

Acute placental failure by SARS–COVID Placentitis: Case presentation

Nang Ohn MRCOG specialty doctor, Kavitha Sivakumar MRCOG Associate Specialist, Rehana Zaman MRCOG Consultant Obstetrician
Noble's Hospital, Isle of Man

Introduction: Cases of unvaccinated pregnant women with SARS-COVID infection in 3rd trimester and subsequently had an intrauterine fetal morbidity and mortality with SARS-COVID placentitis.

Case 1: 26 year old smoker, multigravida with high BMI presented at 32+4 week gestation with reduced fetal movement in October 2021. It was her third pregnancy and first pregnancy was straightforward, uneventful and had normal vaginal delivery at term with average weight baby. Another pregnancy was miscarriage. She was admitted on day 9 of positive COVID test and had declined COVID vaccination. She was asymptomatic with normal observations and the blood tests were normal. The growth scan at 28th week gestation was normal. Admission CTG was pathological and in spite of conservative measures, it did not recover. Decision was made for emergency caesarean section and baby was delivered by category 2 LSCS after loading dose of magnesium sulphate, maintenance dose and one dose of steroid. Male 1.85kg baby was delivered with suboptimal cord gases results who needed resuscitation with inflation breaths and was transferred to the neonatal unit. Postnatal period was uneventful. Placenta histology showed typical features of COVID placentitis with increased peri villous fibrin deposition, chronic intervillitis and villous trophoblast necrosis. Immunohistochemistry for SARS-COV-2 was positive. There was evidence of inutero release of meconium.



