role in the manifestation and progression of COVID-19 in these vulnerable populations.

MATERIALS AND METHODS

We conducted this literature review to study the COVID-19 infection during pregnancy and its effects on the mother, fetus and involved pathophysiology. For this literature review we searched for relevant articles in English language, for key terms directing on, but not limited to, inflammation, thrombosis, vascular change, COVID-19, Pregnancy and Long-term effect of COVID-19 in pregnancy. The search was not restricted to any study design. All the studies with potential information regarding COVID-19 in pregnancy, pregnancy outcome in COVID-19, pathophysiology of pregnancy with COVID-19 infection were included. Research articles were screened and selected using PubMed, Google Scholar and Cochrane. The search method also looked through the articles' reference lists. The most relevant 21 articles in all were reviewed (Tables 1 and 2). We excluded duplicate studies from the final search.

INFLAMMATION

SARS-CoV-2 infection during pregnancy induces an inflammatory response that can impact biochemical markers and have long-term effects on both mother and child.[13] In COVID-19 during pregnancy, inflammation, driven by cytokine release, notably IL-6 and TNF-alpha, plays a pivotal role, impacting maternal and fetal health. This cytokine storm leads to tissue damage, especially in the lungs, increasing the risk of severe outcomes like preterm birth and preeclampsia.[14] Elevated inflammatory markers, such as C-Reactive Protein (CRP), ferritin and D-dimer, reflect disease severity and guide treatment. Long-term, persistent inflammation may lead to cardiovascular and respiratory issues in mothers and neurodevelopmental abnormalities in babies. Understanding these inflammatory mechanisms is crucial for effective management and improved outcomes.[15]

SARS-CoV-2 enters cells via Angiotensin-Converting Enzyme-2 (ACE-2) receptors, highly expressed at the maternal-fetal junction and alveolar epithelial cells.[16] The virus's spike protein binding to ACE2 down-regulates these receptors, leading to excessive angiotensin II production and reduced vasodilator angiotensin (I-VII). Elevated Angiotensin II activates the AT1 Angiotensin Receptor (AT1R) pathway, inducing the production of inflammatory Cytokines (CK) and increasing pulmonary vascular permeability. Studies on severe COVID-19 cases reveal significantly elevated levels of various inflammatory markers in peripheral blood, including Interleukin-1β (IL), IL-2, IL-6, IL-7, Granulocyte colony stimulating factor (G-CSF), Macrophage Inflammatory Protein-1 alpha (MIP-1α), Tumor necrosis factor alpha -α (TNF), CRP, troponin, ferritin and D-dimer. Increased IL-6 and IL-8 are associated with gestational pathologies like miscarriage, preeclampsia and preterm delivery.[13,17-22] SARS-CoV-2 infection decreases CD-4+, CD8+ and NK cell levels, particularly in critically ill patients.[17-22] Despite decreased T cells, COVID-19 exhibits an increased Th17 response, with altered Treg/Th17 cell ratios. Inflammatory markers such as IL-6, IL-8, TNF-α and CRP are often elevated in pregnant women with SARS-CoV-2 infection. These markers are associated with gestational pathologies like miscarriage, preeclampsia and preterm delivery.[13] Additionally, studies have reported altered levels of immune cells such as CD4+, CD8+, Natural Killer (NK) cells and changes in the Treg/Th17 cell ratio in response to the infection.[23,24] Elevated cytokines and immune dysregulation can lead to an inflammatory environment in the placenta, affecting fetal development. Placental inflammation due to SARS-CoV-2 particles manifests as histiocytic intervillositis with diffuse perivillous fibrin deposition and damage to syncytiotrophoblasts. Histopathology reveals intervillositis with intervillous fibrin deposition, consistent with inflammation in proven cases of trans-placental transmission from SARS-CoV-2 positive mothers.[21,22]

Elevated levels of maternal IP-10 are associated with miscarriage and preeclampsia, but the long-term effects of IP-10 exposure during pregnancy are currently undefined.[22] However, inflammatory responses induced by the virus can increase the risk of obstetrical complications and potentially impact the mother's health, including an increased risk of developing Non-Communicable Diseases (NCDs) in the future. Maternal infection with SARS-CoV-2 can impact the developing fetal brain through multiple pathways, including Maternal Immune Activation during key neurodevelopmental windows in pregnancy, direct fetal infection of neurologic tissues via transplacental transmission of the virus, or compromised placental function leading to adverse pregnancy outcomes associated with an increased risk of neurologic injury (e.g., fetal growth restriction, preterm birth, abruption). Detecting such injuries to the fetal brain is challenging, but an increasing body of evidence links infectious and inflammatory events during pregnancy to neuropsychiatric consequences for the child later in life.[23] Studies suggest an increased risk of neurodevelopmental disorders associated with prenatal infection, including neurodevelopmental diagnoses and Autism Spectrum Disorder (ASD).[18] Mechanisms by which viral infection could lead to autism include direct teratogenic effects and indirect effects of inflammation and maternal immune activation on the developing brain. Brain imaging studies have shown that the immune response to viral infection disrupts the development of brain regions and structures.[25] Therefore, long-term follow-up is required for babies born to COVID-positive mothers diagnosed with an inflammatory response to monitor signs of autism.[26] An infant showed a pediatric inflammatory multisystem-like syndrome with coronary artery ectasia temporarily associated with SARS-CoV-2, requiring admission and care in the Neonatal Intensive Care Unit (NICU),

despite being negative for SARS-CoV-2. Inflammatory mediators transferred from the placenta to the fetus can lead to neurologic injury, affecting the child's cognitive development and behaviour later in life.[27] SARS-CoV-2 infection during pregnancy induces inflammation, affecting biochemical markers and potentially leading to long-term effects on both the mother and child. The mechanisms responsible for long-term complications in offspring due to SARS-CoV-2 infection are still poorly understood, but inflammation has significantly impacted infant growth and development. Continuous monitoring and follow-up of pregnant women and their children exposed to the virus are crucial to understanding the full impact of the infection on maternal and child health.

