

# Stillbirth, Surveillance of Fetal Wellbeing and SARS-CoV-2 Infection

January 2022 Update

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## Key Points

- There is a risk of stillbirth with maternal SARS-CoV-2 infection
- The risk of fetal / perinatal death relates to both maternal complications from severe COVID-19 illness and placental damage from SARS-CoV-2 placentitis
- The risk of fetal death from SARS-CoV-2 placentitis is of the order of 1%; current reports suggest this risk is mitigated by COVID-19 vaccination

## Guidance for Antenatal Care – fetal wellbeing

### *Justification*

Pregnant women should be informed that there is evidence of a risk of stillbirth with maternal SARS-CoV-2 infection. They should be advised that the risk of fetal death ranges from 0.5 to 2% in COVID-19 disease from all current data, and that information gathering is still ongoing. The risk of fetal death relates to both maternal complications from severe COVID-19 disease and placental disease even when COVID-19 is asymptomatic or associated with mild symptoms.

Studies have suggested impairment of placental function from SARS-CoV-2 infection as a plausible mechanism of stillbirth, and therefore the fetal wellbeing of women with COVID-19 disease should be cared for accordingly. Pregnant women should be advised of the particular importance of monitoring fetal movements. They should be asked to present immediately if they have any concerns regarding fetal movements, irrespective of current COVID-19 status.

Stillbirths reported due to SARS-CoV-2 placentitis appear to be acute in nature, that is to say, occurring within 7-21 days of a maternal COVID-19 diagnosis. Stillbirths have been a feature of both the *alpha* and *delta* waves of the COVID-19 pandemic; there is as yet no data on the *omicron* variant but it is expected to have the same potential to cause placentitis, at least in the unvaccinated population. Fetal growth restriction is not a reported feature in these cases, presumably due to the acute course of the condition. From current reports, fetal/perinatal deaths appear have occurred in the unvaccinated population. It is possible that focal SARS-CoV-2 placentitis will lead to chronic placental insufficiency and fetal growth restriction; the impact of vaccination is as yet unknown in this regard. It is not known whether Doppler abnormalities precede the stillbirths, and the liquor volume was normal in the cases reported. However, in most affected pregnancies a reduction in fetal movement was noted. Based on these observations it is unlikely that ultrasound will be useful in detection or prediction of adverse outcome in the acute phase of COVID-19, as these changes are usually found in more chronic forms of uteroplacental insufficiency. It is therefore likely that fetal movement awareness with CTG surveillance, following baseline ultrasound examination, is the optimum form of monitoring of fetal wellbeing with maternal COVID-19 infection after 24 weeks.

Recommendations for antenatal surveillance of the fetus following a diagnosis of COVID-19 in a pregnant woman are as follows:-

### *COVID-19 at a gestation greater than 24 weeks:*

Initial evaluation should be with CTG and baseline ultrasound:

- A CTG should be performed at the time of diagnosis of COVID-19, for evaluation of fetal wellbeing. This is also an opportunity to discuss the importance of monitoring fetal movements with the pregnant woman.

- If there is an abnormality on CTG, or if the CTG is difficult to interpret (as with lower gestations) then fetal ultrasound for biophysical score should be performed and the management directed as per standard guidance with this investigation.
- Any concern following this evaluation should be discussed with a senior Obstetrician/Fetal Medicine Specialist.
- An ultrasound scan for biometry, AFV and UADs should be scheduled. This ultrasound should be performed as soon as is reasonably practicable (and as soon after the COVID-19 diagnosis as feasible).
- If there is an abnormality found on this scan appropriate follow up should be discussed with a senior Obstetrician/Fetal Medicine Specialist.

Follow on management:

- Further surveillance can be individualised and may be with weekly CTGs, where Ultrasound is then requested in the event of a concern
- Repeat ultrasound examination should be performed for fetal growth, AFV and UADs at 2 and 4 weeks following the initial COVID-19 diagnosis.
- Other ultrasound scans should be as for usual indications.
- If women are being monitored as inpatients due to symptomatic COVID-19 illness then daily CTGs are advised.
- For some women admission to the maternity unit may be more practical and/or safer in the short term and/or during acute illness, and daily monitoring arranged.
- After the initial 4 weeks, decisions around ongoing surveillance should be individualised.