Picture 1- antepartum cardiotocograph



Picture 2- antepartum cardiotocograph

Cord pH – Arterial- 7.184, Base excess- -9.7
Vernous- 7.213, Base excess- -9

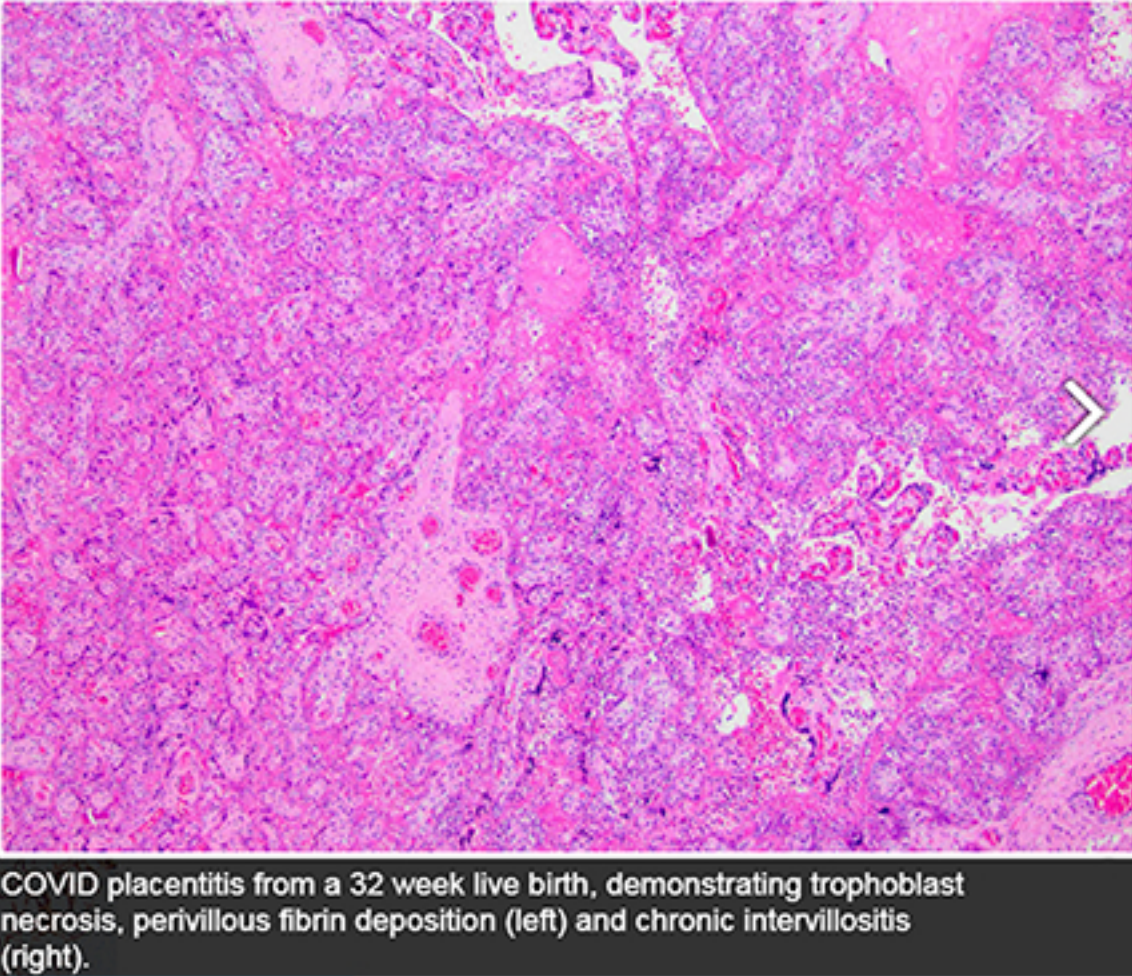
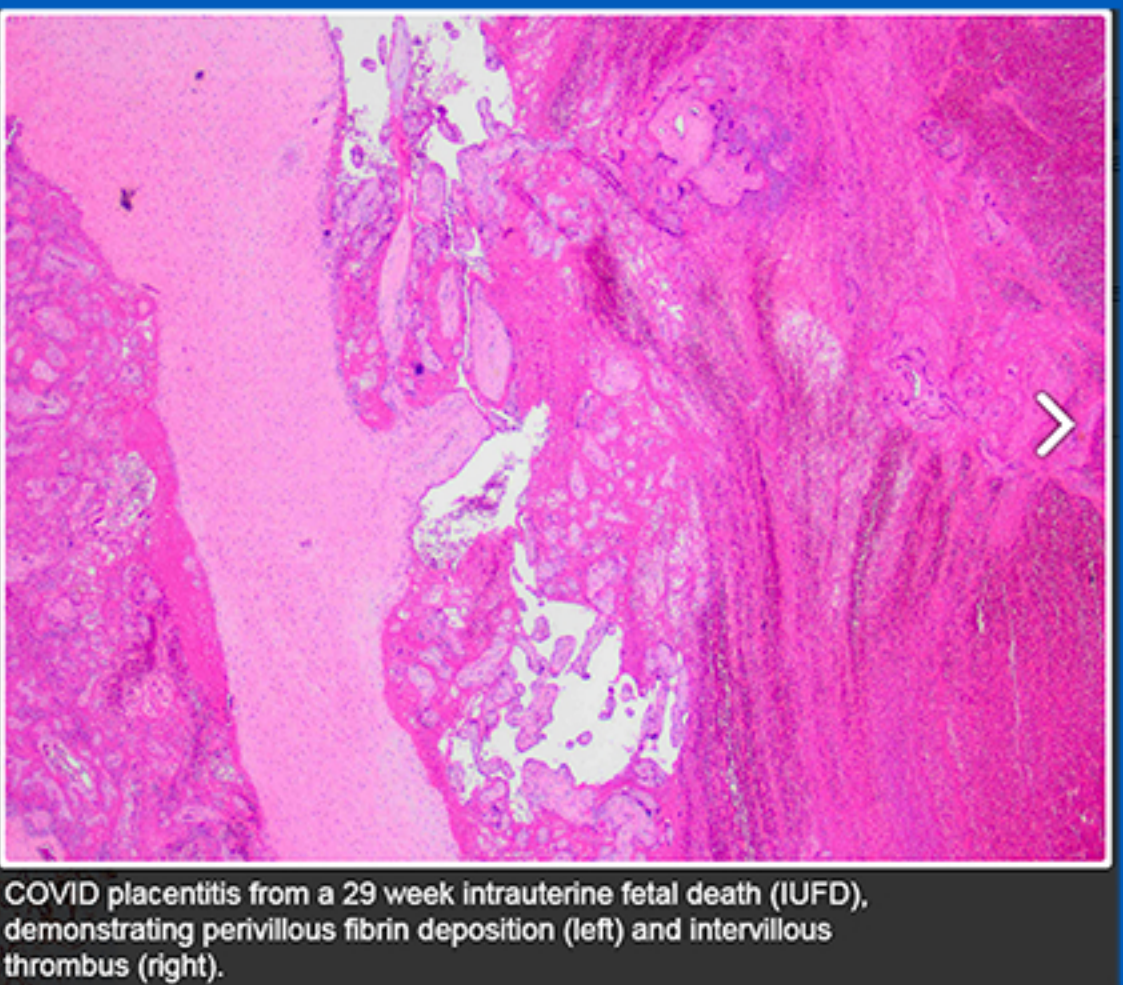
Case 2: 34 year old primigravida presented in labour at 38+5 gestation on day 11 of positive COVID test. She was counseled for COVID vaccination since antenatal booking period but she declined. She had controlled thyrotoxicosis on Propylthiouracil and had regular follow up under the joint care of endocrinologist. Her antenatal period was uneventful until admission and all the antenatal blood tests and fetal growth scans were within normal range. At the beginning of October 2021, she contracted COVID, was moderately unwell with breathlessness but did not need hospital admission. After coming out of isolation at 38weeks and 5 days gestation, she was reviewed for antenatal check which was found to be within normal range. The next day, she attended the maternity ward with spontaneous rupture of membrane and was found to have offensive and light meconium stained amniotic fluid. She was clinically well with normal observations and was examined to be in established labour. Fetal heart beat was undetectable and sadly, it was confirmed IUFD by real time ultrasound. She progressed labour quickly and spontaneous vertex delivery was completed without complication. Completely externally normal looking, fresh stillborn female baby, weighing 4.028 kg was delivered. She was supported by the bereavement team and postnatal period was uneventful. Post-mortem examination revealed baby showing signs of acute asphyxia. Placental analysis confirmed COVID placentitis with high viral load which had led to acute placental failure.



