Royal College of Midwives

Royal College of Obstetricians & Gynaecologists

Coronavirus (COVID-19) Infection in Pregnancy

Information for healthcare professionals

Version 16: Published December 2022

RCPCH Royal College of Paediatrics and Child Health *Leading the way in Children's Health*

RCOA Royal College of Anaesthetists

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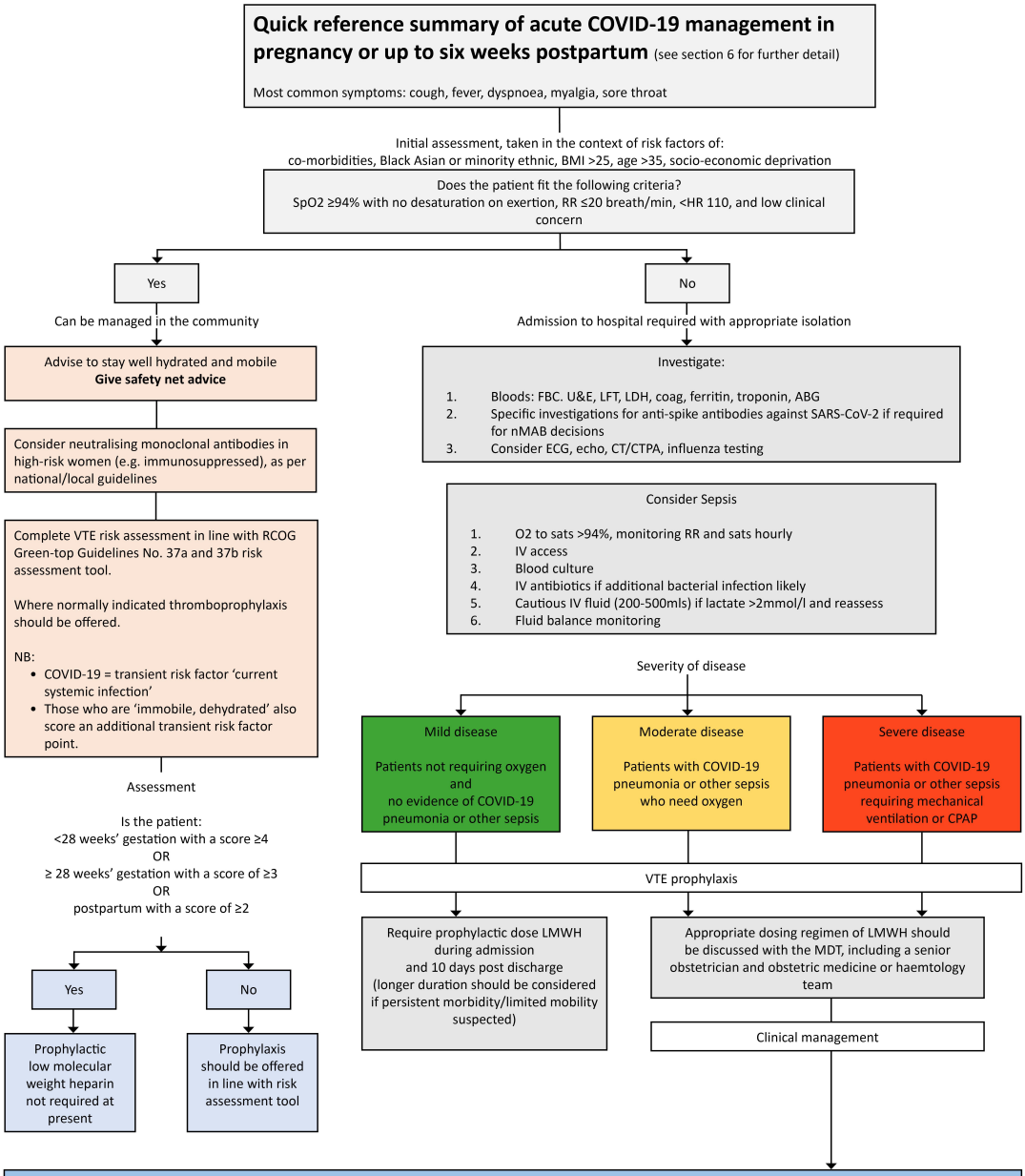
Quick reference summary of acute COVID-19 care



Approach to clinical managemen

(adapted with permission from M Nana and C Nelson-Piercy, and modified with additions from Bart's NHS Trust with permission from K Wiles,

BMI, body–mass index; SpO2, oxygen saturation; RR, respiratory rate; HR, heart rate; FBC, full blood count; U&E, urea and electrolytes; LFT, liver function test; LDH, lactate dehydrogenase; ABG, arterial blood gases; ECG, electrocardiogram; ECHO, echocardiogram; CTPA, computed tomography (CT) pulmonary angiogram; IV, intravenous; CPAP, continuous positive airway pressure; VTE, venous thromboembolism; LMWH, low-molecular weight heparin; MDT, multidisciplinary team; CRP, C-reactive protein.

Executive summary

Background and epidemiology

- Pregnant women appear no more or less likely to contract SARS-CoV-2 than the general population, and more than two-thirds of identified pregnant women have no symptoms. The most common symptoms of COVID-19 in pregnant women are cough, fever, sore throat, dyspnoea, myalgia and loss of sense of taste.
- There is evidence that pregnant women may be at increased risk of severe illness from COVID-19 compared with non-pregnant women, particularly in the third trimester. The overall risk of death remains very low.
- Risk factors associated both with being infected and hospitalised with COVID-19 include being unvaccinated, Black, Asian and minority ethnic backgrounds, having a body–mass index above 25 kg/m^2, having a pre-pregnancy co-morbidity, (e.g. diabetes or hypertension), a maternal age of 35 years or older, living in increased socioeconomic deprivation, and working in healthcare or other public-facing occupations.
- There is no reported increase in congenital anomalies incidence because of COVID-19 infection. Vertical transmission is uncommon.
- Maternal COVID-19 infection is associated with an approximately doubled risk of stillbirth and may be associated with an increased incidence of small-for-gestational age babies. The preterm birth rate in women with symptomatic COVID-19 appears to be two to three times higher than the background rate; these are primarily iatrogenic preterm births.

Vaccination

- Vaccination in pregnancy against COVID-19 is strongly recommended and pregnant women are a priority group for vaccination.
- There is no evidence to suggest that COVID-19 vaccines affect fertility. Women planning a pregnancy or fertility treatment can receive a COVID-19 vaccine and do not need to delay conception.
- More than 347 150 women in the UK and USA have had a COVID-19 vaccine in pregnancy with no concerning safety signals. There is excellent real-world evidence of vaccine efficacy with 98% of women admitted to hospital with severe COVID-19having not had the vaccine.
- Those who have had two doses and a booster (or three doses) of a vaccine are 88% less likely to be admitted to hospital with the Omicron variant than those who have not been vaccinated.
- Two vaccine doses alone are less effective than two doses and a booster against the Omicron variant, and women are advised to receive a booster dose.
- COVID-19 vaccines can be given at any time in pregnancy, including periconception, the first trimester, peri-birth and postpartum. In pregnancy, the preference is to offer the Pfizer-BioNTech or Moderna vaccines.
- Pregnant women receiving a COVID-19 vaccine show similar patterns of reporting for common minor adverse effects to non-pregnant people. The rare syndrome of vaccine-induced thrombosis and thrombocytopenia (VITT) has been reported after the Oxford-AstraZeneca and the Janssen vaccines. It is an idiosyncratic reaction not associated with any of the usual venous thromboembolism risk factors. There is no evidence that pregnant or postpartum women are at higher risk of VITT than non-pregnant age-matched women.
- Breastfeeding women can receive a COVID-19 vaccine without having to stop breastfeeding.

Venous thromboembolism

- All pregnant women admitted with confirmed or suspected COVID-19 should be offered prophylactic low molecular weight heparin, unless birth is expected within 12 hours or there is significant risk of haemorrhage. The dose may need to be individualised for women with severe complications of COVID-19.
- All women who have been hospitalised and have had confirmed COVID-19 in pregnancy, or up to 6 weeks postpartum, should be offered thromboprophylaxis for at least 10 days following hospital discharge. A longer duration of thromboprophylaxis should be considered for women with persistent morbidity.

