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EFFECT OF COVID ON FETUS IN WOMB: A REVIEW ARTICLE

Obstetrics & Gynaecology

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ABSTRACT

The effect of COVID 19 on pregnancy and its vertical transmission has been seen to pose severe complications resulting in a need for proper diagnosis and treatment planning in such cases. Although much has not been discovered in this field but by the access to recent published articles and current research the pathogenesis, clinical features and treatment protocol can be established. COVID 19 has been seen to have a fatal effect also thus it is very important to provide special attention to pregnant women with COVID 19. In this review we will take into consideration the symptoms, transmission, physiological adaptation and the diagnostic and therapeutic alterations of COVID 19 during pregnancy. In this article little has also been discussed about vaccination for COVID 19 in pregnant women.

KEYWORDS

BACKGROUND:

COVID 19 was declared a global pandemic disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1]Patient shows characteristics of ever, cough, sore throat, myalgia, and fatigue indicative of viral pneumonia.[2,3,4,5]

Classification of COVID-19 can be divided into severe (defined as tachypnoea[≥30 breaths per min], oxygen saturation ≤93 % at rest, or PaO_2/FiO_2 ratio <300 mm Hg) and critical (respiratory failure requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care).[6]

Individuals who are susceptible to the virus have been reported to be the elderly (>65 years), individuals with a compromised immune system, meaning those with other underlying or chronic infections, and perhaps pregnant women.[4,5,7] Reports have indicated that women are more vulnerable to respiratory infections during pregnancy.[7]

In this article the main topic discussed is the impact of COVID 19 on pregnant women.

Covid-19-infected pregnant women : Symptoms

There are 3 stages of the COVID 19 virus:[8,9]

Sr.no	Stage	Clinical Presentation
1.	I: Incubation Phase(upto 5 days from the day of infection)	Asymptomatic Survive in the host undetected
2.	II	Virus is now detectable with minor or mild symptoms such as a fever.
3.	III	Severe symptoms arise including respiratory distress and subsequently death

Symptoms:[5,10,11,12]

1. Extremely high fever
2. Coughing
3. Headaches
4. Difficulty in breathing
5. Pneumonia
6. Diarrhoea
7. Haemoptysis
8. Excessive sputum

Fatal cases involved conditions such as respiratory distress, cardiac injury, RNA-anemia and grand-glass opacities [5].

Mother-to-child: covid-19 transmission:

It's not always the case that fetal infection or harm results from viral infection of placental cells. Neonatal test results for SARS-CoV-2 have been reported in 15 reports so far with positive cases being rare.[13] Even in the presence of SARS-CoV-2 positivity, severe neonatal respiratory diseases seem to be uncommon. The results of PCR-based SARS-CoV-2 testing do not clearly indicate whether infection occurs in utero, during labor or delivery, or whether transmission from the infected mother or asymptomatic hospital staff occurs in the first few days after birth.

Antibody tests, however, have produced fresh proof that vertical transmission is a possibility. Increased levels of immunoglobulin (Ig)M and immunoglobulin (Ig)G for SARS-CoV-2 have been found in some infants born to mothers with COVID-19. IgM has a higher molecular weight and cannot cross the placenta, whereas IgG can passively pass from mother to baby in utero. Although all of the newborns in reports to date have been asymptomatic and tested negative for SARS-CoV-2 viral RNA at birth, the presence of circulating SARS-CoV-2 IgM in the neonate suggests vertical transmission of the virus.[14,15]

It is still unclear how viruses enter the placenta through what mechanisms. SARS-CoV-2 uses the ACE2 receptor to enter cells in the lungs, and the serine protease TMPRSS2 is thought to be responsible for cleaving the spike glycoprotein to enable fusion. To ascertain whether ACE2 +/ TMPRSS2 are expressed on placental cells, single-cell RNA sequencing data analysis was incorporated into three studies. Li et al.[16] combined data from a previous study of two-term placentae samples[17] with publicly available single-cell transcriptome profiles from decidua and placenta samples at 6-12 week gestation.[18]

First-trimester decidual stromal and perivascular cells, as well as villous cytotrophoblast and syncytiotrophoblast in both first trimester and term samples, were found to express the ACE2 gene, according to their findings. However, a different study using the same first trimester data set[18] discovered that the expression of ACE2 in placental and decidual cell populations was typically only very low level.[19] In addition to newly generated data from a single placenta from the second trimester and their own preexisting data from the third trimester placenta and fetal membranes, Pique-Regi et al.[20] used the same resource for first-trimester analysis.[18]

To counteract the potential bias from low fractions of syncytiotrophoblast cells in single-cell transcriptomic studies, which can arise from a lack of dissociation of large multinucleated cells, they also included data from single-nuclear RNA sequencing. They focused on the colocalization of ACE2 and TMPRSS2, which they discovered to be minimal in both the placenta throughout pregnancy and the fetal membranes in the third trimester. The expression of ACE2 and TMPRSS2 was discovered in the trophoblast, blastocyst, and hypoblast of human embryos in a subsequent study that looked into potential transmission pathways in the first trimester.[21] This finding suggests that fetal infection via this pathway is possible.

