Considering the effects of COVID-19 infection on the pregnant mother and fetus; a review article

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Abstract

COVID-19 has emerged as a new viral illness with potential for significant morbidity and mortality. Pregnant women are high risk for contracting the virus or suffering from complications, however data regarding the effect of COVID-19 on pregnancy is limited to case reports from affected countries. The pathophysiology of COVID-19 infection may provide insights of the threat to mother and fetus. In this review we collate available evidence of harm caused by COVID-19 to mothers and their offspring in all trimesters. Obstetricians must understand the risks posed by this pandemic to effectively counsel women who are currently pregnant or planning conception.

Background

What is a coronavirus?

Coronaviruses are a group of structurally related RNA viruses that primarily cause upper respiratory tract infections in humans. The name corona, meaning crown, comes from the distinct appearance of the virus on electron microscopy, where the outer lipid membrane is punctuated by crown-like spikes[1]. Historically, coronaviruses were recognised as a cause of the common cold but in recent years several dangerous new strains have emerged which can result in fatal illnesses. These new coronaviruses are the cause of SARS (Severe Acute Respiratory Syndrome), MERS (Middle Eastern Respiratory Syndrome) and most recently COVID-19. They are all zoonoses and appear to have been transmitted to humans from bats via intermediate animal hosts. COVID-19, which is caused by the SARS-COV-2 virus, has vastly exceeded the global impact of SARS and MERS to become a major new cause of worldwide morbidity and mortality.

How is COVID-19 different from other coronavirus infections?

The pace of COVID-19 spread has been unprecedented and far outstripped that of the other novel coronaviruses. COVID-19 was first identified in Wuhan, China in December 2019 and only 4 months later was declared a pandemic by WHO [2]. At time of writing, there are 722,646 confirmed cases of COVID-19 in over 190 countries, with 33,983 deaths [3]. By comparison, the 2002-2003 SARS outbreak infected 8096 people before it was brought under control, with 774 deaths [4]. The SARS-COV and SARS-COV2 viruses show a high degree of sequence homology within their genetic material (82%) and initial studies suggested that their molecular biology is similar[5]. Both viruses are predominantly spread by respiratory droplets and contact

with contaminated surfaces (fomites). So why is it that quarantine measures which were so effective against SARS [6] have struggled to contain COVID-19?.

There are several possible explanations. COVID-19 appears to have a higher transmissibility than SARS [7], with peak viral shedding earlier in the course of the illness when patients exhibit fewer symptoms [8]. In addition, COVID-19 is generally a milder illness than SARS and may even be asymptomatic. These asymptomatic cases still shed virus, however, and may account for the majority of transmissions [9, 10]. This combination of factors allowed COVID-19 to spread quickly through communities before severe cases were identified, making public health measures much more difficult to implement [11].

What is the pathogenesis of COVID-19?

All coronaviruses enter the host cell by binding to a cell surface receptor with peptidase activity. In the case of SARS-COV-2, the entry receptor is angiotensin converting enzyme 2 (ACE2) [12]. The physiological function of this is to convert angiotensin II to angiotensin I, which is a vasodilator, and is an essential control mechanism within the renin-angiotensin-aldosterone system to control blood pressure by mediating salt and water homeostasis. It may also have a significant role in mediating amino acid transport across the intestinal epithelium [13]. ACE2 is present in abundance on type 2 alveolar cells of the lungs, as well as stratified epithelial cells of the GI tract, cardiac myocytes, kidney proximal tubules and bladder urothelium, which may all be at risk of infection[14]. The spike proteins of SARS-COV-2 bind to ACE2, resulting in enzymatic activity and a conformational change of the spike that allows fusion of the viral and host cell membranes and entry of the nucleocapsid to the cell.

On entry to the host cell, the RNA genome is translated into a single long polypeptide by the host ribosome, then cleaved by viral-specific proteases to form many non-structural proteins. A number of these viral proteins will then coalesce to form a multi-protein replicase-transcriptase complex, which results in further replication and transcription of the viral genome [1]. The function of most of the viral proteins remains unknown, however it is likely that these interfere with normal host cell processing.