Labour and birth

- In women with symptomatic COVID-19, there may be an increased risk of fetal compromise in active labour and of caesarean birth. Women with symptomatic suspected or confirmed COVID-19 should be advised to labour and give birth in an obstetric unit with continuous electronic fetal monitoring. This is not required for asymptomatic infection.
- Senior obstetric and medical input for a woman with severe or critical COVID-19 should be sought, particularly for decision making about birth.
- The level of personal protective equipment (PPE) required by healthcare professionals caring for a woman with COVID-19 who is undergoing a caesarean birth should be determined by national and local guidelines.
- Water birth is not contraindicated for women who are asymptomatic of COVID-19, providing adequate PPE can be worn by those providing care. Women with symptomatic COVID-19 should not labour or birth in water.

Clinical deterioration

- Chest imaging is essential for the evaluation of an unwell woman with COVID-19. It should be performed when indicated in pregnant women, and not delayed because of radiation exposure concerns.
- A woman's care should be escalated urgently if signs of decompensation develop. These signs include: increasing oxygen requirements or fraction of inspired oxygen (FiO_2) above 35%, increasing respiratory rate above 25 breaths/minutes or a rapidly rising respiratory rate despite oxygen therapy, a reduction in urine output, acute kidney injury or drowsiness.
- For unwell pregnant women in the third trimester, an individualised assessment should be undertaken by a multidisciplinary team to decide if maternal stabilisation is required before birth can be undertaken safely. Following this, decisions concerning emergency caesarean birth or induction of labour should be prioritised, either to facilitate maternal resuscitation (including the need for prone positioning) or because of concerns regarding fetal health.
- Aspirin may be beneficial for adults with severe COVID-19. This potential benefit must be weighed up against the increased risk of major bleeding events but, in those who have been taking prophylactic aspirin in pregnancy, it seems reasonable for this to be continued. COVID-19 can be associated with thrombocytopenia, however, and aspirin should be discontinued if the platelet level is less than 50×10^9/l.
- Oxygen should be titrated to ensure saturations of 94–98% using escalation through nasal cannula, face mask, venturi mask, non-rebreather mask, non-invasive positive airway pressure (e.g. continuous positive airway pressure [CPAP]), intubation and intermittent positive-pressure ventilation (IPPV), and extracorporeal membrane oxygenation (ECMO) as appropriate.
- Caution should be applied to fluid balance and intravenous (IV) fluid management. Hourly fluid input/output charts should be recorded in women with moderate to severe symptoms of COVID-19, aiming to maintain a neutral fluid balance in labour. When required, fluid boluses in volumes of 250–500 ml may be employed.
- Women requiring oxygen should be offered corticosteroids with PPI cover. Corticosteroid therapy should be given for 10 days or up to discharge, whichever is sooner, for women who are unwell with COVID-19 and requiring oxygen or ventilatory support. If steroids are not indicated for fetal lung maturity, treatment should be with oral prednisolone 40 mg once a day, or IV hydrocortisone 80 mg twice daily, for 10 days or until discharge, whichever is sooner. If steroids are indicated for fetal lung maturity, prescribe intramuscular dexamethasone 12 mg twice (24 hours apart), immediately followed by oral prednisolone 40 mg once a day, or IV hydrocortisone 80 mg twice daily, to complete a total of 10 days or until discharge, whichever is sooner. IV methylprednisolone is an alternative especially for intensive care units more familiar with this preparation.
- Tocilizumab (interleukin-6 receptor antagonist) has been shown to improve outcomes, including survival, in hospitalised patients with hypoxia and evidence of systemic inflammation (C-reactive protein at or above 75 mg/l). Its use in pregnancy should be strongly considered.
- Strongly consider treatment with neutralising monoclonal antibodies (nMAB's) in pregnant and breastfeeding women who are unwell in hospital settings, particularly if they are unvaccinated and/or have additional risk factors for severe illness. Monoclonal antibodies are also recommended for those in the community who meet specific very high-risk criteria.
- Remdesivir should only be considered in pregnant women with COVID-19 who are not improving or who are deteriorating.
- Hydroxychloroquine, lopinavir/ritonavir and azithromycin should not be used as they are ineffective for treating COVID-19 infection. Molnupiravir, Baricitinib and Paxloid are also not recommended in pregnancy.
- Women who have been seriously or critically unwell from COVID-19 should be offered an ultrasound scan to assess the fetal biometry. It seems reasonable to arrange the first scan within the first 14 days following recovery and to consider further ultrasound monitoring on an individual basis.

Postnatal care

- Women should be informed that COVID-19 infection is not a contraindication to breastfeeding.

Coronavirus (COVID-19) Infection in Pregnancy – Summary of updates

Version	Date	Summary of changes
16.0		Updating epidemiology and vaccine safety data. Refocussing of guidance to clinical key clinical aspects of care, including removal of pandemic service delivery advice (antenatal, intrapartum and postpartum), triage recommendations and escalation plans. Grading of main evidence and strength of recommendations.

1 Purpose and Scope

This document aims to provide clinical guidance to healthcare professionals who care for pregnant women with COVID-19. The advice in this document is provided as a resource for UK healthcare professionals based on a combination of available evidence, good practice and expert consensus opinion. The guidance may also be relevant to other healthcare systems but may need to be adapted for the local environment.

Within this document we use the terms 'pregnant woman' and women's health. However, it is important to acknowledge that it is not only people who identify as women for whom it is necessary to access care. Obstetrics and gynaecology services, and delivery of care, must therefore be appropriate, inclusive, and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

1.1 Identification and assessment of evidence

This clinical guidance has been developed by a multidisciplinary group using the best available evidence retrieved by regular literature reviews undertaken by a member of the RCOG Library team. Bespoke search strategies are currently performed on Pubmed, MIDIRS Maternity and Infant Care database, and WHO global literature on Coronavirus disease databases. Search strategies and criteria have been updated over time to reflect the evolving nature of the coronavirus pandemic. Further details about the RCOG literature searching process can be obtained by contacting library@rcog.org.uk.

This version of the guidance was developed by a multidisciplinary group of authors listed in Acknowledgments. While this document has not been subject to an open peer review or formal stakeholder consultation process, specific individuals and groups were asked to review its content prior to publication. These are also listed in Acknowledgments and include a wide range of external stakeholders including lay representatives, other Royal Colleges and professional associations and representatives from the governments across England and the devolved nations. The evidence and recommendations in previous versions of this guidance were ungraded. Most of the evidence and recommendations in this guidance have now been classified using the system outlined in Appendix II. Where recommendations are based on expert opinion (rather than published evidence), these are presented as Good Practice Points within the document.

No external funding was received in order to develop this guidance.

1.2 Epidemiology

SARS-CoV-2 is the strain of coronavirus which causes COVID-19. It was first identified in Wuhan City, China, towards the end of 2019.*[1]* As with all viruses, mutations lead to the emergence of new strains. To date, five of the new strains of the COVID-19 virus are of concern and have been termed the Alpha, Beta, Gamma, Delta and Omicron variants. These variants have specific traits which may include increased transmissibility or more severe disease.*[2]* The Delta variant, for example, seems to be associated with more severe disease than some other variants: 1:10 symptomatic women admitted to hospital with the Alpha variant needed admission to intensive care whereas this was 1:7 for symptomatic women with the Delta variant.*[3]*

1.3 Transmission

The virus can be readily isolated from respiratory droplets or secretions, faeces and probably to a much lesser extent fomites (objects). Transmission is known to occur most often through close contact with an infected person. With regard to vertical transmission (transmission from woman to her baby antenatally or intrapartum), evidence suggests that vertical transmission is uncommon.*[4]* If it does occur, it appears to not be affected by mode of birth, delayed cord clamping, skin-to-skin contact, method of feeding or whether the woman and baby stay together (rooming in).*[5][6][7][8][9][10][11][12][13]*

There is, however, good evidence of transplacental transmission of antibodies against COVID-19 following maternal infection. Several studies*[14][15][16][17]* have demonstrated the presence of immunoglobulin G (IgG) umbilical cord blood samples suggesting that passive immunity might be transferred to the neonate. IgG levels in cord blood have been reported to be higher with longer intervals between maternal infection and birth.*[14][17][18]* Six months after birth, SARS-CoV-2 IgG antibodies have been detected in infant blood samples following infection in pregnancy. This was not detectable in all infants, but when detected, IgG levels were significantly lower than levels at birth. This raises the possibility of waning passive immunity in infants following maternal COVID-19 infection.*[14][17][18]*

1.4 Effect of COVID-19 on pregnant women

1.4.1 Symptoms of COVID-19 in pregnant women

Summary points

- Pregnant women with no comorbidities do not appear any more or less likely to contract the infection than the general population.
- Pregnant women with comorbidities such as pre-existing diabetes, body–mass index (BMI) >25 kg/m^2 and gestational diabetes on insulin are at increased risk of contracting SARS-CoV-2 infection.
- The majority of pregnant women who are infected with SARS-CoV-2 are asymptomatic.
- Most symptomatic women experience only mild or moderate cold/flu-like symptoms.
- The main symptoms of COVID-19 in pregnancy.