The long-term effects of SARS-CoV-2 infection can be diverse and impactful, particularly on the cardiovascular, respiratory and neurological systems. Infection may lead to heart problems, including myocarditis, which can result in arrhythmias and other cardiac issues.[28] Persistent symptoms such as fatigue, headache, attention disorders, hair loss and dyspnea are common, along with respiratory complications like cough, chest discomfort, reduced pulmonary diffusing capacity and even pulmonary fibrosis. Neurological effects such as dementia, depression, anxiety and obsessive-compulsive disorders have also been reported.[29] Additionally, symptoms like hair loss, tinnitus and night sweats can persist. Interestingly, certain symptoms like fatigue, polypnea and alopecia appear more prevalent in females, highlighting potential gender-specific effects. These long-term consequences underscore the need for ongoing research and healthcare support for individuals recovering from COVID-19 to manage and mitigate these lasting effects effectively.

Inflammatory processes triggered by SARS-CoV-2 can directly harm neurons or result from microglia/astrocyte activation, leading to cytokine production and oxidative stress.[30] Placental inflammation increases the risk of severe fetal complications, impacting fetal growth and development. Infants born to COVID-positive mothers may exhibit elevated cytokines at delivery, linked to altered fetal development.[31]

VASCULAR CHANGES

SARS-CoV-2 infection during pregnancy can lead to significant vascular changes that impact both the mother and child, with potential long-term consequences. The virus enters cells via Angiotensin-Converting Enzyme-2 (ACE-2) receptors, highly expressed at the maternal-fetal junction and alveolar epithelial cells. The binding of the virus's spike protein to ACE2 down-regulates these receptors, leading to excessive angiotensin II production and reduced Vasodilator angiotensin (I-VII). This imbalance activates the AT1R pathway, inducing the production of inflammatory cytokines and increasing pulmonary vascular permeability.[25] These vascular changes can result in adverse outcomes for both the mother and child. In the context of COVID-19 infection during pregnancy, notable vascular changes and placental insufficiency have been observed. The spike protein of SARS-CoV-2, implicated in cell signalling, has been linked to hyperplasia and hypertrophy of vascular smooth muscle and endothelial cells.[26] Evidence suggests that pregnant women who test positive for SARS-CoV-2, even without severe COVID-19 symptoms, undergo placental vascular remodelling, marked by changes in placental arteries associated with potential alterations in blood flow between the mother and fetus. Cases of fetal thrombotic vasculopathy have been reported in instances of vertical transmission of human SARS-CoV-2. Studies have linked COVID-19 infection to Acute Respiratory Distress Syndrome (ARDS), characterized by increased vascular wall thickness and reduced lumen diameter.[21] Placental arteries from mothers with COVID-19 during pregnancy exhibited severe vascular wall thickening and lumen occlusion. Histopathological analyses revealed a two-fold increase in wall thickness and a five-fold decrease in the lumen area, pointing towards significant placental vascular remodelling. Immunohistochemistry findings highlighted smooth muscle proliferation and fibrosis as key contributors to this remodelling process.[32] Moreover, placentas from COVID-positive mothers displayed a significant increase in Maternal Vascular Malperfusion (MVM) compared to controls. Pathological findings consistent with MVM included decidual arteriopathy, fibrinoid necrosis and amniotic membrane arteriole hypertrophy. Fetal vascular malperfusion emerged as a prevalent pathology.[33]

The long-term consequences of these vascular changes are still being studied, but they can have lasting effects on both maternal and child health. Maternal inflammation and vascular changes may adversely affect intrauterine conditions, exposing the fetus to neurodevelopmental disorders. Additionally, the altered immune activity in the placenta and cord blood of infants born to infected mothers indicates a potential impact on the neonatal immune system. Biochemical parameters can also be affected by these vascular changes. Overall, understanding the mechanisms underlying these changes and their effects on biochemical parameters is crucial for developing effective strategies to manage and mitigate the impact of COVID-19 on pregnant individuals and their offspring.

THROMBOSIS

SARS-CoV-2 infection during pregnancy induces a maternal hypercoagulable state, leading to adverse perinatal outcomes, including intramural non-occlusive thrombi in placentas.[13] COVID-19 triggers a Prothrombotic state through hyperactivation of inflammatory and hemostatic pathways, primarily mediated by the cytokine storm observed in severe cases.[13] Pregnant individuals with symptomatic COVID-19, especially during the third trimester, have an increased likelihood of preterm birth, compounded by the inherent Prothrombotic state of pregnancy.

Table 1: Characteristics of included studies.