*COVID-19 at a gestation less than 24 weeks:*

When the infection is acquired in the first or early second trimester of pregnancy, a detailed morphology / anomaly ultrasound scan at 20–22 weeks of gestation is indicated, and these pregnancies should be monitored carefully after recovery.

It is reasonable to consider sonographic assessment of fetal growth in the third trimester thereafter; this could be individualised as a single 28- or 32-week fetal growth scan, for example. Decisions around ongoing surveillance should be individualised.

## **Evidence Summary – Stillbirth**

The updated 2020 BMJ living systematic review reported that compared with pregnant and recently pregnant women without the disease, pregnant women with COVID-19 were at higher risk of stillbirth (OR 2.84, 95% CI 1.25–6.45). The overall number of stillbirths was small. (1)

The UKOSS/ISARIC/Co-CIN April 2021 report comments that due to delays in units notifying stillbirths and neonatal deaths and time lags in receipt of data to allow for cross-checking, MBRRACE-UK ‘cannot yet make any confident interpretation of stillbirth and neonatal mortality rates for 2020’. (2)

A large study in England (3) reported a statistically significant two-fold increase in stillbirth for women with a laboratory confirmed SARS-COV-2 infection at the time of birth (OR 2.21 95% CI 1.58–3.11). This study was unable to differentiate between severity of COVID-19 disease in the cohort, and was not able to quantify risk of stillbirth based on historical COVID-19 infection at any other time during pregnancy. The report includes births up to January 2021.

A systematic review of 42 studies from 2020 (4) also reported a two-fold increase in stillbirth (OR 2.11) associated with maternal SARS-CoV-2 infection.

However, reports from 2020 on placental pathology in cases of SARS-CoV-2 infection did not show specific histological patterns and comparative cohorts found no evidence that COVID-19 during the third trimester influenced placental histology. (5, 6)

A large study in India reported doubling of the stillbirth rate in the second wave of the pandemic (34 per 1000 births between February 2021 and May 2021) compared with the first wave (15 per 1000 births between April 2020 and January 2021). (7) As of March 31, 2021, there were 4805 pregnancies with COVID-19 in Canada reported to CAN-COVID; stillbirth (>20 weeks) rates were 10.6 per 1000 (95% CI: 6.6% - 16.8%) compared to 5.44 per 1000 (95% CI: 5.1% - 5.7%) in the general population. (8)

An August 2021 systematic review (of 56 studies) aimed to report the spectrum of placental pathology findings in pregnancies complicated by COVID-19. (9) A significant proportion of women with SARS-CoV-2 infection in pregnancy showed placental histopathologic abnormalities, suggesting placental hypoperfusion and inflammation. The authors conclude that additional ultrasound scans throughout pregnancy might be required in women presenting with objective risk factors for growth restriction, such as a previous complicated pregnancy, abnormal placental biomarkers, or increased pulsatility index in the uterine arteries, because SARS-CoV-2 infection in these women may worsen an already compromised placenta. (9)

Studies that have reported increased risk of developing hypertension in pregnancy (10) following COVID-19 disease add to the narrative of placental involvement with SARS-CoV-2 infection, and therefore confirm that women recovering from severe infection with COVID-19 should be monitored accordingly. INTERCOVID (11) – a large, longitudinal, prospective, international observational study showed that COVID-19 during pregnancy is strongly associated with preeclampsia, especially among nulliparous women. This association was independent of any risk factors and pre-existing conditions. COVID-19 severity did not seem to be a factor in this association. (11)

Six stillbirths were identified nationally in Ireland's third wave of COVID-19 (December 2020 – March 2021), along with one fetal death at 20 weeks' gestation. In all cases, there was a recent maternal COVID-19 diagnosis and the placentas in all cases had features of what had been reported previously as 'SARS-CoV-2 placentitis' (12). For these seven cases, it was agreed that COVID-19 was the significant factor that resulted in the stillbirth of these infants (13). This condition appears to occur a relatively short time after contracting COVID-19 infection, ranging up to 21 days from experiencing symptoms. Maternal COVID-19 symptoms varied from none to moderate. (13) Three other cases of SARS-CoV-2 placentitis in the third trimester of pregnancy were identified from births in April-June 2021, where an emergency delivery (following a presentation with reduced fetal movements and abnormal CTG) resulted in a good outcome for the mothers and babies involved. From the January–March HPSC data, this implied a risk of COVID-19 related stillbirth in pregnant women with COVID-19 of 1 in 120 cases. (13)

This experience of stillbirth caused by COVID-19 disease was not confined to Ireland and internationally a small number of stillbirths (US, Spain, UK, Canada) were similarly attributed to SARS-CoV-2 placentitis after thorough clinical / pathological examination and published in the international literature (14, 15, 16, 17, 18, 19, 20) throughout 2021.