It appears likely that SARS-CoV-2 enters the placental tissues through an alternate mechanism given the absence of ACE2 and TMPRSS2 coexpression in the placenta.[22,23] Other proteases have also been linked

to this. Throughout gestation, the placenta exhibits high levels of DPP4 and CD147 expression, which may play a role in cell entry.[22] The ability to cleave the spike glycoprotein binding at the S1/S2 site has been demonstrated for furin, trypsin, and cathepsins B and L[23,24,25]. Also capable of cleaving this site, plasmin has been discovered as a potential therapeutic target for tranexamic acid to block cell entry.[26] Although neonatal positivity at birth was unpredictable, SARS-Cov-2 viral RNA has been found in amniotic fluid in cases reports of serious maternal disease.[27,28,29]

Physiological Adaptations to Pregnancy and their ramifications for covid-19

A. Immunological Response

A single-stranded RNA virus with a capsule, COVID-19, exists.[30] Like other viruses, the immunological response to COVID-19 depends on a functional immune system. A COVID-19 infection can cause a mild illness in which the immune system successfully eliminates the virus or a severe illness with a high mortality rate.[30] Uncertainty exists regarding where pregnant women fall on this spectrum. Pregnancy-related immune responses to infections are altered as a result of the immune system's adaptation to the growth of a semiallogenic fetus.[31,32,33] Understanding the pathophysiology and molecular mechanisms of COVID-19 and examining them in the context of the modulated maternal immune response are crucial for comprehending the COVID-19 phenotype during pregnancy.

SARS-CoV-2, which is transmitted by respiratory droplets, direct contact with fomites, close person-to-person contact and possibly by aerosols generated,[34,35,36] enters the body via the nasal passage and infects pulmonary cells via the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) and uses transmembrane serine protease 2 (TMPRSS2) for S protein priming.[30] The SARS-CoV-2 is most likely to enter cells where ACE-2 and TMPRSS2 are colocalized.[37] Following SARS-CoV-2 infection, the virus replicates and is released, killing the host cell through pyroptosis (inflammation-mediated programmed cell death brought on by a pathological stimulus).[38]

This causes the release of damage-associated molecular patterns (DAMPs), such as ATP and nucleic acids, which cause nearby cells to become inflamed. The chemoattractants that draw monocytes, macrophages, and T cells to the infection site during this proinflammatory response include IL-6, C-X-C motif chemokine 10 (CXCL10), and type 1 interferons.[39,40] The lung's integrity may be compromised by this positive feedback loop's excessive inflammation, which could then invite the infection of additional (host) microbes.[30,39] SARS-CoV-2-induced inflammation may also cause a "cytokine storm" that can result in multisystem organ failure . Severe COVID-19 is believed to be brought on by this overactive inflammation, which is also linked to high morbidity and mortality.[30,39]

It is likely that the immune system responds to viral infection appropriately in patients with minor symptoms. T-helper 1 cluster differentiation 4 (Th1 CD4+) T cells are drawn to the inflammatory response brought on by viral entry and can eliminate infected cells before the virus replicates and spreads .[41] By phagocytosing the neutralized viruses and apoptotic cells, macrophages clear the virus and block it from spreading further.[39,41]

B. Respiratory Response

Anatomical changes are also present in the respiratory system, in addition to the systemic immunological changes of pregnancy that may have an effect on lung function. Respiratory function changes as a result of physiological changes to the chest shape and elevation of the diaphragm brought on by diaphragmatic splinting by the gravid uterus. Despite a 30–40% increase in tidal volume, functional residual capacity, end-expiratory volumes, and residual volumes from early pregnancy all decrease as a result of the chest volume reduction. Pregnant women may be more vulnerable to severe respiratory infections because of the decreased total lung capacity and inability to clear secretions.[43]

C. Coagulation Response[44]

According to a study involving 184 critically ill patients (24% female), COVID-19 is linked to high rates of thromboembolic complications in the general population. Of these, 31% experienced thrombotic events . The cause of this is the activation of coagulation pathways, which may lead to disseminated vascular coagulopathy (DIC), fibrinolysis, and dynamic hypercoagulation along with thrombocytopenia.

In addition to increased thrombin production and intravascular inflammation, pregnancy is a hypercoagulable condition. Higher levels of circulating coagulation and fibrinolytic factors, like plasmin, are present during pregnancy and may play a role in the pathogenesis of SARS-CoV-2 infection. Women who are pregnant are more likely to experience fatal thromboembolic events. As a result, thrombosis risk factors for pregnant women with COVID-19 may be additive or synergistic. A case report describing the death of a woman at 29 week gestation with COVID-19 due to a sizable pulmonary embolism and a basilar artery embolism supports this theory. According to current recommendations, clinicians should have a low threshold for investigating potential thromboembolism in all pregnant women with confirmed COVID-19 until 10 days after delivery.