Sl. No.	Author	Title	Country	Study type	Total cases	Diagnostic test
1	Prochaska E., *et al.*, 2020	COVID-19 in pregnancy: Placental and neonatal involve men.	USA	Review article	45	IgG, IgM, CD_4 count, Proinflammatory Cytokines, IL-6, IL-6β, TNF-α, CR.
2	Valdespino-Vázquez MY, *et al.*, 2021	Fetal and placental infection with SARS-CoV-2 in early pregnancy.	Mexico	Case report	1	CBC, LDH
3	Benhamou D, *et al.*, 2020	Coagulation changes and thromboembolic risk in COVID-19 obstetric patients.	France	Review article	3	PT, APTT, INR ratio, Platelet count, D-dimer, Thrombocytes.
4	Yamamoto L., *et al.*, 2020	SARS-CoV-2 infections with emphasis on pediatric patients: a narrative review.	Brazil	A narrative review	64	Circulatory ACE-2 levels, TMPRSS2, Immunoglobulins, CBC, CD_4 and CD_8, Lymphocyte, LDH, AST, ALT, CRP, Ferritin, CK, D-dimer, IL-2, IL-4, IL-6, IL-7, IL-10, TNF-α, CCL-2, CCL-3, CCL-5, Interferon, γ-induced protein.
5	Shuid AN *et al.*, 2021	Association between Viral Infections and Risk of Autistic Disorder: An Overview.	Malaysia	Narrative review	42 + 2 babies	IL-6, RT-PCR test from Breast milk, amniotic fluid, placenta, neonatal throat, anal swab.
6	Rabiei M., *et al.*, 2021	Maternal and fetal effects of COVID-19 virus on a complicated triplet pregnancy: a case report.	Iran	A woman	1	RT-PCR test and Anti-SARS-CoV-2 antibodies.
7	Guo F, *et al.*, 2021	A Comprehensive Review of the Management of Pregnant Women with COVID-19: Useful Information for Obstetricians.	Iran	Comprehensive review	72,521	CRP, ALT, AST, CBC, ACE2, D-dimer.
8	Mahyuddin AP., *et al.*, 2021	Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2s.	China	Case series	40	RT-PCR test from vaginal secretions, amniotic fluid, breast milk and umbilical cord blood, Histological examination, SARS antibody, ACE2, TMPRSS2.
9	Selzman CH, *et al.*, 2020	A pilot trial of human amniotic fluid for the treatment of COVID-19.	Singapore, Santiago Chile, Taiwan.	Case report	10	CRP

Sl. No.	Author	Title	Country	Study type	Total cases	Diagnostic test
10	Schoenmakers S., *et al.*, 2021	Severe Acute Respiratory Syndrome Coronavirus 2 Placental Infection and Inflammation Leading to Fetal Distress and Neonatal Multi-Organ Failure in an Asymptomatic Woman.	USA	Case report	47	RT-qPCR, IG against SARS-CoV-2 tested from the maternal, umbilical cord and neonatal blood. Immuno-histochemical investigation against SARS-CoV-2 antigen expression, with SARS-CoV-2 RNA *in situ* hybridization and TEM.
11	Fenizia C, *et al.*, 2022	Pregnant Women Develop a Specific Immunological Long-Lived Memory Against SARS-COV-2.	Cambridge	Prospective study	1	Radiological chest assessment, Hb, WBC, Hepatic and Renal function tests, CRP, Antibody production, T-cell memory subsets.
12	Stenton S, *et al.*, 2022	SARS-COV2 placentitis and pregnancy outcome: A multicentre experience during the Alpha and early Delta waves of coronavirus pandemic in England.	USA, Australlia, Oman, Qatar, Brazil, Ireland, Rassia, UK, Russia, Newzeland, France, Germany.	Cohort study	39	TEM, Histopathological analysis
13	Carbonnel M, *et al.*, 2022	Plasticity of natural killer cells in pregnant patients infected with SARS-CoV-2 and their neonates during childbirth.	UK	Prospective Mater Cov cohort study.	59	NK cell, Cytokines.
14	Sasaki LP., *et al.*, 2022	Cerebrospinal fluid analysis of pregnant women at early stages of COVID-19	France	Prospective observational study.	18	RT-PCR from CSF.
15	Jin JH, *et al.*, 2022	Two Cases of SARS-CoV-2-Positive Mothers and Their New-borns in Korea.	Brazil	Two case report	34	Histopathological analysis.
16	Nitschke P, *et al.*, 2022	J-Edited Diffusional Proton Nuclear Magnetic Resonance Spectroscopic Measurement of Glycoprotein and Supramolecular Phospholipid Biomarkers of Inflammation in Human Serum	Korea	Original research paper	14	J-Edited Diffusional Proton Nuclear Magnetic Resonance Spectroscopic, Lipo-Protein concentration, Glycoproteins.
17	Arun S, *et al.*, 2022	Multisystem inflammatory syndrome in a neonate with severe hemophilia - a diagnostic challenge in COVID times: a case report.	Australlia, Spain, Columbia.	Australia	2	Anti-COVID-192 IgG antibody test, Inflammatory markers, LDH, Ferritin, D-dimer.

Sl. No.	Author	Title	Country	Study type	Total cases	Diagnostic test
18	Naidu AG., *et al*, 2020	COVID-19 during pregnancy and postpartum: I) Pathobiology of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) at maternal-fetal interface.	USA	Review article	99	CRP
19	Naidu AG., *et al*, 2020	COVID-19 during Pregnancy and Postpartum: II) Antiviral spectrum of maternal lactoferrin in fetal and neonatal defense.	USA, Sweden	Review article	2	Lactoferrin levels, ACE2
20	Lipińska-Opałka, *et al*., 2022	Vitamin D deficiency and the course of SARS-CoV-2 infection.	France	Research paper	55	CBC, AT, LDH, Inflammatory markers-ferritin, CRP, ESR.
21	Madera-Acosta, *et al*., 2020	The case of a pregnant woman with ARDS due to COVID-19 treated with Hydroxychloroquine, Azithromycin and Remdesivir and delivery of a healthy baby during mechanical ventilation through cesarean section.	USA	Case report	1	Chest X-ray, Computed Tomography, Angiography, WBC, Procalcitonin.

CBC: Complete blood count; TNF: Tumor necrosis factor; LDH: Lactate dehydrogenase; AT: Amino transaminase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; CK: Creatine kinase; IL: Interleukin; IG: Immunoglobulin G; RNA: Ribonucleic acid; TEM: Transmission electron microscopy; Hb: Haemoglobin; WBC: White blood cells; CSF: Cerebrospinal fluid; ESR: Erythrocyte sedimentation rate; INR: International normalized ratio.