The exact pathogenic mechanisms of COVID-19 are not yet understood but are thought to be similar to SARS. Examination of lung tissue from a patient who died of severe COVID-19 showed diffuse alveolar damage with pneumocyte desquamation and hyaline membrane formation, indicative of ARDS (Acute Respiratory Distress Syndrome). Pneumocytes showing viral cytopathic changes were also seen, suggesting direct viral damage[15]. Severe COVID-19 disease is associated with a dramatic increase in secretion of pro-inflammatory cytokines, including IL-2, IL-10 and TNF α [16]. This cytokine storm is very similar to that seen in secondary haemophagocytic lymphohistiocytosis (sHLH), a high-mortality hyperinflammatory syndrome, suggesting that death in severe COVID-19 may be partially immune-mediated[17].

What is the clinical picture of COVID-19?

COVID-19 generally presents with fever (77-98%), cough (46-82%) and myalgia or fatigue (11-52%) in those who show symptoms and require hospital admission. The mean incubation period is thought to be 4 days, estimated range from 2-14 days [18]. Of those patients who require admission, approximately 19% enter a severe or critical condition, with 5% requiring intensive therapy unit admission and intubation [19]. This is generally due to pneumonia. In these patients, a deterioration of symptoms occurs from day 8 onwards, with patients developing shortness of breath indicative of acute respiratory distress syndrome (ARDS).

On admission to hospital, blood tests often show mild lymphopenia (83%) and thrombocytopaenia (36%). Liver transaminases may be mildly deranged. C-reactive protein (CRP) is slightly elevated in non-severe disease (<40mg/L) but predictably rises to 60-160 mg/L in severe and fatal cases [20]. A raised D-dimer also appears to be associated with severe disease [20]. Computer tomography (CT) imaging of the chest tends to show bilateral infection with ground-glass opacities and multiple areas of consolidation. The diagnosis of COVID-19 is confirmed by RT-PCR of nose and throat swabs or respiratory secretions.

Of those who become seriously ill, estimates suggest a mortality rate of 50-80%, generally due to acute respiratory failure secondary to ARDS, secondary infection or cardiac events (including COVID-19 myocarditis)[16, 20, 21]. Those who become seriously ill are more likely to be older, have underlying medical conditions or immune suppression. Pregnancy has also been suggested as a risk factor for severe COVID-19 disease.

How might COVID-19 affect pregnant women and their babies?

On March 16th, 2020, the UK government issued advice on self-isolation for members of the population who were deemed to be 'vulnerable' to COVID-19 infection. This included women who were pregnant, regardless of gestational age [22]. The evidence in favour of isolation in pregnancy has since been questioned, particularly with regards to pregnant healthcare workers. The latest guidance from the Royal College of Obstetricians and Gynaecologists on COVID-19 sought to address this by recommending a removal from patient-facing roles in those healthcare workers who were beyond 28 weeks gestation. Those who remain within the first or second trimester could continue to work with reasonable precautions to avoid infectious contact [23].

What is the theoretical risk of COVID-19 infection in pregnancy?

The theoretical risk of COVID infection in pregnancy should ideally be considered in two categories:

1. What is the risk to the mother, including the risk of progression to severe disease?
2. What are the risks to the fetus, including transmission, in-utero infection and post-natal disease?

Why is a pregnant woman 'at risk'?

There is no doubt that pregnancy results in modulation to the maternal immune system. It was initially proposed that pregnancy itself as an immunosuppressive state, in order to prevent rejection of a semi-allogenic fetus [24]. However, it seems far more likely that the maternal immune system adapts during pregnancy in order to strike a balance between fetal tolerance and maternal susceptibility to infection, effects which may be mediated by oestrogen and progesterone [25]. Indeed, epidemiological data does not suggest an increased susceptibility to infections in pregnancy, however the course and prognosis of a disease may be altered.