D. Endothelial Cell Function[44]

Acute respiratory distress syndrome (ARDS) is the main cause of death in COVID-19. A growing body of research points to the importance of pulmonary endothelial cell dysfunction in the development and progression of ARDS. In a healthy state, endothelial cells are surrounded by mural cells (pericytes), which also inhibit immune cell entry to reduce inflammation and express anticoagulant factors to prevent coagulation. This endothelial barrier becomes compromised in ARDS, which causes tissue edema, excessive inflammation, and hypercoagulability. Endothelial cell dysfunction is linked to several risk factors for COVID-19, including growing older, obesity, diabetes mellitus, and cardiovascular disease.

Diagnostic and therapeutic alternatives for covid-19 during pregnancy

As with all medical issues during pregnancy, the top priority should be to confirm a diagnosis, stabilize the woman's condition, and avoid inappropriately withholding standard investigations and therapies due to fetal concerns. Clinicians need to be aware that pregnancy has different reference ranges for pertinent investigations (table 1). The severity of some women's illnesses have gone unrecognized because relevant reference ranges during pregnancy have not been understood, particularly the fact that respiratory rate and oxygen saturation do not change during pregnancy, according to reviews of maternal deaths from COVID-19.[45,46]

The use of chest radiography, a ventilation/perfusion (V/Q) scan, or computed tomography pulmonary angiography (CTPA) in pregnant women who have a suspected case of covid-19 should not be discouraged. Women can rest easy knowing that a transatlantic flight carries a radiation dose one to six times higher than a chest x-ray. 29 When pregnant with covid-19, chest radiography and CTPA changes are similar to those in non-pregnant people, typically displaying bilateral consolidation and occasionally including pneumothoraxes or pneumomediastinum.[47]

The development of evidence-based therapies for managing COVID-19 has advanced quickly, and the majority of these therapies are safe to use during pregnancy when weighed against the risks. Data have revealed that, even when admitted to an intensive care unit, only about a quarter of pregnant women who would benefit from such therapies actually receive them.[48,49]Management during pregnancy needs to be as similar to management outside of pregnancy as possible. To reduce maternal morbidity and mortality, clinicians who are unsure about the use of treatments during pregnancy should seek urgent advice, for example from obstetricians or other skilled obstetricians.

A frequently updated policy on managing COVID-19 during pregnancy has been maintained by the Royal College of Obstetricians and Gynecologists in the UK.An algorithm and practice advisory recommendations are provided by the American College of Obstetricians and Gynecologists for "outpatient assessment and management for pregnant women with suspected or confirmed novel coronavirus (covid-19).[50] A multidisciplinary team's input is crucial, and if a patient's condition worsens, senior decision makers must be notified right away.

Conclusions and future research recommendations

It is challenging to determine with certainty whether pregnant women are at an increased risk of COVID-19's severe consequences based on the available evidence. The majority of women will experience a mild or asymptomatic illness with no long-term effects, but some centers have noticed an increase in the number of pregnant women needing mechanical ventilation and ICU admissions. Identification of risk

factors and a conclusive comparison of cohorts that are pregnant and those that are not pregnant are both impossible in the absence of fine-grained population level data.

Since COVID-19 testing is not universal, it is likely that the majority of cases go undiagnosed. Although probable, vertical transmission seems to be uncommon and has little effect on the majority of neonates. Again, though, this cannot be evaluated in its entirety until routine neonatal testing is implemented. There are still many unanswered questions, including whether COVID-19 is a standalone risk factor for preterm birth, whether pregnancy-related infection will likely have long-term negative effects on the fetus, and whether this effect is dependent on gestational age at infection.

Pregnant women are almost always excluded from more than 300 clinical trials looking at potential therapeutic options, despite worries about their increased vulnerability to COVID-19.[51] Pregnant participants are infrequently enrolled in clinical trials, not even those examining medications with a well-established safety profile during pregnancy, like hydroxychloroquine. To build a fair and well-informed evidence base with information from a representative population, researchers should be urged to take pregnant women and other underrepresented groups into consideration.

List Of Abbreviations:

	Abbreviation	Full Form
1.	COVID 19	Corona Virus Disease
2.	SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
3.	RNA	Ribonucleic Acid
4.	ACE2	Angiotensin-converting enzyme 2
5.	TMPRSS2	Transmembrane protease, serine 2
6.	CXCL	Chemokine (C-X-C motif) ligand
7.	DAMP	Damage-associated molecular patterns
8.	ATP	Adenosine triphosphate
9.	ARDS	Acute respiratory distress syndrome
10.	CTPA	Computed tomography pulmonary angiography

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