Prothrombotic factors such as VII, VIII, X, XII, Von Willebrand factor and fibrinogen exhibit elevated levels in COVID-19-positive pregnant individuals. Conversely, Protein S levels decrease and fibrinolysis is altered. Pulmonary thromboses, both macrovascular pulmonary embolism and microvascular thromboses, contribute to the pathophysiology, with an increased incidence of arterial thrombosis and extracorporeal circuit thrombosis. Immuno-thrombosis, driven by inflammation and tissue factor expression, results in pulmonary microvascular thrombosis and contributes to respiratory dysfunction. Placental thrombotic complications, including pre-eclampsia, preterm delivery and Hemolysis, Elevated Liver enzyme levels and Low Platelet levels (HELLP) syndrome, are associated with abnormal or injured maternal vessels and intervillous thrombi in placentas from COVID-positive mothers.[34] Cytokines like IL-1, IL-2, IL-6, TNF-α, macrophage and neutrophil activation play pivotal roles in coagulation system activation and anticoagulant pathway inhibition. The resulting thrombotic inflammation involves platelets, Reactive Oxygen Species (ROS) and cytokine-induced pathology.[35] COVID-positive patients exhibit higher levels of cytokines, chemokines and growth factors during infection, contributing to increased thrombin, fibrinogen, VWF and factor XII. Complications related to coagulation abnormalities encompass pulmonary and renal microangiopathy, arterial and venous thromboembolism and arterial and venous catheter thrombosis. While thrombotic events are rare in children with COVID-19, a Proinflammatory and procoagulant state has been noted in Multisystem Inflammatory Syndrome in Children (MIS-C).[36]

COVID-19 survivors, including children born to infected mothers, may experience Post-Acute Sequelae of COVID-19 (PASC) or long-COVID, characterized by persistent hyperactivation of platelets, micro-clot formation, autoantibody formation, dysregulated immunity, multi-organ dysfunction and potential SARS-CoV-2 reactivation. Endothelial dysfunction caused by SARS-CoV-2 infection may lead to inflammation and thrombosis, further exacerbated by disruption of the endothelial glycocalyx, inhibiting coagulation and adhesion of immune cells and platelets. The persistence of thrombo-inflammation in long-COVID patients, with micro-clots in the lungs and circulation, may contribute to symptoms like fatigue and breathlessness.[37,38]

Studying these mechanisms in SARS-COV-2 infected mothers is crucial for several reasons. Firstly, understanding these mechanisms can help us to identify the specific pathways through which the virus affects the Inflammatory system, Vascular system and Thrombotic system leading to targeted therapeutic interventions. Secondly, it can provide insights into the pathogenesis of COVID-19 in pregnancy, which can aid in

Table 2: Key findings and effect on Biochemical markers.

Sl. No.	Author	Key findings	Diagnostic analysis and Biochemical markers
1	Prochaska E., *et al.*, 2020	Vertical transmission of SARS-CoV-2 is rare, but placental and fetal infections are possible. Infected placentas show inflammatory, thrombotic and vascular changes. These changes can lead to adverse obstetric and neonatal outcomes. Exposed infants may face long-term, multi-systemic defects. Children of infected mothers might have neurologic inflammation before birth.	Mothers with SARS-CoV-2 had a significant increase in Maternal Vascular Malperfusion (MVM) compared to controls. MVM included decidual arteriopathy, fibrinoid necrosis and amniotic membrane arteriole hypertrophy. Fetal vascular malperfusion was the most common pathology. Intramural, non-occlusive thrombi were noted in placentas. Villitis was observed. One placenta from a woman with pneumonia and hypoxia showed chorioamnionitis and funisitis.
2	Valdespino-Vázquez MY, *et al.*, 2021	Congenital SARS-CoV-2 infection is possible during the first trimester, targeting fetal organs like lungs and kidneys. In utero transmission of SARS-CoV-2, though rare, can occur in early pregnancy.	Increased neutrophils Decreased lymphocyte count Higher LDH concentration.
3	Benhamou D, *et al.*, 2020	Avoid tranexamic acid in women with COVID-19-associated DIC. Coagulation disorders, thrombotic events, antiphospholipid syndrome.	Prolonged PT and APTT, Thrombocytopenia, Leukopenia, Lymphopenia, Increased D-dimer levels, Elevated International Normalized Ratio (INR) values. Increased levels of ACE-2, TMPRSS2, LDH, AST, ALT, CRP, Ferritin, CK, Immunoglobulins, D-dimer, IL2, IL4, IL6, IL7, IL10, IP-10, TNF-α, CCL2, CCL3, CCL5. CD4 and CD8 lymphocyte depletion, Changes in neutrophil/lymphocyte ratio.
4	Yamamoto L., *et al.*, 2020	It is important for pediatricians to stay updated on COVID-19 specifics in pediatric patients, including virus characteristics, diagnosis and evolving therapeutic approaches. Coagulation disorders, thrombotic events and anti-phospholipid syndrome may also be present.	Elevated levels of CRP, D-dimer and troponin were observed. Children exhibit fewer ancillary laboratory abnormalities than adults, Leukopenia, Lymphopenia CD4 and CD8 Lymphocyte depletion, Thrombocytopenia and altered neutrophil/lymphocyte ratios in severe cases. Markers like LDH, AST, ALT, CRP, ferritin, Creatine kinase and D-dimer may increase.
5	Shuid AN *et al.*, 2021	Maternal inflammation may adversely affect intrauterine conditions, potentially exposing the fetus to neurodevelopmental disorders. Maternal IL-6 was inversely associated with offspring cognitive development at 12 months of age. Cytokine network dysfunction may be the potential pathogenic process linking viral infections with the risk of ASD in children.	RT-PCR tests conducted on breast milk, amniotic fluid, placenta, neonatal throat and anal swab samples showed no detection of SARS-CoV-2 in pregnant women with COVID-19. Higher levels of IL-6 were observed.