Pregnant women do not appear to be any more or less likely to contract the infection than the general population.*[19]* The INTERCOVID multinational study of unvaccinated women,*[20]* however, has shown that pregnant women with pre-existing diabetes, obesity, and gestational diabetes on insulin have significant increased chance of contracting SARS-CoV-2 infection compared with pregnant women without these comorbidities. Women with diabetes had nearly double the risk of SARS-CoV-2 infection (RR 1.94, 95% CI 1.55–2.42), those overweight and obese had a 20% increased risk (RR 1.20, 95% CI 1.06–1.37) and women who developed insulin-dependent gestational diabetes mellitus had an increased risk of SARS-CoV-2 infection (RR 1.79, 95% CI 1.06–3.01).*[20]*

The majority of pregnant women who are infected with SARS-CoV-2 are asymptomatic: studies reporting on universal screening in pregnancy found a range of 73% (24) to 86% (25) of women who tested positive for SARS CoV2 were asymptomatic.*[21][22]* Most symptomatic women experience mild or moderate cold/flu-like symptoms.*[23]* The PregCOV-19 Systematic Review*[21]* included over 293 000 pregnant women worldwide with suspected or confirmed COVID-19. In this review, the overall rate of COVID-19 diagnosis in pregnant and recently pregnant women attending or admitted to hospital for any reason was 9%. The most common symptoms of COVID-19 in pregnant women were cough and fever (both 36%). Less frequent symptoms were dyspnoea (19%), myalgia (17%), loss of sense of taste (9%) and diarrhoea (5%).*[24]*

It is unclear whether pregnancy will impact on the proportion of women who develop prolonged signs and symptoms after an acute SARS-CoV-2 infection (so-called 'long COVID' or post-COVID-19 condition). The National Institute for Health and Care Excellence (NICE) has produced a rapid guideline outlining the care of individuals who develop long-term effects of COVID-19.*[21][25]*

The Omicron variant is more infectious, but it associated with less severe disease than the Delta variant, with lower risk of short-term adverse maternal and perinatal outcomes.*[26]* The Omicron variant may be associated with less severe disease than the Delta variant, but it is more infectious. Symptoms such as a sore throat appear to be more common in infection from the Omicron variant, whereas symptoms such as altered sense of smell appear less common.*[27]* Omicron has similar mortality outcomes as pre-Delta variants in unvaccinated pregnant women.*[28]*

1.4.1.1 Frequency of severe illness in pregnant women

COVID-19 ranges from asymptomatic infection through to mild disease (no evidence of pneumonia or hypoxia), moderate disease (viral pneumonia), severe disease (severe pneumonia, e.g. with SpO_2 below 90% on room air) and critical disease (Acute Respiratory Distress Syndrome [ARDS], sepsis, septic shock, or complications such as pulmonary embolism or acute coronary syndrome).

Admission for COVID-19 infection appears to be more common in later pregnancy. In the UKOSS study,*[29]* most women were hospitalised in the third trimester or peripartum (bearing in mind that admission at term to give birth will contribute to this distribution). Symptomatic COVID-19 was principally diagnosed in the third trimester: 83% of symptomatic women were diagnosed at or beyond 28 weeks, with 52% diagnosed at or beyond 37 weeks. The reason for hospital admission was known for a subset of pregnant women in the UKOSS study. For asymptomatic women, the reason for admission was principally to give birth (68%). For symptomatic women, the reasons for admission were roughly a third for symptomatic COVID-19, a third to give birth, and a third for other reasons.

Data suggest that maternal mortality has increased during the pandemic. UK maternal mortality is estimated to be 20% higher

than in previous recent years (12/100 000 maternities compared to 10/100 000) although the rise in maternal death is not all attributed directly to COVID-19. The estimated SARS-CoV-2 associated maternal mortality rate for the MBRRACE rapid review period of 1 June 2020 to 31 March 2021 was 2.4 per 100 000 (95% CI 1.3–4.0). Twenty-four women with SARS-CoV-2 infection were reported to MBRRACE-UK;*[30]* 20 during pregnancy or in the immediate postpartum period (up to 6 weeks postnatal) and four during the extended postpartum period (up to 1 year). Nineteen deaths were because of COVID-related respiratory or thrombotic disease. Of note, in the same time period, the Office for National Statistics reported 319 deaths of women aged 20–39 in England and Wales with COVID-19 mentioned on the death certificate.

Overall pregnancy outcomes for women with COVID-19 are worse than for women without COVID-19. PregCov-19 (Dec 2019–Apr 2021) and a subsequent RCOG meta-analysis looking at studies published after between October 2020 to January 2022 have calculated odds ratios of key maternal outcomes (Table 1) and perinatal outcomes (Table 2).

1.4.1.2 Data from studies comparing severity of COVID-19 in pregnant and non-pregnant women

There is evidence that pregnant women may be at increased risk of severe illness from COVID-19 compared with non-pregnant women, particularly in the third trimester. The most consistent signal of increased severity of COVID-19 in pregnancy is an increase in ICU admissions for pregnant women. However, ICU admission rates must be interpreted with caution as the threshold for ICU admission for a pregnant woman may be lower than for a non-pregnant woman.

Outcomes are worse for pregnant women with COVID-19 compared to non-pregnant women with COVID-19. The PregCov-19 Systematic Review Consortium*[21]* (Dec 2019–Oct 2020) and a subsequent RCOG meta-analysis looking at studies published after this date (Oct 2020–Jan 2022) have calculated odds ratios for outcomes (Table 2).

Table 1. Maternal outcomes PregCov-19 versus RCOG meta-analysis

	PregCov-19, OR (95% CI)	RCOG meta-analyses, OR (95% CI)
ICU admission	2.13 (1.54–2.95)	2.40 (2.25–2.57)
Mechanical ventilation	2.59 (2.28–2.94)	1.49 (1.33–1.66)
Death	0.96 (0.79–1.18)	1.39 (1.23-–1.57)

Note: This table makes comparisons to version 2 of PregCov-19 systematic review (search date October 2020, publication acceptance February 2021). A further update to PregCov-19 systematic review has recently been released (search date April 2021, publication acceptance May 2022). The more current data is captured by the RCOG meta-analyses (search until Jan 2022). All data from PregCov-19 in the body of this guideline reflect the May 2022 version unless stated otherwise.

Studies on the risk of severe disease from COVID-19 in pregnancy are summarised in Appendix III, Table 2. The care of pregnant women with severe COVID-19 is covered in section 4 of this guidance.

1.5 Risk factors for hospital admission with COVID-19 infection in pregnancy

Summary points

- Risk factors that appear to be associated both with COVID-19 infection and admission to hospital with COVID-19 include:
  - Being unvaccinated.
  - Black, Asian or other minority ethnic background.
  - Having a BMI of 25 kg/m^2 or more.
  - Pre-pregnancy co-morbidity, such as pre-existing diabetes or chronic hypertension.
  - Maternal age 35 years or older.*[21][31]*
  - Living in areas or households of increased socioeconomic deprivation (data not specific to pregnancy).*[32]*
- In addition to these, the risk of becoming infected with SARS-CoV-2 is higher in individuals who are more exposed, for example, those working in healthcare or other public-facing occupations.

In the PregCOV-19 Systematic Review,*[21]* the maternal risk factors associated with severe COVID-19 were: age 35 years and older, OR 1.56 (95% CI 1.19–2.04); BMI 30 kg/m^2 and above, OR 1.84 (95% CI 1.46–2.31); chronic hypertension, OR 1.75 (95% CI 1.40–2.20); and pre-existing diabetes, OR 2.90 (95% CI 1.93–4.34).

The UKOSS/ISARIC/CO-CIN study*[33]* in the UK described the characteristics of 5479 pregnant women with confirmed SARS-CoV-2. The estimated incidence of pregnant women admitted to hospital with SARS-CoV-2 aged 35 and older was 8.93/1000 maternities (95% CI 8.49–9.39), pregnant women with a BMI at 30 kg/m^2 and above 10.18/1000 maternities (95% CI 9.70–10.68), and pregnant women of Black, Asian or other minority ethnic background 18.06/1000 maternities (95% CI 17.12-19.04), 18.83/1000 maternities (95% CI 17.36–20.42) and 8.17/1000 maternities (95% CI 7.35–9.07) respectively.