Gross description
•Placentas affected by COVID placentitis often show tan-yellow, firm areas similar to the appearance seen in massive perivillous fibrin deposition



Microscopic description
•Trophoblast necrosis and chronic histiocytic intervillitis with variable perivillous fibrin deposition and in situ detection of virus by immunohistochemistry (IHC), in situ hybridization (ISH) or electron microscopy Placentas affected by COVID placentitis also often have numerous intervillous thrombi



Discussion

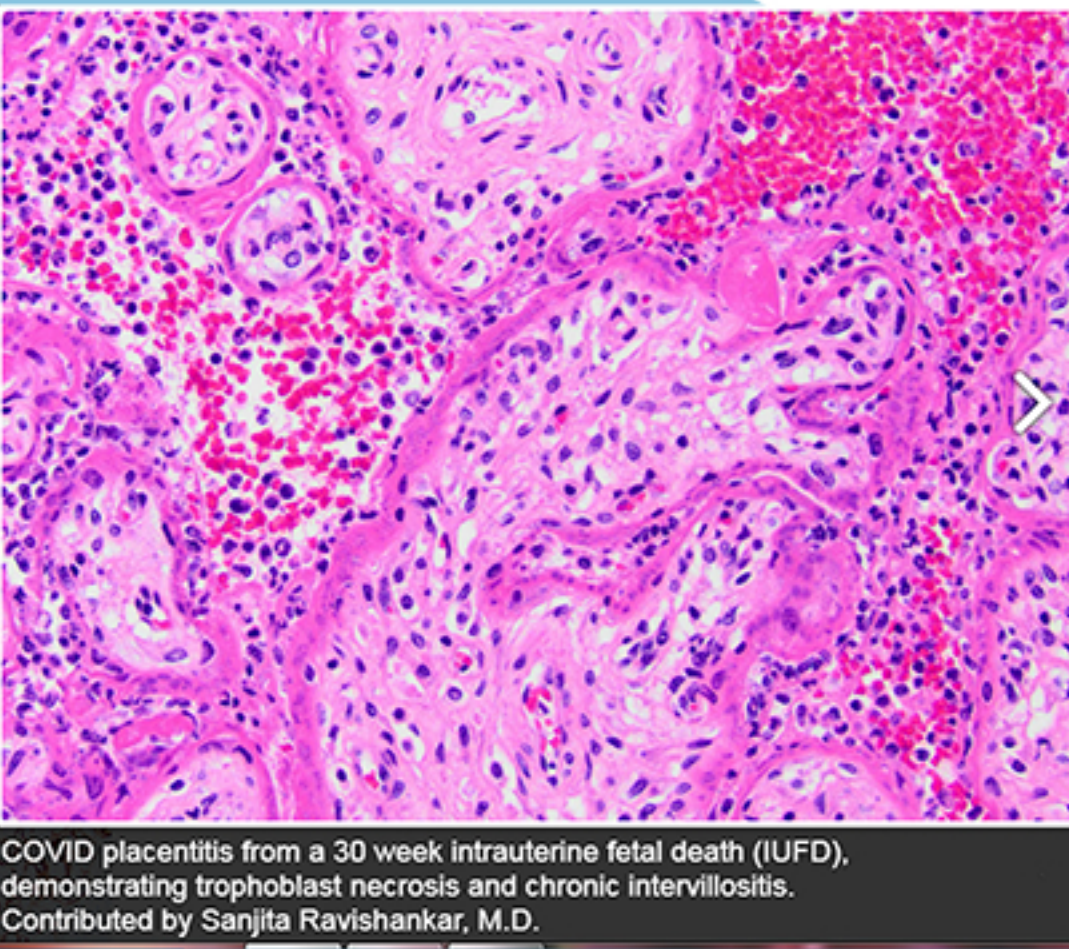
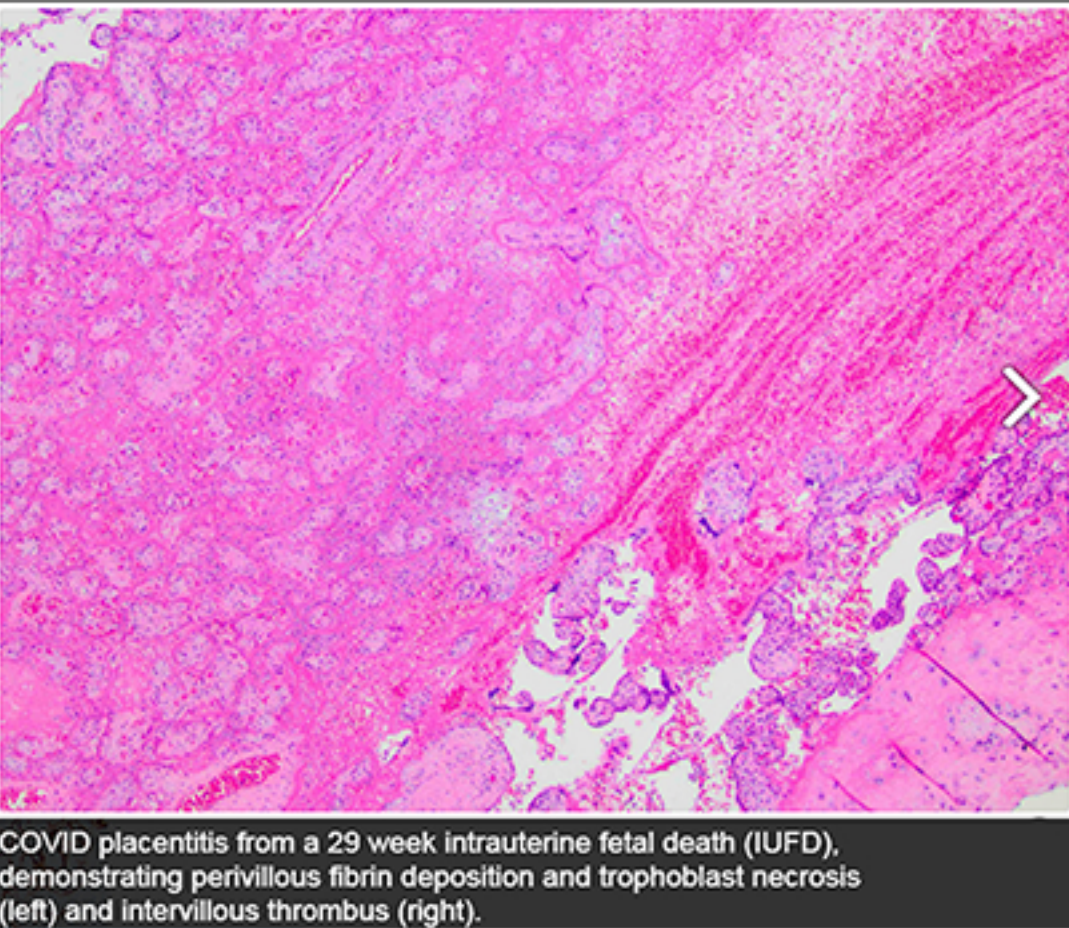
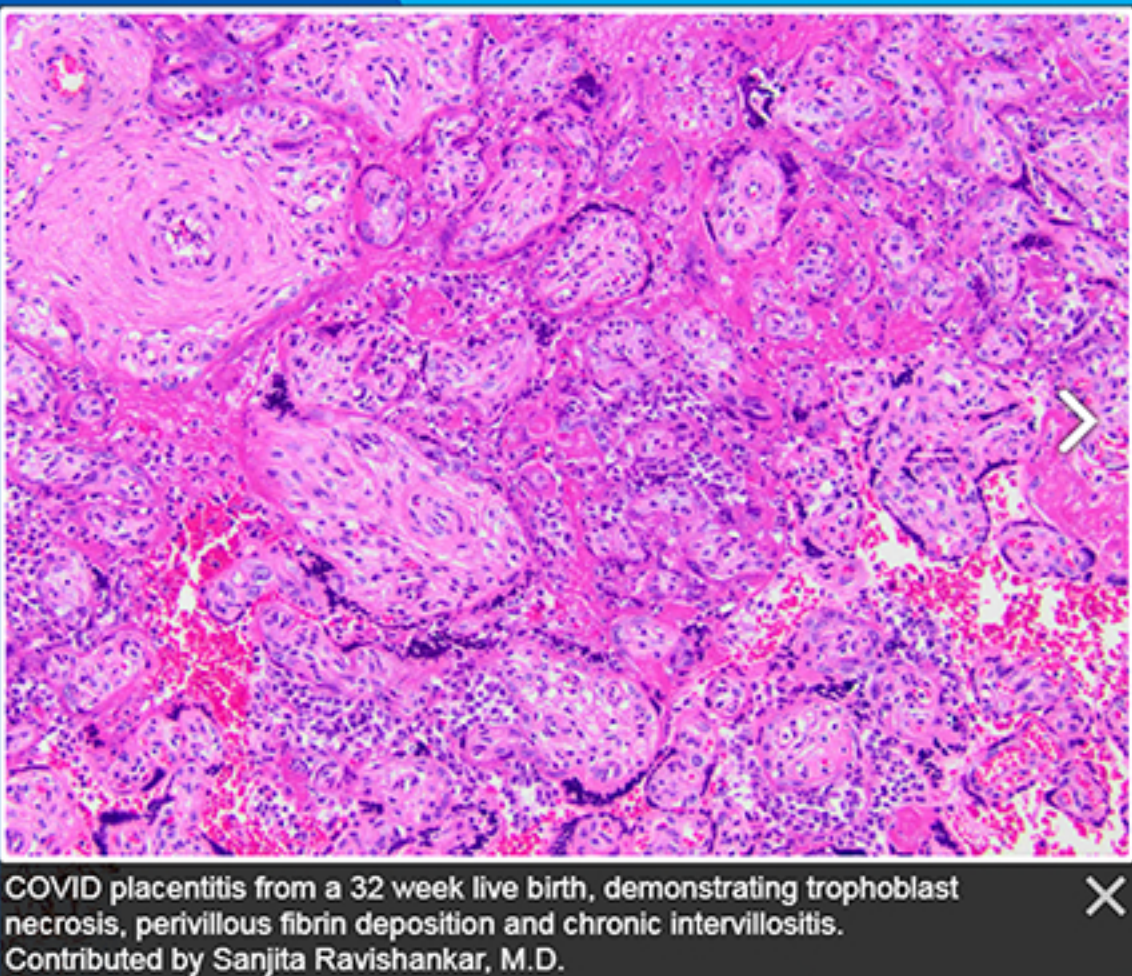
SARS-CoV-2 infection poses increased risks of poor outcomes during pregnancy, including preterm birth and stillbirth. There is also developing concern over the effects of SARS-CoV-2 infection on the placenta, and these effects seem to vary between different viral variants. Vast majority of placentas from mothers infected by SARS-CoV-2 show no specific gross or histologic findings regardless of maternal symptom severity or bulk detection of virus in the placenta. COVID-19 placentitis occurs in 1 - 3% of placentas of infected mothers and is associated with transplacental maternal - fetal transmission of SARS-CoV-2.