Sl. No.	Author	Key findings	Diagnostic analysis and Biochemical markers
6	Rabiei M., *et al.*, 2021	In a complicated triplet pregnancy, maternal COVID-19 infection, despite mild symptoms, led to exacerbated placental insufficiency in two fetuses, with the third testing positive for COVID-19 after birth. There is a possibility of acute placental insufficiency leading to fetal hypoxia and the potential for vertical transmission should be considered.	RT-PCR tests were positive in 17 cases of neonatal secretions, 8 cases of placental tissue, 3 cases of breast milk and 1 case of amniotic fluid. Anti-SARS-CoV-2 antibodies were positive in three infants.
7	Guo F, *et al.*, 2021	Increased D-dimer levels are difficult to interpret since they are often elevated during pregnancy. Pregnant women may have a higher probability of ICU admission and endotracheal intubation. It is strongly recommended to administer anticoagulant drugs at therapeutic doses to pregnant women severely infected with COVID-19. Currently, there are no reports of obvious side effects from vaccines. Pregnant and lactating women should be encouraged to receive vaccination. The IgG produced by the vaccine may be transmitted to neonates through breastfeeding, providing some protective effect.	Increased CRP, ALT and AST levels. Lymphopenia, Leukocytosis, increased Neutrophil ratio and Eosinopenia. The interaction between the virus and ACE2 may cause hypertension in COVID-19 pneumonia patients, which can be easily misdiagnosed as pre-eclampsia in pregnant women.
8	Mahyuddin a AP., *et al.*, 2021	Placental histopathology from women with mild COVID-19 showed maternal vascular malperfusion and inflammatory changes. Histological examination revealed sparse viral particles, vascular malperfusion and inflammation in the placentas of pregnant women with COVID-19. The presence of ACE-2 and TMPRSS2 receptors, involved in SARS-CoV-2 entry, may explain the relative insensitivity to trans-placental infection.	PCR tests from different clinical samples from mother and child (vaginal secretions, amniotic fluid, breast milk and umbilical cord blood). Histological examination showed sparse viral particles, vascular malperfusion and inflammation in the placentas of pregnant women with COVID-19.
9	Selzman CH, *et al.*, 2020	Patients receiving a higher dose of intravenous Human Amniotic Fluid (hAF) showed a reduction in C-reactive protein and improved clinical outcomes. No hAF-related adverse events were noted.	CRP

Sl. No.	Author	Key findings	Diagnostic analysis and Biochemical markers
10	Schoenmakers S., *et al.*, 2021	Placental findings showed SARS-CoV-2 particles, generalized inflammation with histiocytic intervillositis, diffuse perivillous fibrin depositions and damage to syncytiotrophoblasts. SARS-CoV-2 placental infection leads to fibrin depositions obstructing fetal-maternal gas exchange, causing fetal distress and necessitating a premature emergency cesarean section. The neonate exhibited a pediatric inflammatory multisystem-like syndrome with coronary artery ectasia, temporarily associated with SARS-CoV-2, requiring NICU admission and care, despite testing negative for SARS-CoV-2.	RT-PCR tests were positive in the oropharynx, maternal blood, vagina, placenta and urine over a period of 6 days. RT-PCR tests for breast milk, faeces and all neonatal samples were negative.
11	Fenizia C, *et al.*, 2022	Analyzed 74 inflammatory response genes at T0, T4, T6 and T24. Initial immune activation at T0 decreased over time, indicating transient immune response. **Upregulated Genes:** **Cytokines/Chemokines:** CSF2, CSF3, IL1Rn, IL6, IL8, IL17A, IL28 **Adhesion Molecules:** CD44, CD209 **Activation Markers:** HAVCR2, AGTR1, AGTR2, PPARγ **Immune Mediators:** MPO, CRP, NOS2 **TLR Signaling:** NOD1, NOD2 **Cholesterol Metabolism:** CH25H, ABCA1, HMGCS1, NR1H3, PDCD1, PTGS2 **Antiviral ISGs:** IFNA2, IFNB, IFI16, IFITM1, MX1 **Cytokine/Chemokine Response:** Upregulated at T0 and early time points: IL1β, IL1ra, IL5, IL6, IL7, IL10, IL13, IL15, IL17, Eotaxin, FGF, GM-CSF, IFNγ, IP10, MCP-1, MIP1β, RANTES, TNFα Decreased over time.	Laboratory analysis and radiological chest assessment were conducted. Therapeutic management was tailored according to clinical findings and guidelines, considering demographic and anthropometric characteristics, lifestyle habits and medical or obstetric comorbidities. Maternal venous blood samples were analyzed every 48 hours, including Haemoglobin (Hb), White Blood Cell count (WBC), hepatic and renal function tests (ALT, AST), inflammation markers (C-reactive protein), specific antibody production, T cell memory subsets and inflammation profile.
12	Stenton S, *et al.*, 2022	Gestational ages: 19 to 41 weeks, mostly in the third trimester. Higher rates of stillbirth and late miscarriage, especially among obese mothers. Cases with only Chronic Histiocytic Intervillositis (CHI). Cases with only Maternal Perfusion Dysfunction (MPFD). Cases with both CHI and MPFD. SARS-CoV-2 placentitis is associated with increased pregnancy loss, particularly in the third trimester. Severe placentitis can occur in asymptomatic women.	Each placenta had a pathological diagnosis of MPFD+/-CHI with positive immunohistochemical staining for SARS-CoV-2 spike protein in the syncytiotrophoblast.