The association between Black, Asian and minority ethnic background and severe COVID-19 in pregnancy echoes findings from before the pandemic which showed women of Black, Asian and minority ethnic background have higher morbidity and mortality in pregnancy than white women. For example, the MBRRACE-UK report of the Confidential Enquiry into Maternal Death and Morbidity 2016–2018*[34]* showed there remains a more than four-fold difference in mortality rates among Black women, three-fold among mixed ethnicity women and an almost two-fold difference among Asian women compared with white women.

The association between Black, Asian and minority ethnic background and severe COVID-19 or death from COVID-19 is not confined to pregnant women. In the UK, 13% of the total population identify as being from a Black, Asian and minority ethnic background, but 30% of all individuals admitted to UK critical care for COVID-19 were from these backgrounds, and furthermore were more likely to die from COVID-19.*[35][36]* In the case of COVID-19, it has been postulated this association may be related to health inequalities or socioeconomic factors, or vitamin D deficiency.*[31][37][38][39]* UK advice recommends vitamin D supplementation to all pregnant women and individuals of Black, Asian and minority ethnic background, regardless of the COVID-19 pandemic.*[40][41]*

1.6 Effect of COVID-19 on pregnancy

There are limited data available for the impact of COVID-19 infection on first- and second-trimester pregnancy loss. A nationwide study in the USA*[42]* reported no increase in the risk of fetal loss prior to 20 weeks of gestation because of COVID-19 infection. Small studies*[43][44]* have also confirmed similar findings, with no statistically significant increase in fetal loss prior to 20 weeks of gestation associated with COVID-19 infection.

Despite over 100 million confirmed COVID-19 infections worldwide, there has been no reported increase in the incidence of congenital anomalies.

The PregCOV-19 Systematic Review (February 2021 version)*[21]* 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). A subsequent RCOG meta-analysis looking at studies published after this date (Table 2) supported these findings of an increased risk of stillbirth (OR 1.80, 95% CI 1.63–1.99). These numbers are similar to the May 2022 PregCov update.*[21]*

Table 2. Perinatal outcomes PregCov-19 versus RCOG meta-analysis

	PregCov-19, OR (95% CI)	RCOG meta-analyses, OR (95% CI)
Preterm birth (often for maternal indications)	1.47 (1.14–1.91)	1.47 (1.44–1.51)
Stillbirth	2.84 (1.25–6.45)	1.80 (1.63–1.99)

Note: This table makes comparisons to version 2 of PregCov-19 systematic review (search date October 2020, publication acceptance February 2021). A further update to PregCov-19 systematic review has recently been released (search date April 2021, publication acceptance May 2022). The more current data is captured by the RCOG meta-analyses (search until Jan 2022). All data from PregCov-19 in the body of this guideline reflect the May 2022 version unless stated otherwise.

There is evidence that COVID-19 infection causes a range of non-specific placental histological changes including fetal and maternal vascular changes, malperfusion, chorioamnionitis, acute inflammatory pathology, chronic inflammatory pathology, increased perivillous fibrin and intervillous thrombosis. Studies*[45][46][47][48]* have described specific histological features in placentas associated with cases of stillbirth and late second trimester miscarriage in relation to infection with both the Alpha and Delta variants. Severe placental lesions in the context of proven COVID-19 placental infection, such as trophoblastic necrosis and massive haemorrhage, causing rapidly deteriorating placental function has been linked to a number of stillbirths in women with COVID-19 infection, described as COVID-19 placentitis.

In one study,*[46]* 10 out of 50 placentas from unvaccinated women who had tested positive for COVID-19 in pregnancy showed evidence of placental COVID-19 infection. Five of these were associated with stillbirth with severe placental changes, while the remaining five had more focal changes in association with possible FGR.*[46][47]*

The largest prospective study*[49]* of 165 unvaccinated women with COVID-19 in pregnancy had six stillbirths, all of which showed severe and extensive histological changes of COVID-19 placentitis obliterating over 75% of the maternal intervillous space. Similar histological lesions affecting less than 25% of the placenta were recorded in seven liveborn neonates, while the remaining 152 placentas of COVID-19-affected pregnancies with livebirths did not show similar findings. The majority (5/6) of these stillbirths had additional maternal risk factors for stillbirth (such as thrombophilia and gestational diabetes). Asymptomatic COVID-19 cases were less likely to develop placentitis (*P*=0.007); even mild COVID-19 symptoms were associated with an increased association with placentitis (*P*=0.007).

This study*[49]* suggests a significant association between COVID-19 infection in women with thrombophilia and an increased risk of COVID-19 placentitis (30% [n=3] had thrombophilia and placentitis; 1.7% [n=1] had thrombophilia without placentitis [*P*=0.008]). Although these numbers are too small to draw robust recommendations, pending further evidence there should be a lower threshold for offering women with thrombophilia who develop COVID-19 in pregnancy additional monitoring, such as serial growth scans. Of note, there are no similar studies looking at vaccinated women, so this may not extrapolate to the vaccinated population.

It appears possible that a relatively sudden, severe placental dysfunction may occur with COVID-19, which appears to be unrelated to severity, but instead to placental COVID-19 infection. This can be associated with a coagulopathy similar to disseminated intravascular coagulation (DIC), characterised by low platelets and low fibrinogen, and is strongly linked to an adverse perinatal outcome. Screening for this is challenging due to its sudden onset.

Maternal COVID-19 infection probably increases the risk of FGR. A published systematic review of 42 studies*[50]* reported an increased risk of low birthweight (OR 1.89, 95% CI 1.14–3.12) associated with maternal COVID-19 infection, and a large multinational study*[51]* also reported a higher low birthweight rate (RR 1.58, 95% CI 1.29–1.94) among women with COVID-19 infection.

Preterm birth is the single biggest cause of neonatal morbidity and mortality in the UK, with about 7% of babies in the UK born preterm.*[52][53]* The preterm birth rate in women with symptomatic COVID-19 appears to be two to three times higher than this background rate. The PregCOV-19 Systematic Review*[21]* estimated the risk of preterm birth at approximately 17%. Most of these preterm births (94%) were iatrogenic.*[31]* The most recent UKOSS study*[29]* confirmed that preterm birth was more likely for women with COVID-19: occurring in 19% of women with symptomatic COVID-19,.*[50][54][55][56]* particularly if COVID-19 infection occurs after 20 weeks gestation.*[57]* Pregnant women with asymptomatic COVID-19 do not, however, seem to be at significantly increased risk of preterm birth (9% for women with asymptomatic COVID-19 versus 7% background rate).Emerging evidence may have highlighted the possibility that implementation of measures for COVID-19 mitigation promoted positive lifestyle and environmental changes related to the occurrence of pregnancies ending preterm.*[58]*

For babies born to women with COVID-19 the overall outcomes are very positive, with over 95% of newborns being born in good condition.*[6][59]* In the updated UKOSS study,*[29]* 19% of babies born in the UK to women with symptomatic SARS-CoV-2 infection were admitted to the neonatal unit. These admissions may, in part, represent the policy of maternity units rather than concerns about wellbeing of the neonate.

A national study in England*[55]* of maternal COVID-19 infection also reported no difference in measures of neonatal morbidity including admission to neonatal unit or readmission, when restricting the analysis to babies born at term. This is indicative that reports of neonatal morbidity for babies born to women with COVID-19 infection is likely to be associated with prematurity.

Maternal COVID-19 is associated with an increased rate of caesarean birth. From the initial UKOSS study,*[31]* 59% of women had caesarean births; approximately half of these were because of maternal or fetal compromise. The remainder were for obstetric reasons (e.g. progress in labour, previous caesarean birth) or maternal request (6%). Of the women having a caesarean birth, 20% required general anaesthesia (GA). Approximately two-thirds of the women who had GA were intubated for maternal respiratory compromise, and the remaining third was to facilitate urgent birth. The updated UKOSS data*[29]* confirmed this trend, with a 49% caesarean birth rate for women with symptomatic COVID-19 versus 29% for a historical control group from 2018.

Appendix III shows meta-analyses on maternal and pregnancy outcomes from studies published between October 2020–January 2022.

2 COVID-19 vaccination in pregnancy

This section aims to summarise, in a format useful for maternity care, the evidence presented in existing COVID-19 vaccination guidance from the UKHSA Green Book*[60]* as well as leaflets and information from Public Health England (PHE) and the NHS.