Despite these risks, many pregnant individuals have been reluctant to be vaccinated against the virus owing to safety concerns. Current extensive data confirms the safety and effectiveness of COVID-19 vaccination during pregnancy, although it will also be necessary to determine the effectiveness of these vaccines specifically against newly emerging viral variants, including Omicron.

Epidemiology
COVID-19 produces severe life threatening disease in pregnant women. Preterm birth is increased due to maternal compromise in severe COVID but not in women with mild symptoms) and stillbirth rate can be increased. Spread to the placenta is uncommon (7%) and fetal transmission through the placenta is rare (1 - 3%) and is typically associated with severe maternal disease. Cases of fetal transmission are almost always associated with histologic COVID-19 placentitis, recognized as chronic histiocytic intervillitis and trophoblast necrosis. However, predictive value of COVID placentitis or viral detection in placental tissue for fetal infection or clinical outcome is low.

Pathophysiology
COVID placentitis may arise due to direct cytotoxicity by active viral replication in the syncytiotrophoblast or immune mediated damage secondary to inflammatory / cytokine response to COVID-19 infection. Fetal vascular malperfusion (fetal thrombosis) may be more frequent among the acute SARS-CoV-2 as compared to the nonacute SARS-CoV-2 group (53.8% versus 18.8%; P = 0.002).

Prognostic factors
No known risk factors for placental viral spread and COVID placentitis among women with SARS-CoV-2 infection. Cases of fetal transmission are almost always associated with COVID-19 placentitis; however, specificity and sensitivity of COVID placentitis for fetal infection and poor clinical outcome is low.



SARS-CoV-2 and the placenta

Placental infection seems to be uncommon. However, SARS-CoV-2-associated coagulation and inflammation occur even in the absence of placental infection, most commonly manifesting as intervillous thrombosis and fibrin deposition. Examination of the decidua in pregnancies affected by SARS-CoV-2 demonstrated local activation of maternal natural killer cells and T cells, including the expression of gene signatures associated with pre-eclampsia. A more severe inflammatory syndrome occurs when the placenta does become infected; namely, SARS-CoV-2 placentitis. This is characterized by histiocytic intervillitis, perivillous fibrin deposition and trophoblast necrosis, and is emerging as a risk factor for fetal distress or demise. SARS-CoV-2 placentitis were rare in the first wave, caused by the original strain of SARS-CoV-2, but became increasingly common in the Alpha and Delta variant waves of the pandemic. We still need data on how the Omicron wave has affected pregnant people.

A series of 68 cases of SARS-CoV-2 placentitis associated with either stillbirth or neonatal death found that the causes of death were likely to be fetal hypoxic-ischaemic injury resulting from severe placental damage, rather than fetal infection with SARS-CoV-2. Placental infection with SARS-CoV-2 does not necessarily equate with fetal infection; in this case series, infection of the fetus was only confirmed in 2 of the 68 cases.

In case 1, presenting symptom for admission was reduced fetal movement of one day duration and cardiotocogram confirmed fetal distress which needed emergency delivery of iatrogenic preterm baby with meconium stained amniotic fluid. Baby recovered well with no detected abnormality apart from prematurity. COVID placentitis was confirmed in histology which was the cause for fetal distress. The outcome could be more devastating if the patient presented late.

In case 2, the patient was reviewed a day before admission by the community midwife as a routine care and all the findings including fetal heart rate were normal. She did not have any significant abnormal symptoms. Within 24 hours, she was admitted and found to have intrauterine fetal death which confirmed fresh still born fetus with signs of asphyxia, confirmed COVID placentitis by histology which was the cause for sudden fetal death in utero. This scenario conveyed the vital message of abrupt and drastic unpredictable devastating effect on fetus by the COVID placentitis. Both of these two patients did not have vaccination and if they were vaccinated, the outcome might not have been this catastrophic.

Safety of COVID-19 vaccination in pregnancy

Vaccination in pregnancy aim to prevent maternal morbidity and mortality, or to confer passive immunity to the infant. The increased potential for severe consequences following SARS-CoV-2 infection in pregnancy makes COVID-19 vaccination of this population particularly attractive. However, pregnant patients naturally want to know whether vaccination is safe for them and their infants.