Modulation to the immune system during pregnancy may result in an environment favouring TH2 (humoral/antibody) rather than TH1 (cytotoxic) immune responses [26]. Pregnant women remain able to mount appropriate antibody responses to vaccines and appear to demonstrate a reduction in pro-inflammatory cytokines but an increase in pro-phagocytotic factors. Innate immunity, driven by macrophages and neutrophils, appears maintained or enhanced [27]. While the concept of immune suppression may be oversimplified, this shift to favour humoral immunity may result in an altered response to viral respiratory pathogens, while an overall functioning of innate immunity would otherwise prevent increased pathogen susceptibility. These changes are thought to be more prominent in the third trimester of pregnancy.

It is important to also consider the cardiovascular and respiratory changes that the body undergoes to adapt to the needs of the developing fetus. There is a modest increase in heart rate and stroke volume during pregnancy, with an overall increase in cardiac output and corresponding left ventricular hypertrophy. To increase oxygen provision and carbon dioxide excretion there is also a reduction in the functional residual capacity and inspiratory reserve volume of the lungs to allow for an increase in tidal volume. The gravid uterus pushes upwards, elevating the diaphragm and altering chest compliance, resulting in difficulties in ventilation. In other words, the pregnant mother operates at the limits of her physiological capacity, which means further deficits to lung function caused by a respiratory infection could result rapidly decompensated disease.

Taken together, we should consider women of advancing gestation to be equally likely to contract SARS-COV-2 as the general population but more at risk of having severe or decompensated disease if present. This is corroborated by evidence from the 2009 influenza pandemic, where pregnant women had an increased risk of hospitalisation, severe disease and pre-term delivery due to fetal distress or deteriorating maternal disease [28].

What is the risk of severe maternal disease with COVID-19?

At the moment, it appears too early to say. There is evidence that pregnant women with SARS suffered from more severe disease than non-pregnant women, with adverse maternal outcomes [29]. The absolute number of pregnant women infected with SARS was small, however it is hypothesised that COVID-19 would have a similar effect in pregnancy [30].

A retrospective analysis of 9 pregnant women in the third trimester of pregnancy confirmed to have COVID-19 on throat swab did not show an increase in severe disease [31]. Larger analysis of pooled patient data has observed no increased risk of developing severe or critical COVID-19 in pregnancy and, as yet, no maternal deaths[32, 33]. Pregnant women appear to have a similar symptom presentation to the general population and a comparable disease course. Sadly, there is one case of a severe maternal infection at 34 weeks, reported as part of a case series of 13 patients[34]. In this case, premature delivery of a stillborn infant was required, and the patient subsequently developed multi-organ failure due to sepsis, requiring extra-corporeal membrane oxygenation.

To date, it appears encouraging that COVID-19 infection does not follow a similar pattern to SARS and H1N1 influenza in pregnancy, although the absolute numbers of infected women remain low.

What is the risk of SARS-COV-2 infection developing in the fetus?

The risk to the developing fetus remains difficult to quantity. Previous data from SARS did not show any specific cases of fetal infection but did demonstrate an increased risk of adverse pregnancy outcomes when maternal disease was present [35, 36].

To date, there is no evidence of vertical transmission of COVID-19 to the fetus, with negative swabs from the neonatal throat, amniotic fluid and placenta [31, 33, 34, 37, 38]. Breast milk samples from early lactation do not show any viral RNA [31, 37]. Placental histology of three confirmed cases of third trimester COVID-19 did not show any evidence of villitis, chorioamnionitis or SARS-COV-2 on qRT-PCR, but diffuse fibrin deposition was present around the villi[39], which could indicate altered placental blood flow.