2.1 Background on COVID-19 vaccines available in the UK

Summary points

COVID-19 vaccine background (in non-pregnant population):

- The phase 3 trials of the six UK approved vaccines assessed protection against COVID-19 after two doses in five, and after a single dose in one. Prior to Omicron:
  - The Pfizer-BioNTech vaccine had an efficacy of 95% (95% CI 90.0–97.9%) against symptomatic COVID-19.*[61]*
  - The Oxford-AstraZeneca vaccine had an efficacy of 66.7% (95%CI 57.4–74.0%) against symptomatic COVID-19.*[62]*
  - The Moderna vaccine had an efficacy of 94.1% (95% CI 89.3–96.8%).*[63]*
  - The Janssen vaccine had an efficacy of 66.1% (95% CI 55.0–74.8%).*[64]*
  - The Novovax vaccine has an efficacy of 89.7% (95% CI 80.2–94.6%).*[65]*
  - The Valneva vaccine has an efficacy of 65.9% (95% CI 65.2–66.6%).*[66]*
- Real-world monitoring has confirmed that one dose of the Pfizer-BioNTech or Oxford-AstraZeneca vaccines confers about 60% protection against symptomatic COVID-19 (Alpha and Delta variants), however, less protection may be conferred against the Omicron variant.*[67]*
- Real-world monitoring has confirmed that one dose of the Pfizer-BioNTech or Moderna vaccines confers about 75% protection against symptomatic COVID-19 which drops to 25% after 25 weeks. Two doses of the Oxford-AstraZeneca vaccine confers around 45–50% protection against Omicron, which falls to almost no effect after 20 weeks.*[67]*
- A booster dose of Pfizer-BioNTech or Moderna confers around 60-75% protection against Omicron, which drops to 25–40% after 15 weeks.*[68]*
- Vaccination with two doses of the Pfizer-BioNTech or Oxford-AstraZeneca vaccines are effective against symptomatic disease secondary to infection by the Delta variant.*[69][70]*
- Those who have had two doses and a booster (or three doses) of vaccine (combined data on Pfizer-BioNTech, Oxford-AstraZeneca and Moderna) are 88% less likely to be admitted to hospital with the Omicron variant than those who have not been vaccinated.*[71]*
- Women should be advised that influenza vaccination is still safe at all gestations of pregnancy and is recommended to protect both the woman and baby from the adverse effects of becoming seriously ill with influenza during pregnancy.
- Women can receive COVID-19 and influenza vaccines at the same time.

2.1.1 Available vaccines in the UK and their mechanisms of action

As of February 2022, six COVID-19 vaccines are approved for use in the UK: the Pfizer-BioNTech vaccine, the Oxford-AstraZeneca vaccine, the Moderna vaccine, the Janssen vaccine, the Novavax vaccine and the Valneva vaccine (Table 3). The Pfizer or Moderna vaccine are specifically recommended as there are most pregnancy data on these.

The Pfizer-BioNTech and Moderna vaccines are messenger RNA (mRNA) vaccines in which mRNA encoding SARS-CoV-2 spike protein is injected via a lipid nanoparticle coat. The mRNA does not go into the nucleus of the host cell, so it remains separate from the host DNA. The host cell produces the spike protein which elicits an immune response.

The Oxford-AstraZeneca vaccine is a viral-vector vaccine in which DNA encoding the SARS-CoV-2 spike protein is injected within a modified adenovirus. The adenovirus vector has been modified so that it cannot replicate, and the spike protein is not expressed on the adenovirus itself. The adenovirus vector serves only to deliver the spike protein DNA into the host cell. The host cell then produces the spike protein, which then elicits an immune response.

Current COVID-19 vaccines offer a lesser degree of protection against the Omicron variant with the level of protection waning more quickly in the months post vaccination.*[72]* Nevertheless, vaccination does protect individuals against symptomatic coronavirus and hospitalisation.*[73]*

Information on other COVID vaccines, which are not currently recommended for pregnant women in the UK, can be found at https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/.

Table 3. Vaccines approved for used in the UK

Vaccine	Type	Mechanism of Action	Efficacy
Pfizer-BioNTech BNT162bN	mRNA	Injection of spike protein coding mRNA leading to antigen expression + immune response development	95% (95% CI 90.0–97.9%)
Moderna MRNA-1273	mRNA	Injection of spike protein coding mRNA leading to antigen expression + immune response development	94.1% (95% CI 89.3–96.8%)
Janssen Ad26.COV2.S	Viral vector	Inactivated modified adenovirus containing viral peptide DNA leads to expression of viral proteins	66.1% (95% CI 55.0–74.8%)
Oxford-AstraZeneca AZD1222	Viral vector	Inactivated modified adenovirus containing viral peptide DNA leads to expression of viral proteins	66.7% (95%CI 57.4–74.0%)
Novovax Nuvavaxiod NVX-Co2373	Spike protein subunit	Injection of spike protein subunit	89.7% (95% CI 80.2–94.6%)
Valneva VLA2001	Inactivated virus	Inactivated COVID virus envelope injected to stimulate immune response	65.9% (95% CI 65.2–66.6%)

UKHSA data have demonstrated the importance of a booster vaccine for protection against the Omicron variant.*[71]* For example, a Pfizer-BioNTech or Moderna booster following two initial doses of the Oxford-AstraZeneca or Pfizer BioNTech vaccines boosted protection against symptomatic Omicron infection from 0–10% protection pre-booster to 50–80% within 1 week. Protection levels of about 40–70% persisted 10 weeks after booster vaccination depending on the exact vaccination regimen administered. There is also evidence that a booster vaccination reduces hospital admission rates with a 68% reduction in hospitalisation from Omicron infection, and an 88% reduction in hospitalisation risk 2 weeks after a booster dose.*[71]*

Studies have shown that 96% of pregnant women admitted to hospital with symptomatic COVID-19 were unvaccinated*[74]* and that 98% of pregnant women admitted to intensive care were unvaccinated.*[74]*

2.1.2 Vaccine safety

The adverse effect profiles of the available vaccines were similar in their phase 3 trials. Most participants in the trials had a minor local reaction (pain, redness or swelling at the injection site). Mild systemic adverse effects like fatigue, headache or myalgia were also common; these were typically short-lived (less than a few days). About 10–20% of participants had a fever after vaccination. In general, adverse events are more common after the first dose than the second dose for the Oxford-AstraZeneca vaccine and more common after the second dose than the first dose for the Pfizer-BioNTech and Moderna vaccines.

These vaccines have continued to be monitored for safety after their authorisation, and an association has emerged between the Oxford-AstraZeneca vaccine and rare cases of serious thrombosis in the context of thrombocytopenia (see section 2.3.1.2). There have also been rare reports of myocarditis and pericarditis following vaccination with Pfizer-BioNTech and Moderna vaccines (see section 2.3.1.3).*[75]*

Recent research raises the possibility of trace amounts of vaccine mRNA being detected in breastmilk briefly after vaccination. These studies present small numbers of cases with inconsistent results, and should therefore be interpreted with caution.*[76][77][78]* Stomach enzymes are known to breakdown mRNA and there is no evidence that, even if any mRNA fragments were absorbed, they would have any adverse effect on the baby. Although more research is awaited, breastfeeding is known to be very important for babies, there are good data showing no adverse neonatal effects following maternal vaccination,

and there also is emerging evidence that vaccination in pregnancy decreases the likelihood of infant hospital admission due to COVID-19.*[79][80]* Breastfeeding following maternal vaccination is therefore still strongly recommended and it should be continued after vaccination.

2.2 Eligibility for the vaccine in pregnancy

Strong recommendation

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Vaccination against COVID-19 is strongly recommended and should be offered to all pregnant women. Pregnant women are recognised as a priority group for vaccination.	**2++**	**B**	There is excellent real-world evidence of vaccine efficacy, with vaccinated pregnant women having a much lower rate of hospital admission and an almost 50:1 lower odds of severe infection compared to unvaccinated women.*[3]* Large published series' have not identified any safety problems with regards to maternal or neonatal risks.

Rationale

The eligibility criteria are based on recommendations from the Joint Committee on Vaccination and Immunisation (JCVI).*[81]* The choice of vaccine is based on the recommendations from the UKHSA Green Book*[60]* and reflects the fact that most of the safety data regarding vaccination in pregnancy comes from the USA where pregnant women were usually offered the Pfizer-BioNTech or Moderna vaccines.

Pregnant women should be offered the Pfizer-BioNTech or Moderna vaccines unless they have already had one dose of the Oxford-AstraZeneca vaccine, in which case they can complete the course with the same vaccine or with an mRNA vaccine (provided there are no contraindications to either). Women should be encouraged to receive a booster dose when eligible.*[82]*

The uptake of COVID-19 booster vaccinations in pregnancy are recommended in line with national government recommendations.