The first countries to offer the COVID-19 vaccine in pregnancy were the United States and Israel, using the mRNA vaccines BNT162b2 (Pfizer) and mRNA-1273 (Moderna), the first data available were on these vaccine and the majority of safety data come from these vaccines.

The Better Outcomes Registry and Network (BORN) comprises 64,234 people vaccinated against COVID-19 during pregnancy in Ontario, Canada. Of the 31,343 individuals, the rate of stillbirth, PTB or infants being born small for their gestational age was not increased, compared with the background rate. A study of 18,399 people vaccinated against COVID-19 during pregnancy in Scotland found no increased risk of PTB or neonatal mortality, compared with the general pregnant population. A study in Israel examined only 390 people vaccinated with BNT162b2 during pregnancy, but also found no increased risk of miscarriage, PTB or infants being born small for their gestational age.

The US Vaccine Safety Datalink system, which includes 31,080 people vaccinated during pregnancy found no indication that COVID-19 vaccination is linked to stillbirth and people who experienced miscarriage were not vaccinated in the preceding 28 days than those who did not miscarry. A similar study carried out in Norway found that, among 18,447 pregnancies, those that ended in miscarriage were no more likely to have received a COVID-19 vaccine in either the preceding 3-week or 5-week period than those that continued.

Seven cohort studies examine the outcomes for those who are vaccinated against COVID-19 in pregnancy, compared with the outcomes of a contemporary cohort of unvaccinated people. There was no increased risk of miscarriage, pre-eclampsia or any adverse outcome at the time of birth associated with COVID-19 vaccination in pregnancy. One study that followed up infants after birth, to an average of 134 days, also found no increased risk of death or hospitalization in the first months of life in infants born following vaccination during pregnancy.

Although each of these approaches to addressing the question of COVID-19 vaccine safety in pregnancy has its own weakness, the findings from each approach gives us confidence that COVID-19 vaccination is not associated with adverse pregnancy outcomes. In the above two cases at my hospital, even though the patients were given the up to date information on vaccine, the patients declined for COVID-19 vaccination simply because they did not want it as they suspect for the vaccine safety in pregnancy. If they had the vaccines, the outcomes of the pregnancy might have changed with possibility of avoiding the devastating late sudden intrauterine death and unexpected emergency premature delivery.