Sl. No.	Author	Key findings	Diagnostic analysis and Biochemical markers
13	Carbonnel M, *et al.*, 2022	The frequency of NK cells in infected women and their neonates correlated with the production of inflammatory cytokines in the serum. NK cells were significantly decreased and were also related to estradiol levels.	The expression of NKG2A and NKp30, as well as degranulation of NK cells in pregnant women with ongoing infection, were both negatively correlated to estradiol level.
14	Sasaki LP., *et al.*, 2022	Pregnant women who tested positive for COVID-19 Symptoms started between 4 to 18 days prior to delivery were included. Some of these women reported anosmia, dysgeusia and headaches, with two fatal cases. The study suggests that peripheral cell damage and parainfectious phenomena may predominate over direct central nervous system injury in the pathophysiology of COVID-19-related early neurological symptoms in pregnant women.	SARS-CoV-2 was not present in the cerebrospinal fluid of COVID-19 patients with early neurological symptoms, even in severe cases.
15	Jin JH, *et al.*, 2022	No clinical evidence of vertical transmission despite placental inflammation. Acute intervillositis with increased intervillous and subchorionic fibrin deposition. Acute necrotizing deciduitis.	RT-PCR tests of neonatal Nasopharyngeal/ Oropharyngeal swab, blood, urine, stool, amniotic fluid, breast milk and rectal swab were negative.
16	Nitschke P, *et al.*, 2022	Clinical evidence of vertical transmission was not found, but the possibility of placental inflammation is described.	Histopathological study showed intervillositis with intervillous fibrin deposition, consistent with findings of inflammation in proven cases of transplacental transmission from SARS-CoV-2 positive mothers.
17	Arun S, *et al.*, 2022	ADE risks may be associated with antibody levels, which can wane over time after vaccination or if derived from prior exposures to other coronaviruses. ADE with mast cells is implicated in Multisystem Inflammatory Syndrome in Children (MIS-C) for infants and possibly in older MIS-C and MIS-A patients. Expanded tropism of SARS-CoV-2 represents a possible ADE risk in COVID-19 patients with disease progression beyond the mild stage.	Maternal and neonatal SARS-CoV-2 RT-PCR test were negative. Anti-SARS-CoV-2 IgG antibody test was Positive in the baby. Elevated inflammatory markers like Lactate dehydrogenase LDH, ferritin and D-dimer. So, the baby was given intravenous immunoglobulin and methylprednisolone. Factor 8 inhibition assay was negative after recovery. Laboratory parameters showed an increase in CRP and other inflammatory markers on day 14.

Sl. No.	Author	Key findings	Diagnostic analysis and Biochemical markers
18	Naidu AG., *et al*, 2020	Maternal Lactoferrin (LF) may serve as a potent innate defense factor against COVID-19. Breast milk LF could play a natural preventive role in MCTC and may also protect the neonate from the COVID-19-Postpartum. Histopathological analysis of placentas from COVID-Positive mothers was more likely to show abnormal or injured maternal vessels and intervillous thrombi. 92% of Cesarean section deliveries occurred to the women who were COVID-Positive pregnant during pregnancy and only 8% of vaginal deliveries were reported. Fetal distress was a common indication for cesarean sections. No maternal deaths were recorded.	Lymphocytopenia (59%) with elevated C-reactive protein (70%) was noted in 91% of COVID-19-Pregnancy patients delivered by cesarean section.
19	Naidu AG., *et al*, 2020	LF demonstrates a regulatory role in redox homeostasis, inflammatory responses, immune modulation and antimicrobial activities during pregnancy. LF may block viral docking sites including putative (ACE2, CD32a) and lectin-type (sialic and GAG) CSRs. An in-depth understanding of LF and other soluble mammalian milk-derived innate antiviral factors may provide insights to reduce co-morbidities and vertical transmission of SARS-CoV-2 infection and may lead to the development of effective nutraceutical supplements.	Mother-to-fetus transmission of SARS-CoV-2 has not been detected in most of the COVID-19-*Pregnancy* cases. This relative absence of vertical transmission may be related to the presence of lactoferrin in the placenta, amniotic fluid and lacteal secretions.
20	Lipińska-Opałka, *et al*., 2022	It is important to implement measures to protect pregnant healthcare workers, who are at increased risk, including immune modulation. The outbreak may have a psychological impact on pregnant patients. Therefore, pregnant women should be educated, provided with psychological support and informed about the subject.	Common laboratory findings in hospitalized COVID-19 patients include lymphopenia, elevated aminotransferase levels, elevated lactate dehydrogenase levels and increased inflammatory markers such as ferritin, C-reactive protein and erythrocyte sedimentation rate.
21	Madera-Acosta, *et al*., 2020	Pregnancy increases the risk of infections and COVID-19 poses a particularly high risk of micro-thrombosis and coagulopathy.	There have been no reported cases of vertical transmission of COVID-19. Supportive care was considered the most significant factor contributing to the patient's eventual positive outcome.

predicting and managing complications. Thirdly, studying these mechanisms can help in developing biomarkers that can be used to identify pregnant individuals at high risk of severe disease. Finally, understanding theses pathophysiological mechanisms can contribute to the development of strategies to prevent or minimize the impact of COVID-19 on maternal and fetal health, ultimately improving outcomes for both mother and child. The detailed effects of inflammation, vascular changes and thrombosis in COVID-19 infections during pregnancy are thoroughly described and illustrated in the accompanying tables and figures.