2.3 Potential fetal and maternal effects

Summary points

- More than 1.3 million women have received COVID-19 vaccination in pregnancy. Follow up of 347 150 pregnant women in the US and UK demonstrates no concerning adverse effects.
- Minor and short-lived adverse effects following COVID-19 vaccination have similar profiles in pregnant and non-pregnant women.
- More serious side effects such as vaccine induced thrombocytopenia and thrombosis or myocarditis are extremely rare.
- Following vaccination, there have been no differences in rates of miscarriage, congenital anomalies, or adverse obstetric or neonatal outcomes.
- 98% of severely ill women requiring ITU admission in the UK are unvaccinated.*[83]*
- There is no reported impact on fertility following COVID-19 vaccination.

Pregnant women were not included in initial large randomised controlled trials testing the safety and adverse effect profiles of the COVID-19 vaccines. Published data indicates that more than 347 150 women from diverse ethnic backgrounds in the UK and USA have had a COVID-19 vaccine in pregnancy with no concerning safety signals.*[68][84][75][85][86][87][85]*

Population registries in Brazil and India, have reported vaccination in a further 1.1 million pregnant women. Large population studies in Norway, Sweden and Canada reported no difference in preterm birth, stillbirth, SGA, low Apgar scores or NICU admission between unvaccinated women and those vaccinated mostly in the 2nd and 3rd trimester women.*[88][89][90][91][92]*

A large retrospective multicentre cohort study looked at the effect of COVID-19 vaccination and booster on maternal-fetal outcomes.*[93]* Vaccinated people compared to unvaccinated matched people had similar rates of hospitalisation, but significantly lower rates of supplemental oxygen use and vasopressor use (0.057, 95% 0.039–0.083, $P < 0.05$) during a maternal COVID-19 infection during Omicron dominance. Vaccinated people had better or comparable birth outcomes than unvaccinated people in a matched cohort: lower rates of stillbirth and similar rates of PTB, SGA, and VLBW. Furthermore, receiving a third mRNA COVID-19 booster dose at least five months following completion of the two-dose mRNA vaccination series was associated with significantly lower rates of maternal COVID-19 infection, COVID-19 related hospitalisation, PTB, stillbirth, and SGA compared to individuals that only received two mRNA doses. Altogether, this supports the conclusion that COVID-19 mRNA vaccination offers protection against adverse maternal-fetal outcomes, and that third boosters support statistically and clinically significant improvement in maternal-fetal outcomes.

Furthermore, a systematic review and meta-analysis from Egypt included 13 studies with a total number of 56 428 patients, looking at maternal and neonatal safety outcomes after SAR-CoV-2 vaccination during pregnancy.*[94]* Analysis showed no statistically significant difference in these and other outcomes: miscarriage (1.56% versus 0.3%. RR 1.23; 95% CI 0.54–2.78); length of maternal hospitalisation (MD 0.00; 95%CI -0.08 to 0.08); incidence of Apgar score≤7 at 5 min (1.47% versus 1.48%. RR 0.86; 95%CI 0.54–1.37); and birthweight (MD -7.14; 95%CI -34.26 to 19.99).

There are no known risks from receiving inactivated or recombinant vaccines in pregnancy, or while breastfeeding,*[95]* and therefore, there is no reason to suppose that the adverse effects from these COVID-19 vaccines should differ for pregnant women compared to non-pregnant women.

2.3.1 Maternal effects

2.3.1.1 Common minor adverse effects

Minor and short-lived adverse effects such as soreness at the injection site, headache and fatigue are common in the general population after a COVID-19 vaccine. A report*[96]* on the first 35 000 pregnant women to receive a COVID-19 vaccine in the USA showed similar patterns of reporting for common minor adverse effects.*[96]* Smaller observational studies*[97][98]* have also reached similar conclusions showing no significant difference between pregnant and non-pregnant women in their symptoms post vaccination, and a reduced incidence of systemic features such as fever in pregnant women.

2.3.1.2 Vaccine-induced thrombosis and thrombocytopenia

The rare syndrome of vaccine-induced thrombosis and thrombocytopenia (VITT) has been reported after the Oxford-AstraZeneca vaccine;*[99][100]* it has also been reported after the Janssen vaccine.*[101]* VITT is an unpredictable, idiosyncratic vaccine reaction (not dissimilar to heparin-induced thrombocytopenia and thrombosis associated with heparin therapy) and it is not associated with typical venous thromboembolism (VTE) risk factors. It has been described as presenting 5–28 days after the first dose, particularly in adults younger than 50 years old. Although pregnancy increases the risk of coagulopathy, there is no evidence that pregnant or postpartum women are at higher risk of VITT than non-pregnant age-matched women.*[60][102]* NICE has produced a rapid guideline [NG200]*[103]* on the clinical management of patients who develop VITT after COVID-19 vaccination.*[104]*

The risk of VITT is extremely low with a first dose of the Oxford-AstraZeneca vaccine (approximately 1:50 000),*[105][106]* and even lower with a second dose for those who were well after the first dose. The UK government has advised that individuals younger than 40 years old should be offered an alternative vaccine to the Oxford-AstraZeneca vaccine based on the risk/benefit ratio for this age group. There is no known risk of VITT with the Pfizer-BioNTech and Moderna vaccines.

2.3.1.3 Vaccine-induced myocarditis or myopericarditis

The development of myocarditis or myopericarditis (inflammation of the muscle layer of the heart and the sac enclosing it) following Moderna vaccination is extremely rare (incidence 0.01%). This should be compared to a higher risk of developing myocarditis or pericarditis following COVID-19 infection (incidence 0.045%), alongside other risks from COVID-19 infection.

A USA study*[107]* reported a higher risk of developing myocarditis or myopericarditis in unvaccinated individuals after COVID-19 infection, estimated to be 450/1 000 000 (0.045%), than in vaccinated individuals. The overall risk of developing myocarditis or myopericarditis is extremely low and is likely to be much lower than the risk of developing these conditions

following COVID-19 infection itself.

A population-based study in Denmark*[108]* reported the rare occurrence of myocarditis or myopericarditis in individuals following vaccination with the Pfizer-BioNTech and Moderna vaccines. Individuals were followed up for an average of 1 year post vaccination. During this period, 69/584 031 (0.01%) individuals were found to develop myocarditis or myopericarditis in the 28 days following vaccination.

Individuals who received the Moderna vaccine had a significant increase in myocarditis or myopericarditis compared with unvaccinated individuals (adjusted hazard ratio 3.29, 95% CI 2.3–6.68). Those who received the Pfizer-BioNTech vaccine had a non-significant increase in myocarditis or myopericarditis compared to unvaccinated individuals (adjusted hazard ratio 1.34, 95% CI 0.9–2.0).

2.3.2 Fetal effects

It is recognised that currently there are no long-term data on COVID vaccinations in pregnancy, but long-term follow-up data from the use of similar vaccines (e.g. whooping cough and influenza) are very reassuring. Pregnancy outcomes following mRNA vaccination (Pfizer-BioNTech and Moderna) appear similar to comparator groups prior to the onset of COVID-19, with preterm birth, SGA and major congenital anomalies detected similar to background incidence.*[96]* None of the women whose babies were born with congenital anomalies had received the COVID-19 vaccine in the first trimester or the periconception period.*[96]*

Findings from the USA*[96]* have not identified any safety problems with regards to maternal and neonatal risks. Spontaneous miscarriage occurred at a similar rate in women who received a COVID-19 vaccine as those who were unvaccinated (104/827, 12.6%), with 92.3% of these miscarriages occurring in the first trimester. More recent studies*[109][110][111][112][113][114]* have confirmed the safety of COVID-19 vaccines in early pregnancy with no increased risk of miscarriage, with a recent systematic review finding a reduction in stillbirth.*[115]* A large population-based cohort study of over 24 000 term newborns identified no adverse outcomes to newborns born to vaccinated women at 4-month follow up.*[115][116]*

2.3.2.1 Antibody transfer

Summary points

- SARS-CoV-2 antibodies in neonatal cord blood and in breast milk have been found following COVID-19 infection in pregnancy, and therefore it should be that passive immunity is conferred.*[15][117]*
- Vaccine-elicited antibodies have been found in neonatal cord blood and breast milk following the administration of a COVID-19 vaccine, and therefore it should be that passive immunity is conferred.*[15][117]*

SARS-CoV-2 antibodies have been found in neonatal cord blood and breast milk following maternal infection; similar findings have been reported following the administration of the COVID-19 vaccine. Two cohort studies of over 100 women established the presence of vaccine-elicited antibodies in infant cord blood and breast milk. Both studies were conducted in the USA and utilised Pfizer-BioNTech or Moderna vaccines.*[15][117]*