US researchers concluded that placental involvement by the virus is characterised by diffuse trophoblast damage disrupting the placental barrier and can be seen in asymptomatic mothers without evidence of vertical transmission. (17) In a pathology series from March 2020-March 2021 definitive placental involvement by SARS-CoV-2 was seen in 2 of 197 (1.02%) placentas. (18) A UK case report of a 25 week stillbirth concluded that COVID-19 infection is associated with similar patterns of histological changes of the placenta to chronic histiocytic intervillitis, (CHI) and massive perivillous fibrin deposition (MPFD), leading to placental insufficiency and fetal death. (19)

Schwartz led a multinational group of 19 perinatal specialists to review the placental pathology findings from infants delivered to mothers testing positive for SARS-CoV-2; this included 5 stillborn infants. They reported that CHI together with trophoblast necrosis accompanies SARS-CoV-2 infection of syncytiotrophoblast in live-born and stillborn infants. (14)

The May 2021 Spanish report details SARS-CoV-2-positive placentas in five stillborn fetuses, with a placental lesion characterized by diffuse trophoblast necrosis; similar to findings in the Irish cases. (16) A case report from Israel in November 2021 showed diffuse trophoblast damage with CHI in a placenta from a 25-week stillbirth and confirmed similarity with other reports of placentitis. (20)

A US report in November 2021 (21) described features of SARS-CoV-2 placentitis (a triad of histiocytic intervillitis, MPFD, and trophoblast necrosis) in 7 placentas (births up to April 2021), of which one was from a stillbirth, and all were in pregnancies with mild or no symptoms of COVID-19 disease. The authors concluded that given the marked effects in most of the placentas observed, 'stillbirth appears to be a plausible and serious sequelae of the massive placental damage imposed by SARS-CoV-2'. (21)

A recently-published French pathology series reported SARS-CoV-2 placental lesions were involved in fetal deaths (10% of cases) by functional placental insufficiency when placental damage is massive, associated with trophoblastic necrosis, CHI and MPFD; stillbirths occurred 1-3 weeks after maternal positive COVID-19 tests in the second and third trimester of pregnancy.(22) This group also reported focal lesions (20% of cases) that did not cause fetal death, raising the possibility that this placental damage could lead to fetal growth restriction in later pregnancy. (22)

A recent report from the COVID-19 in pregnancy in Scotland cohort (COPS) includes linked data from national databases on a total of 139,136 pregnancies in 126,749 women. By mid-October 2021, a total of 567 babies born within 28 days of maternal COVID-19 diagnosis. (23) Of these, eight were stillbirths (fetal deaths  $\geq$ 24 weeks) and one was an early neonatal death giving an extended perinatal mortality rate in this population of 15.9 per 1000 births (background rate in 2020, 6.3 per 1,000 total births). All perinatal deaths occurred in women who were unvaccinated at the time of COVID-19 diagnosis. The authors do not have access to individual case details. (23) In December 2021, Public Health Scotland reported they had identified 684 babies born within 28 days of their mother having COVID-19 during pregnancy. The rate of stillbirth or neonatal death among these babies was 20.5/1,000 births which is considerably higher than the 6.3/1,000 births usually seen in Scotland. (24)

COVID-19 documented at delivery was associated with increased risk for stillbirth (aRR = 1.90; 95% CI = 1.69–2.15), with a stronger association during the period of Delta variant predominance in the US (aRR = 4.04; 95% CI = 3.28–4.97). (25) During the Delta period (July–September 2021) in the US, 1,171 stillbirths were documented, involving 2.70% of deliveries with COVID-19 compared with 0.63% of deliveries without COVID-19 (aRR = 4.04; 95% CI = 3.28–4.97). Among deliveries with COVID-19 disease, chronic hypertension, multiple-gestation pregnancy, placental abruption, sepsis, acute respiratory distress syndrome, mechanical ventilation, and ICU admission were associated with a higher prevalence of stillbirth – meaning the role of maternal complications needs further examination in this cohort. Specific placental pathologies were not reported. (25)