CONCLUSION

By comprehensively examining these mechanisms, this review seeks to provide insights that can inform clinical management strategies and improve outcomes for pregnant women and children affected by COVID-19. Additionally, this review

emphasizes the significance of monitoring relevant biochemical markers associated with these mechanisms, highlighting their potential as early indicators of disease severity and response to treatment. Ultimately, this research paper contributes to the broader understanding of COVID-19's impact on maternal and child health, providing a foundation for further research and public health interventions in this critical area.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

COVID-19: Coronavirus Disease 2019; **IL-6:** Interleukin 6; **TNF-alpha:** Tumor Necrosis Factor Alpha; **NICU:** Neonatal Intensive Care Unit; **MIS-C:** Multisystem Inflammatory Syndrome in Children; **NCDs:** Non-Communicable Diseases; **ASD:** Autism Spectrum Disorder; **IP-10:** Interferon Gamma-Inducible Protein 10; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2; **ACE-2:** Angiotensin-Converting Enzyme 2; **AT1R:** Angiotensin Type 1 Receptor; **CRP:** C-Reactive Protein; **G-CSF:** Granulocyte Colony Stimulating Factor; **MIP-1α:** Macrophage Inflammatory Protein-1 Alpha; **Th17:** T-helper 17; **Treg:** Regulatory T cells; **NK:** Natural Killer; **CD4+:** Cluster of Differentiation 4-positive; **CD8+:** Cluster of Differentiation 8-positive; **VWF:** Von Willebrand Factor; **HELLP:** Hemolysis, Elevated Liver enzymes and Low Platelet count; **ROS:** Reactive Oxygen Species; **PASC:** Post-Acute Sequelae of COVID-19; **VTM:** Vertical Transmission of Microorganisms.

REFERENCES

1. Nasa P, Juneja D, Jain R, Nasa R. COVID-19 and hemolysis, elevated liver enzymes and thrombocytopenia syndrome in pregnant women - association or causation? World J Virol. 2022; 2022:20. doi: 10.5501/wjv.v11.i5.310, PMID 36188744.
2. Kleinwechter HJ, Weber KS, Mingers N, Ramsauer B, Schaefer-Graf UM, Groten T, *et al.* Gestational diabetes mellitus and COVID-19: results from the COVID-19-Related Obstetric and Neonatal Outcome Study (CRONOS). Am J Obstet Gynecol. 2022; 2022:20.e1-631.e19. doi: 10.1016/j.ajog.2022.05.027, PMID 35580632.
3. Smith ER, Oakley E, Grandner GW. Clinical risk factors of adverse outcomes among women with COVID-19 in the pregnancy and postpartum period: A sequential, prospective meta-analysis. Am J Obstet Gynecol. 2022.
4. Rauch A, Dupont A, Goutay J, Caplan M, Staessens S, Moussa M, *et al.* Endotheliopathy is induced by plasma from critically ill patients and associated with organ failure in severe COVID-19. Circulation. 2020; 2020:20. doi: 10.1161/CIRCULATIONAHA.120.050907, PMID 32970476.
5. Wastnedge EA, Reynolds RM, van Boeckel SR, Stock SJ, Denison FC, Maybin JA, *et al.* Pregnancy and COVID-19. Physiol Rev. 2021; 2021:20. doi: 10.1152/physrev.00024.2020, PMID 32969772.
6. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. J Med Virol. 2021; 2021:20. doi: 10.1002/jmv.26232, PMID 32592501.
7. Harmon AC, Cornelius DC, Amaral LM, Faulkner JL, Cunningham MW, Wallace K, *et al.* The role of inflammation in the pathology of preeclampsia. Clin Sci (Lond). 2016; 2016:20. doi: 10.1042/CS20150702, PMID 26846579.
8. Xu SW, Ilyas I, Weng JP. Endothelial dysfunction in COVID-19: an overview of evidence, biomarkers, mechanisms and potential therapies. Acta Pharmacol Sin. 2023; 2023:20. doi: 10.1038/s41401-022-00998-0, PMID 36253560.
9. Varrias D, Spanos M, Kokkinidis DG, Zoumpourlis P, Kalaitzopoulos DR. Venous thromboembolism in pregnancy: challenges and solutions. Vasc Health Risk Manag. 2023; 2023:20. doi: 10.2147/VHRM.S404537, PMID 37492280.
10. Daru J, White K, Hunt BJ. COVID-19, thrombosis and pregnancy. Thromb Update. 2021; 2021:20. doi: 10.1016/j.tru.2021.100077, PMID 38620710.
11. Krishna U, Bhalerao S. Placental insufficiency and fetal growth restriction. J Obstet Gynaecol India. 2011; 2011:20. doi: 10.1007/s13224-011-0092-x, PMID 23024517.
12. Yamamoto L, Santos EH, Pinto LS, Rocha MC, Kanunfre KA, Vallada MG, *et al.* SARS-CoV-2 infections with emphasis on pediatric patients: a narrative review. Rev Inst Med Trop Sao Paulo. 2020;62:e65. doi: 10.1590/S1678-9946202062065, PMID 32901762.
13. Prochaska E, Jang M, Burd I. COVID-19 in pregnancy: placental and neonatal involvement. Am J Reprod Immunol. 2020;84(5): e13306. doi: 10.1111/aji.13306, PMID 32779810.
14. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, Tarhriz V, Farjami A, Ghasemian Sorbeni F, *et al.* COVID-19 infection: an overview on cytokine storm and related interventions. Virol J. 2022; 2022:20. doi: 10.1186/s12985-022-01814-1, PMID 35619180.
15. Patel SV, Pathak JM, Parikh RJ, Pandya KJ, Kothari PB, Patel A. Association of inflammatory markers with disease progression and the severity of COVID-19. Cureus. 2024;16(2): e54840. doi: 10.7759/cureus.54840, PMID 38533136.
16. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, *et al.* Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol. 2020; 2020:20. doi: 10.1002/path.5471, PMID 32418199.