There is some suggestion that timing of vaccination in pregnancy or during lactation may influence the level of passive immunity conferred to the neonate, with two studies*[96][117]* reporting that production of IgG antibodies and their subsequent transfer are improved following a second dose of either vaccine. Similar to natural infection, IgA titres appear to remain stable for several weeks following vaccination, with mRNA vaccines suggesting continual transference of antibodies during lactation.*[118]*

Real world data demonstrates that infants of women who were vaccinated in pregnancy are less likely to be hospitalised in the first 6 months of life compared to infants from unvaccinated pregnancies. Population level data also finds that infants of vaccinated mothers are less likely to have a positive COVID-19 test in first four months of life.*[119][120]*

2.4 Recommended vaccine timing in relation to stage of pregnancy or breastfeeding

2.4.1 Timing of vaccination in pregnancy

Strong recommendation

Recommendation	Evidence Level	Strength	Rationale for the recommendation
COVID-19 vaccines can be given at any time in pregnancy.	2+	C	The safety data following vaccination are reassuring for all stages in pregnancy. As far as possible, women should be offered both doses and a booster before giving birth if time allows, or before entering the third trimester, bearing in mind that it takes time for immunity to develop and protection is higher after the second dose and a booster of the vaccine.*[60]*
Breastfeeding women can receive a COVID-19 vaccine; there is no need to interrupt breastfeeding to receive a dose of the vaccine.	2+	C	There have been no adverse events reported in infants to breastfeeding women who received a vaccine.*[81][95]*
Vaccination is strongly recommended in those planning to conceive, and in those undergoing treatment for sub-fertility. There is no need to delay conception in those recently vaccinated.	2+	C	There is no evidence to suggest COVID-19 vaccinations affect female fertility.*[109][110][111][112][113]*

Rationale

There is no robust evidence to guide the timing of vaccination in pregnancy; the recommendations above is based on expert opinion rather than experimental data.

The COVID-19 vaccines are considered to be safe and effective. Pregnant women are more likely to become seriously unwell when compared to non-pregnant women and have a higher risk of their baby being born prematurely if they develop COVID-19 in their third trimester (after 28 weeks of gestation).

As far as possible, women should be offered both doses and a booster dose before the entering the third trimester if time allows, or before giving birth, bearing in mind that it takes time for immunity to develop and protection is higher after the second dose and a booster of the vaccine.*[60]* Studies reporting women who had COVID-19 vaccination in the first trimester show no increased risks of miscarriage, congenital anomaly or other adverse outcomes. As of March 2022, over 53% of pregnant women have received one or more COVID vaccine.

There is no evidence to suggest COVID-19 vaccinations affect fertility. A meta-analysis of published research showed no impact of COVID-19 vaccination upon reproductive markers in men (sperm concentration, motility and volume), women (biochemical pregnancy rate, clinical pregnancy rates) or in reproductive hormone levels. *[121]* Vaccination is strongly recommended regardless of conception intentions or pregnancy status.

2.4.2 Timing in the postpartum period

Women in the immediate postpartum period should be offered vaccination in line with the general (non-pregnant) population.*[60]*

2.4.3 Timing with breastfeeding

The JCVI advice*[81]* published on 28 February 2022 stated there is no known risk in giving available COVID-19 vaccines to breastfeeding women. In general, there are no known risks from receiving inactivated or recombinant vaccines in pregnancy, or while breastfeeding,*[95]* and therefore, there is no reason to suppose that the adverse effects from these COVID-19 vaccines should differ for pregnant women compared to non-pregnant women.

Breastfeeding women should be offered vaccination at the same time as the general population. Emerging safety data across numerous studies on over 5000 lactating women identified no major adverse effects or significant impact on breastfeeding.*[122]* Women do not need to interrupt breastfeeding in order to receive a dose of a COVID-19 vaccine.

2.4.4 Timing for women who are planning a pregnancy/undergoing fertility treatment

The JCVI advises that women do not need a pregnancy test before vaccination, and that women planning a pregnancy do not need to delay pregnancy after vaccination.*[81]* The British Fertility Society and Association of Reproductive and Clinical Scientists*[123]* advise people of reproductive age to have a COVID-19 vaccine, including those individuals who are planning a pregnancy. COVID-19 vaccination is advised for women during fertility treatment, and there is no need to delay fertility treatment after receiving a COVID-19 vaccine.

There is no evidence that the current vaccination programme of adults in the UK has affected rate of fertility, conception, fetal abnormality and childbirth.*[124][125]* Several studies*[109][110][111][112][113][126]* in humans have shown no increase in the rate of miscarriage following vaccination and vaccination in the first trimester has no impact on rates of congenital anomaly. COVID-19 vaccinations do not impact outcomes following assisted reproduction.*[127]* The speculation that immunity to the spike protein could lead to fertility problems is not supported by evidence.*[128]* Most people who contract COVID-19 will develop antibodies to the spike protein and there is no evidence of reduced fertility problems in people who have already had COVID-19.

2.5 How should women be counselled?

Summary points

- Pregnant women should be supported to come to an informed decision about vaccination.
- Of pregnant women admitted to hospital with COVID-19 symptoms, 97% were unvaccinated. Of those with moderate-severe COVID-19, less than 1% had received COVID-19 vaccination.*[3]*
- An informed decision-making process should cover the options for timing of vaccination, the benefits and risks of vaccination and of declining vaccination.
- The RCOG Information sheet and decision aid can be used to aid counselling.

It is a pregnant woman's choice to have a vaccination against COVID-19. If a pregnant woman is undecided whether to get the COVID-19 vaccine, the role of the healthcare provider is to enable the pregnant woman to make her decision through an informed decision-making process (Appendix IV). It is not necessary to show evidence of this discussion prior to the pregnant women receiving their vaccination (as is the same for the general population presenting for COVID-19 vaccination).

A pregnant woman should have the opportunity to access reliable information about COVID-19 vaccine in pregnancy, for example from the NHS, UKHSA or the RCOG. An informed decision-making process involves supporting a pregnant woman to understand the options available (including the risks and benefits of those options) and to make a decision based on the evidence and her personal preference.*[129][130]* Should a woman decide not to receive a COVID-19 vaccination this decision should be recorded.

3 Venous thromboembolism prevention

Strong recommendation

Recommendation	Evidence level	Strength	Rationale for the recommendation
It should be recognised that the incidence of venous thromboembolism in pregnancy is increased with severe COVID-19 infection. Any association with mild or moderate infection is less certain.	**2+**	**C**	An observational cohort study observed a VTE incidence of 6% in a severe–critical group but only 0.2% in a mild–moderate group and none in an asymptomatic group ($P < 0.001$).
Women who are not unwell should stay hydrated and mobile.	**4**	**D**	The additional risk of VTE is likely to be low
Pregnant women admitted with confirmed or suspected COVID-19 who are: • **on low-flow oxygen and at low risk of bleeding should be offered a therapeutic dose of low molecular weight heparin (LMWH) for thromboprophylaxis, unless birth is expected within 24 hours.** • **on high-flow oxygen, CPAP, non-invasive ventilation or invasive ventilation should be offered a prophylactic dose of LMWH.**	**4**	**D**	There haemorrhagic risks of therapeutic anticoagulation in very unwell patients may outweigh any benefits of VTE prevention.
All pregnant women who have been hospitalised and have had confirmed COVID-19 should be offered thromboprophylaxis for 10 days following hospital discharge. A longer duration of thromboprophylaxis should be considered for women with persistent morbidity.	**4**	**D**	Individualised care is appropriate.
If women are admitted with confirmed or suspected COVID-19 within 6 weeks postpartum, they should be offered thromboprophylaxis for the duration of their admission and for at least 10 days after discharge. Consideration should be given to extending this until 6 weeks postpartum for women with significant ongoing morbidity.	**4**	**D**	Individualised care is appropriate.

Rationale

Pregnancy is a hypercoagulable state.*[131]* The existing RCOG Green-top Guidelines No. 37a*[132]* and 37b*[133]* on VTE prevention and management should support decision making during COVID-19 infection.

Evidence*[134][135]* indicates that individuals admitted to hospital with moderate and severe COVID-19 are hypercoagulable. This risk is likely to be multifactorial, including the reduced mobility resulting from hospital admission or choosing to self-isolate at home, and other associated obstetric or maternal morbidities. Consequently, the cumulative risk is difficult to quantify. In the MBRRACE rapid report*[136]* one women died from a confirmed thromboembolic event and a second woman experienced a sudden deterioration that may be attributed to a thromboembolic event. A study*[56]* has estimated the rate of thromboembolic events in relation to COVID-19 disease severity: 6% in a severe-critical group, 0.2% in a mild-moderate group and none in an asymptomatic group ($P < 0.001$ for trend across severity).