Effectiveness of COVID-19 vaccination in pregnancy

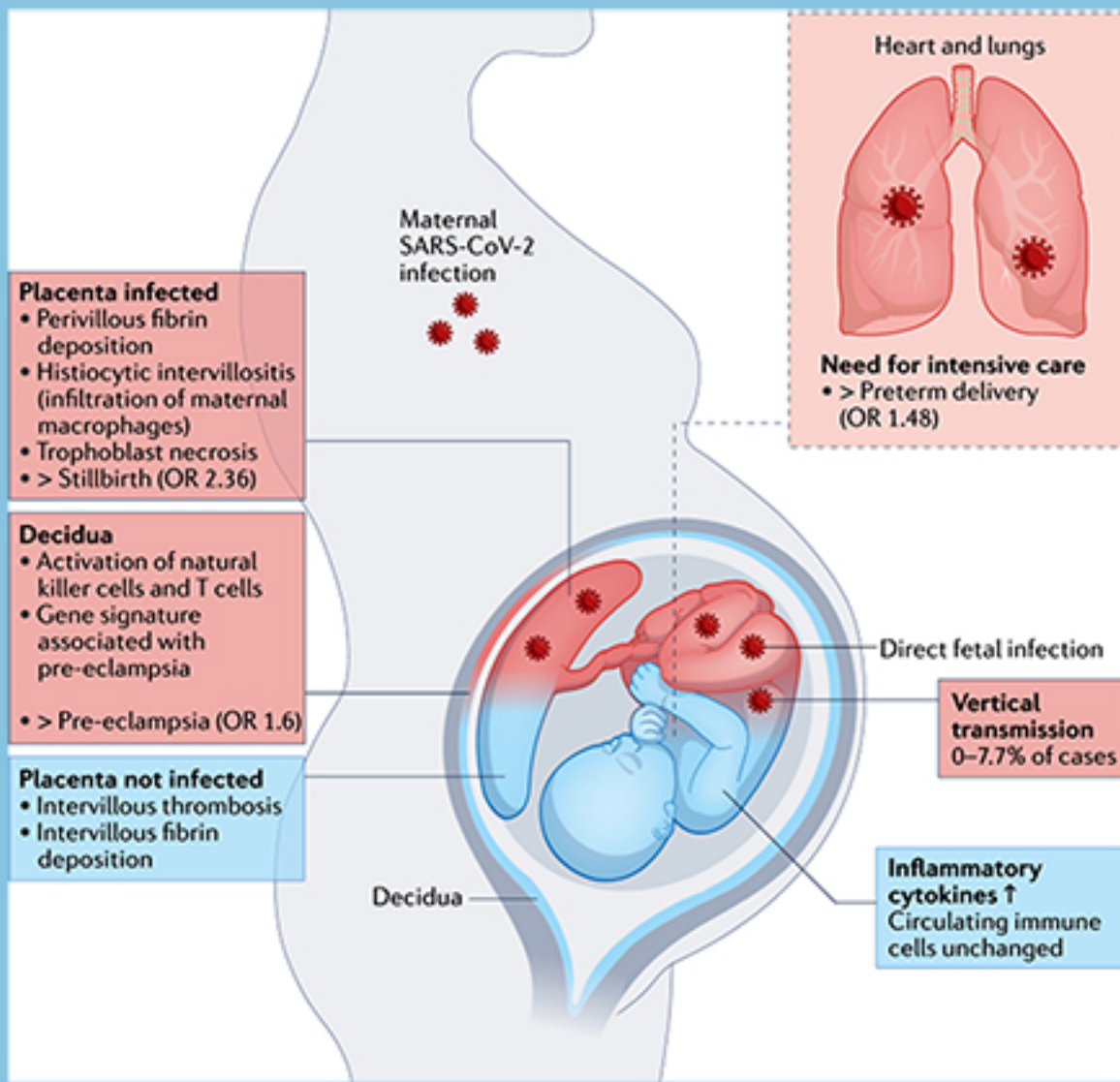
Two reports found that the titres of anti-Spike, anti-RBD (receptor binding domain of the Spike protein) and SARS-CoV-2 neutralizing antibodies were the same in the vaccinated pregnant groups and age and sex-matched non-pregnant controls. Importantly, both of these studies found higher virus-specific antibody titres associated with COVID-19 vaccination compared with SARS-CoV-2 infection, underlining the benefits of vaccination even in those who have already been infected. A third study, also found that overall titres of antibodies did not differ between the groups and after only one dose of vaccine, antibody effector functions were induced with delayed kinetics in the pregnant group compared with the non-pregnant group: following the second dose, there was no significant difference between the groups. Comparing vaccine responses across trimesters using this approach, there was subtle reduction in antibody effector functions following vaccination in the second trimester, compared with vaccination in the first or third trimesters, which might reflect trimester-specific immune alterations that are known to be associated with a somewhat more quiescent state in the second trimester.

UK surveillance data have not been used to model vaccine effectiveness, but nevertheless point to COVID-19 vaccination being effective in pregnancy, particularly against severe disease. In Scotland, 68% of the pregnant population was unvaccinated by October 2021, but unvaccinated individuals accounted for 77.4% of all SARS-CoV-2 infections, 90.9% of COVID-19 hospitalizations and 98% of intensive care unit admissions among pregnant people; furthermore, all perinatal deaths following SARS-CoV-2 infection in pregnancy occurred in unvaccinated individuals. These data sets were collected largely during the period when the Alpha variant was dominant, but with some contribution from the Delta wave. As the Omicron variant becomes prominent, it will be important to determine the effectiveness of vaccination specifically against this strain. It will also be necessary to determine the extent to which vaccination provides protection specifically against COVID-19-associated pregnancy complications.

Conclusion

SARS-CoV-2 infection poses significant risks to pregnant people and their infants, but COVID-19 vaccination is safe in pregnancy. This underlies the recommendation that pregnant people receive the COVID-19 vaccine, which is now being made by public health bodies all over the world. Despite these recommendations, in many countries uptake of the COVID-19 vaccine in pregnancy remains low, so it is essential that we continue to communicate this message to those who are making the decision about COVID-19 vaccination, for themselves and their infants. strong public health messaging is needed, but more importantly we must ensure that midwives and obstetricians are adequately equipped to counsel their patients on the benefits of COVID-19 vaccination.

Fig. 1: Direct versus indirect effects of SARS-CoV-2 infection on the fetus and placenta



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