17. Shuid AN, Jayusman PA, Shuid N, Ismail J, Kamal Nor NK, Mohamed IN. Association between viral infections and risk of autistic disorder: an overview. Int J Environ Res Public Health. 2021; 2021:20. doi: 10.3390/ijerph18062817, PMID 33802042.
18. Rabiei M, Soori T, Abiri A, Farsi Z, Shizarpour A, Pirjani R. Maternal and fetal effects of COVID-19 virus on a complicated triplet pregnancy: a case report. J Med Case Rep. 2021; 2021:20. doi: 10.1186/s13256-020-02643-y, PMID 33602315.
19. Guo F, Yang X. A comprehensive review of the management of pregnant women with COVID-19: useful information for obstetricians. Infect Drug Resist. 2021; 2021:20. doi: 10.2147/IDR.S325496, PMID 34466003.
20. Mahyuddin AP, Kanneganti A, Wong JJ, Dimri PS, Su LL, Biswas A, *et al.* Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2s. Prenat Diagn. 2020; 2020:20. doi: 10.1002/pd.5765, PMID 32529643.
21. Archuleta C, Wade C, Micetic B, Tian A, Mody K. Maternal COVID-19 infection and possible associated adverse neurological fetal outcomes, two case reports. Am J Perinatol. 2022; 2022:20. doi: 10.1055/a-1704-1929, PMID 34814196.
22. Taglauer ES, Dhole Y, Boateng J, Snyder-Cappione J, Parker SE, Clarke K, *et al.* Evaluation of maternal-infant dyad inflammatory cytokines in pregnancies affected by maternal SARS-CoV-2 infection in early and late gestation. J Perinatol. 2022; 2022:20. doi: 10.1038/s41372-022-01391-9, PMID 35449446.
23. Selzman CH, Tonna JE, Pierce J, Vargas C, Skidmore C, Lewis G, *et al.* A pilot trial of human amniotic fluid for the treatment of COVID-19. BMC Res Notes. 2021; 2021:20. doi: 10.1186/s13104-021-05443-9, PMID 33482902.
24. Sasaki Y, Darmochwal-Kolarz D, Suzuki D, Sakai M, Ito M, Shima T, *et al.* Proportion of peripheral blood and decidual CD4(+) CD25(bright) regulatory T cells in preeclampsia. Clin Exp Immunol. 2007; 2007:20. doi: 10.1111/j.1365-2249.2007.03397.x, PMID 17459078.
25. Suzuki YJ, Nikolaienko SI, Dibrova VA, Dibrova YV, Vasylyk VM, Novikov MY, *et al.* SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells. Vascul Pharmacol. 2021; 2021:20. doi: 10.1016/j.vph.2020.106823, PMID 33232769.
26. Gychka SG, Brelidze TI, Kuchyn IL, Savchuk TV, Nikolaienko SI, Zhezhera VM, *et al.* Placental vascular remodeling in pregnant women with COVID-19. PLOS One. 2022;17(7): e0268591. doi: 10.1371/journal.pone.0268591, PMID 35905056.
27. Lee SK, Kim JY, Lee M, Gilman-Sachs A, Kwak-Kim J. Th17 and regulatory T cells in women with recurrent pregnancy loss. Am J Reprod Immunol. 2012; 2012:20. doi: 10.1111/j.1600-0897.2012.01116.x, PMID 22380579.
28. Kamphuis KLP, Krasemann TB, Rousian M, Broekhuizen M, Steegers EA, *et al.* Severe acute respiratory syndrome coronavirus 2 placental infection and inflammation leading to fetal distress and neonatal multi-organ failure in an asymptomatic woman. J Pediatr Infect Dis Soc. 2021; 2021:20. doi: 10.1093/jpids/piaa153.
29. Almutairi MM, Sivandzade F, Albekairi TH, Alqahtani F, Cucullo L. Neuroinflammation and its impact on the pathogenesis of COVID-19. Front Med (Lausanne). 2021; 2021:20. doi: 10.3389/fmed.2021.745789, PMID 34901061.
30. Chowdhury S, Bappy MH, Desai S, Chowdhury S, Patel V, Shahraj MD, *et al.* COVID-19 and pregnancy. Discoveries. 2022; 2022:20. doi: 10.15190/d.2022.6.
31. Shirbhate E, Pandey J, Patel VK, Kamal M, Jawaid T, Gorain B, *et al.* Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention. Pharmacol Rep. 2021; 2021:20. doi: 10.1007/s43440-021-00303-6, PMID 34176080.
32. Edlow AG. Neurodevelopmental outcomes at one year in offspring of mothers who test positive for SARS-CoV-2 during pregnancy. medRxiv. 2021.
33. Shamshirsaz AA, Paidas M, Krikun G. Preeclampsia, hypoxia, thrombosis and inflammation. J Pregnancy. 2012; 2012:20. doi: 10.1155/2012/374047, PMID 22175023.
34. Ahmad F, Kannan M, Abdul W, Ansari AW. Role of SARS-CoV-2-induced cytokines and growth factors in coagulopathy and thromboembolism. Cytokine Growth Factor Rev. 2022; 2022:20. doi: 10.1016/j.cytogfr.2021.10.007, PMID 34750061.

35. Fenizia C, Cetin I, Mileto D, Vanetti C, Saulle I, Di Giminiani MD, *et al.* Pregnant women develop a specific immunological long-lived memory against SARS-CoV-2. Front Immunol. 2022; 2022:20. doi: 10.3389/fimmu.2022.827889, PMID 35251011.
36. Naidu SA, Clemens RA, Pressman P, Zaigham M, Kadkhoda K, Davies KJ, *et al.* COVID-19 during pregnancy and postpartum. J Diet Suppl. 2022; 2022:20. doi: 10.1080/19390211.2020.1834049, PMID 33164601.
37. Naidu SA, Clemens RA, Pressman P, Zaigham M, Davies KJ, Naidu SA. COVID-19 during pregnancy and postpartum: II) Antiviral spectrum of maternal lactoferrin in fetal and neonatal defense. J Diet Suppl. 2020; 2020:20. doi: 10.1080/19390211.2020.1834047.
38. Lipińska-Opałka A, Milart J, Kubiak JZ, Kalicki B. Vitamin D deficiency and the course of SARS-CoV-2 infection. Pediatr Med Rodz. 2021; 2021:20. doi: 10.15557/PiMR.2021.0002.

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