On 7 December 2021, the NETHOSS Registry (26) included 9,620 pregnant women with a proven COVID-19 diagnosis, between 1 March 2020 to 1 May 2021. Of this group, 58 women were reported to have experienced intrauterine fetal death after previous infection with SARS-CoV-2.(26) In August, Dutch researchers reported a 'Unique Severe COVID-19 Placental Signature Independent of Severity of Clinical Maternal Symptoms' in 4 placentas, with features consistent with earlier descriptions of placentitis. (27) The authors commented that these findings correlated with fetal distress but not maternal clinical symptoms and suggested that close fetal monitoring and delivery in cases of fetal distress can prevent adverse pregnancy outcomes due to COVID-19 related placental disease. (27)

Since July 2021, the Netherlands has reported 13 stillbirths (28), which are directly attributed to the placenta being damaged by the coronavirus. The researchers describe placental necrosis and inflammation akin to the placentitis described in the Irish and US cases. None of the mothers who had these stillbirths were vaccinated. (28)

In Ireland's later Delta wave of the COVID-19 pandemic (September to December 2021), five fetal deaths >20 weeks and two early neonatal deaths have now been attributed to SARS-CoV-2 placentitis. (29) None of the mothers were vaccinated against COVID-19. A US group has reported two cases of stillbirth within 14 days of maternal delta-variant SARS-CoV-2 infection; both fetal deaths were secondary to SARS-CoV-2 placentitis, leading to severe placental damage and insufficiency, and the mothers were unvaccinated. (30)

The latest information from the UKOSS study of COVID-19 in pregnancy, released as part of an infographic summary on 16 December 2021, shows that almost all women admitted from May to October 2021 with symptomatic COVID-19 in pregnancy were unvaccinated. Over the same time period the authors report a 2% risk of pregnancy loss and a 2% risk of stillbirth in this hospitalised cohort. (31)

There have also been reports in the literature suggesting that rates of stillbirth might have changed during the COVID-19 pandemic, as *indirect* effects of the pandemic. A reduction in health-care-seeking behaviour, as well as reduced provision of maternity services and the effects of lock-down policies, has been suggested as a possible cause (32, 33). Reduced staffing means less time to record stillbirths correctly, hence further adding to the data gaps and invisibility. (33) However, published COVID-19 case series from France, Denmark, Canada, Spain, Sweden and Germany, albeit all based on 2020 data, showed either no change in stillbirth rates or a reduction in fetal deaths.

A 2021 systematic review reported that global maternal and fetal outcomes have worsened during the COVID-19 pandemic, with an increase in maternal deaths, stillbirth and ruptured ectopic pregnancies. (34) These authors identified significant increases in stillbirth (pooled OR 1.28; 12 studies) during versus before the pandemic.

As yet, there are very few reports evaluating 2021 perinatal outcome data and the impact of the third and fourth waves of the COVID-19 pandemic. Lockdown restrictions from March 2020 to March 2021 in a high-income setting in Melbourne, in the absence of high rates of COVID-19 disease, were associated with a significant increase in preterm (20 to 36 weeks) stillbirths (0.26% vs 0.18%, aOR 1.49, 95%CI 1.08 to 2.05, P =0.015). (35) This was accompanied by a significant reduction in iatrogenic preterm birth <37 weeks for fetal compromise. The authors suggest it is plausible that fewer episodes of in-person care during lockdown reduced the detection of growth-restricted fetuses via routine obstetric examination or maternal reports of decreased fetal movements. (35) A UK report on obstetric interventions and outcomes from March 2020-February 2021 found very small decreases in preterm birth and small-for-gestation birth rates and very small increases in induction of labour and elective and emergency caesarean section during the COVID-19 pandemic, while stillbirth rates remained similar. (36)

Finally, the stillbirth rate for vaccinated women who gave birth (3.35 per 1,000, 95%CI 2.71 to 4.15) was similar to the rate for unvaccinated women (3.60 per 1,000, 95%CI 3.40 to 3.81) giving birth in the UK between January and August 2021. (37) In the COPS cohort in Scotland by mid-October 2021, a total of 3,809 babies had been born to women who had received COVID-19 vaccination during pregnancy. (23) Six of these births were stillbirths and eight babies died within 28 days of birth, giving an extended perinatal mortality rate of 3.7 per 1000 total births, which is in line with the background extended perinatal mortality rates of 6.3 per 1,000 total births in 2020 and 5.7 per 1,000 total births in 2019. (23)

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