This begs the question – is it possible for SARS-COV-2 to infect the fetus? Most cases of vertical transmission of infection diseases in pregnancy are via haematogenous spread across the placenta. This seems an unlikely route for SARS-COV-2. Single cell analysis of early pregnancy specimens using RNA-sequencing has revealed that while the syncitiotrophoblast of the placenta does express ACE2, the fetal blood does not [40]. This, presumably, does not preclude the direct passage of viral particles present in high levels during maternal viraemia, or through breaches in the placental barrier. Ascending infection from the maternal genital tract cannot be ruled out, as SARS-COV-2 is yet to be isolated from genital fluids[41]. However, it could it be possible for SARS-COV-2 to enter the amniotic fluid in cases of premature rupture of membranes (PROM). In these circumstances there would be a theoretical risk of viral entry to the fetal lung or gastrointestinal epithelium.

In the absence of first trimester studies of maternal COVID-19 infection, or any cases of proven fetal infection, we cannot conclude whether maternal COVID-19 would result in fetal anomalies. However, it is reassuring that SARS-19 did not result in fetal teratogenicity, despite an overall increase in poor obstetric outcomes. At this point, should we reassure our patients that the risk of anomalies is unlikely, but not proven? Certainly, this is an area worthy of urgent study. Erring on the side of caution and acknowledging the lack of reassuring evidence regarding the effect of COVID-19 on the early human embryo, the European Society of Human

Reproduction and Embryology (ESHRE) in a statement from the 19th of March 2020 advised all patients defer getting pregnant until the epidemic ends[42]. This statement was echoed by other national and international societies and resulted in almost complete cessation of fertility treatments of any sort [43].

The risk of transmission of infection to the neonate at the time of birth remains unquantified. In the reported case studies above, all babies were born by caesarean section. There are five cases of infection early in the neonatal period to SARS-COV-2 positive mothers, however in each case it was deemed possible for neonatal COVID-19 infection to have been acquired by transmission in the neonatal period, with placental, uterine and amniotic fluid swabs either negative or not performed[44, 45]. The risks of vaginal delivery are unknown, but presumably small.

What would be the indirect effects of maternal COVID-19 on the fetus?

There is a theoretic risk of indirect fetal injury during maternal COVID-19 infection as a result of 1) severe maternal sepsis, 2) maternal cytokine storm resulting in placental injury or 3) direct placental infection resulting in placental disease. The effect on the fetus would likely be secondary to the gestation at which the insult was received and the severity of the initial maternal infection.

Disease in the first trimester could result in miscarriage due to placental or maternal infection, with a potential need for uterine evacuation in severe cases. In later gestations, placental injury from infection or cytokine damage might result in fetal hypoxia, manifesting as intra-uterine growth restriction or fetal distress, or placental abruption. SARS pregnancies appeared to demonstrate an increase in miscarriage when disease was acquired in the first trimester and intra-uterine growth restriction at latter gestations, however the patient numbers are too small to conclude a significant effect[35, 36].

As yet, there is little data to suggest whether this may be true – all but 2 of the 55 reported cases of infection in Chinese patients occurred in the third trimester with a short interval between maternal infection and delivery. To date, there are 3 reported cases of PROM and 5 of fetal distress necessitating delivery [31, 34, 46], which may indicate an increased risk of fetal distress during labour. Multiple cases of delivery between 32-36 weeks gestation have been reported, but it is not clear whether these were iatrogenic or due to spontaneous onset of premature labour. There is one documented case of stillbirth in a woman suffering with COVID-19 whose neonate tested negative at delivery [34], but no reports of miscarriage. Intra-uterine growth restriction cannot be inferred from the present data due to a lack of maternal demographics allowing for personalised growth calculations.

How are we managing pregnant women in the UK with known or suspected COVID-19 infection?

The Royal College of Obstetricians and Gynaecologists have released new guidance for the management of COVID-19 in pregnancy, which is constantly evolving as our information on the pandemic is growing[23]. This document outlines how individual units should treat confirmed or suspected cases of COVID-19, including how to minimise the risk of spread to others within the department.

Some key points to highlight are:

- As initial data may represent an increased risk of fetal distress in labour, secondary to maternal sepsis or fetal hypoxia, all women with COVID-19 should be managed on a maternity unit with continuous fetal monitoring in labour.
- Due to the theoretical risk of growth restriction to the developing fetus after maternal COVID-19 infection the RCOG have advised for all women who have suffered COVID-19 symptoms to attend for a growth scan 2 weeks following the resolution of symptoms.
- If maternal investigations for suspected severe COVID-19 are required, specifically a CT chest, this should not be delayed due to concerns regarding fetal x-ray exposure, as it is valuable to facilitate maternal treatment.

- In women who have suspected or confirmed COVID-19 infection in the third trimester, elective delivery should be delayed, if it is safe to do so, until after maternal recovery.
- Breast-feeding should still be encouraged, as no evidence suggests SARS-COV-2 can be transmitted in the breast milk, however symptomatic mothers should attempt to avoid aerosol transmission to the neonate with good hand hygiene, and the provision of face masks where necessary. Delayed cord clamping is not contra-indicated.

How should we explain the risks of COVID-19 infection in pregnancy to our patients, when we don't fully understand them ourselves?

The emergence of this new disease poses a significant challenge for the healthcare systems across the globe. Pregnant women, being a particularly vulnerable group, have been faced with additional uncertainties related to the effect of the virus on the pregnancy as well as their health and wellbeing. It is therefore important for any obstetrician and gynaecologist to be very frank with women attempting to start a pregnancy, as well as those that are already pregnant, that the evidence for significant harm or lack thereof is very limited. We must inform women that due to the pressures on the emergency services, there may be a delay in seeing them if they present with early pregnancy complications, such as pain or bleeding and that confirmation of a miscarriage or ectopic pregnancy may be delayed. Similarly, treatment options may be reduced due to availability of theatre or anaesthetic staff, or lack of personal protective equipment in cases of confirmed COVID-19 positive patients.

Recent concerns regarding the risk of spread COVID-19 during laparoscopic surgery has put in question the routine application of this well-established procedure as the mainstay of treatment of ectopic pregnancies [47]. Laparoscopies will still be carried out with additional precautions; however, some units may choose to forgo this approach completely and offer open surgery as the only surgical option. First trimester combined screening for aneuploidies may also be delayed or stopped completely for the time being. This may result in an increased rate of aneuploid pregnancies detected later with additional physical and psychological comorbidities as a result of late diagnosis and mid trimester terminations. Current evidence seems to indicate an increased risk of caesarean deliveries in women affected by COVID-19 and these are also not without immediate and long-term comorbidities. As the situation is dynamic, it is our responsibility as healthcare professionals to keep up with the developments and relay any relevant information to our patients in order to alleviate the high parental anxieties and more importantly, do no harm.

Further areas of research

The COVID-19 pandemic remains an international public health concern of previously unparalleled proportions. Clearly, this is a constantly evolving situation. Any recommendations that are made can only be based on current evidence and are likely to change as our knowledge is updated.

It is a relief that there is no current suggestion of vertical transmission to the unborn fetus, though larger case studies will be required to determine this for definite and ensure there is no direct teratogenic effect of fetal infection. Case-control studies following infected women through the first trimester onwards will provide important information to elucidate this and will allow for correlation of maternal and fetal outcomes with infection. In response to this, the UK Obstetric Surveillance System (UKOSS) have created a system for mandatory reporting of all confirmed cases of COVID-19 in pregnancy to assess the incidence within the population and monitor outcomes.

Monitoring of COVID-19 in pregnancy will remain a challenge. At present, Public Health England will only permit testing of those patients whose symptoms are severe enough to require admission to hospital. A large cohort of asymptomatic or mildly affected SARS-COV-2 positive women will not be included within the UKOSS study as a result of this. Any data obtained as a result of this, or other, studies may be skewed towards the more severe end the spectrum of maternal and fetal disease. It will be many years before the longer-term effects of COVID-19 on pregnancy are understood.

Contributions to authorship

AR conceived the article and researched the original manuscript. DG, MB and LP provided specialist input, intellectual guidance and assistance with writing. All authors contributed to edits and approved the final draft.

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Conflicts of Interest

No authors have conflicts of interest to declare

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