The above recommendations are based on expert consensus opinion. VTE prevention for an unwell woman with COVID-19 is considered in section 4.2.

Good practice statement

Good Practice Points

- Women should have a VTE risk assessment performed during their pregnancy in line with RCOG Green-top Guideline No. 37a. Infection with SARS-CoV-2 should be considered a transient risk factor and trigger reassessment.
- Thromboprophylaxis initiated for pregnant women who have tested positive for COVID-19 should be continued until they have recovered from the acute illness (between 7 and 14 days).
- Advice should be sought from a clinician with expertise in VTE for women with ongoing morbidity and limited mobility.

4 Managing clinical deterioration of COVID-19

4.1 How should a pregnant woman requiring hospital admission with symptoms suggestive of COVID-19 be investigated?

Summary points

- Pregnant and postpartum women presenting with COVID-19 should be investigated and treated the same as non-pregnant women unless there is a clear reason not to do so.
- The decision for admission or for self-directed care at home depends on the overall clinical picture. Care at home should include clear advice on what to do if a woman feels she needs further advice or is deteriorating. In some instances this may involve home monitoring of oxygen saturation levels.
- Women presenting with a fever should be cared for in line with RCOG Green-top Guideline No. 64a *Bacterial Sepsis in Pregnancy*. Testing for SARS-CoV-2 and other respiratory viruses should be offered in parallel to a full sepsis assessment in line with the UK Sepsis Trust Sepsis Screening and Action Tool.
- Bacterial (rather than viral) infection should be considered if the white blood cell count is raised (lymphocytes are usually low with COVID-19) and antibiotics should be commenced.
- Radiographic investigations should be performed as for a non-pregnant adult; this includes chest X-ray and computerised tomography (CT) of the chest. Urgent chest imaging is essential for the evaluation of an unwell woman with COVID-19 and should be performed promptly when indicated.
- A diagnosis of pulmonary embolism or heart failure should be considered for women presenting with chest pain, worsening hypoxia or a respiratory rate above 20 breaths/minute (particularly if there is a sudden increase in oxygen requirements), or in women whose breathlessness persists or worsens after expected recovery from COVID-19. Additional tests to investigate for possible differential diagnoses, including electrocardiogram, echocardiogram, CT pulmonary angiogram, ventilation perfusion lung scan, should be considered.
- Ferritin and C-reactive protein are usually raised in COVID-19. D-Dimer is also usually raised and is therefore not useful as a positive predictor of VTE in pregnancy.
- Disseminated intravascular coagulation can also occur, with low platelets and low fibrinogen levels, and sometimes prolonged prothrombin time and/or activated partial thromboplastin time. This may not always be related to disease severity but, in some instances, may relate to placental COVID-19 infection.
- Women reporting reduced fetal movements in the context of current or recent COVID-19 infection should be advised to attend for assessment. If fetal assessment is non-reassuring, further investigations should ideally include a FBC and coagulation screen (including fibrinogen level). A new finding of thrombocytopenia or low fibrinogen level in this context should prompt careful ongoing assessment for fetal compromise.

The clinical symptoms of COVID-19 overlap with those of a variety of other clinical conditions. Healthcare providers should consider all differential diagnoses for women who present with a fever in pregnancy and follow the advice and guidance of the RCOG Green-top Guideline No. 64a.*[137]*

Several studies*[138]* have shown decreased lymphocyte counts in the general population affected by COVID-19. One systematic review*[139]* noted decreased lymphocyte counts in pregnant women.

A DIC-like coagulopathy may rarely occur after only relatively mild disease in pregnancy. In contrast to COVID-19 in non-pregnant individuals there may be low platelets and fibrinogen, and aggressive treatment (including with cryoprecipitate) and earlier birth may be warranted.

4.2 How should a pregnant, or recently pregnant, woman with suspected or confirmed COVID-19 who is clinically deteriorating be cared for?

Summary points

Organisation and principles of care:

- Obstetricians should be familiar with and follow local guidelines for the initial investigation and care of women presenting with

possible COVID-19.
- Women with suspected COVID-19 should be treated as if positive until test results are available.
- The priority for medical care should be to stabilise the woman's condition with standard therapies.
- An urgent MDT meeting should be arranged for any unwell woman with suspected or confirmed COVID-19. This includes women who are requiring oxygen to maintain saturations between 94% and 98%, women with a respiratory rate above 20 breaths/minute and women with a heart rate greater than 110 beats/minute. This should ideally involve senior decision makers and may include: a consultant obstetrician, consultant anaesthetist, midwife-in-charge, consultant neonatologist, neonatal nurse-in-charge, intensivist responsible for obstetric care, an obstetric physician, a respiratory physician, the infection control and critical care outreach teams. The discussion should be shared with the woman, and her family if she chooses. The following should be considered:
  - Key priorities for medical care of the woman and her baby, and her birth preferences.
  - The most appropriate location of care (e.g. ICU, 'COVID bays', specific COVID-19 wards, isolation room in infectious disease ward or other suitable isolation room) and lead specialty.
  - Concerns among the team regarding special considerations in pregnancy, including the health of the baby.
- A consultant in obstetrics and gynaecology should review all pregnant and recently pregnant women with suspected or confirmed COVID-19 who are in hospital at least daily, particularly if they are admitted to a bed outside of the maternity unit.
- If appropriate, a designated team member should be responsible for regularly updating the woman's family about her health, and that of the baby.

Observations and investigations:

- Clinicians should monitor both the absolute values and trends of the hourly observations, including heart rate, respiratory rate and oxygen saturation.
- Clinicians should be aware that young, fit women can compensate for deterioration in respiratory function and are able to maintain normal oxygen saturations until sudden decompensation.
- Units should have an escalation plan for the care of pregnant and postnatal women with COVID-19.
- A woman's care should be escalated urgently if any of the following signs of decompensation develop:
  - increasing oxygen requirements or FiO_2 above 35%,
  - increasing respiratory rate despite oxygen therapy of, or above, 25 breaths/minutes or a rapidly rising respiratory rate,
  - reduction in urine output when this is being monitored,
  - acute kidney injury (serum creatinine levels above 77 µmol/l in women with no pre-existing renal disease),
  - drowsiness, even if the oxygen saturations are normal.
- The possibility of myocardial injury should be considered, as the symptoms are similar to those of respiratory complications of COVID-19.
- Clinicians should be advised to seek support from haematology if evidence of COVID-19-related coagulopathy develops.
- The appropriateness and frequency of fetal heart rate monitoring should be considered on an individual basis, accounting for the gestational age and the maternal condition.

Planning for the birth of the baby:

- For pregnant women in the third trimester who are unwell, an individualised assessment should be undertaken by the MDT to decide whether emergency caesarean birth or induction of labour should be performed, either to facilitate maternal resuscitation (including the need for prone positioning) or because of concerns regarding fetal health.
- The level of personal protective equipment (PPE) required by healthcare professionals caring for a woman with COVID-19 who is undergoing a caesarean birth should be determined by national and local guidance.
- If maternal stabilisation is required before birth and can be undertaken safely, this is the priority, as it is in other maternity emergencies.
- If urgent intervention for birth is indicated for fetal reasons, then birth should be expedited as for usual obstetric indications, provided the maternal condition is stable.
- When iatrogenic preterm birth is required, the administration of antenatal corticosteroids to promote fetal lung maturation and magnesium sulfate for fetal neuroprotection should be considered by the MDT.

A useful summary on supportive care for adults diagnosed with COVID-19 has been published by the WHO.*[140]* Specific guidance on the care of patients with COVID-19 who are admitted to critical care has been published by NICE and SIGN.*[141][142]*

As discussed in section 3, infection with SARS-CoV-2 requiring admission to hospital is associated with an increased risk of VTE. All pregnant and recently pregnant women should be assessed for risk of VTE and prescribed thromboprophylaxis with LMWH unless there is a contraindication. The dose of LMWH should be considered on an individual basis and discussed with the MDT. There is currently not enough evidence in pregnant women to recommend therapeutic anticoagulation routinely in the absence of suspected or proven VTE. Women who take LMWH thromboprophylaxis during pregnancy should discontinue this if their platelet count falls below 50 x 10^9/l and their care should be discussed with a haematologist.

While most patients with severe COVID-19 infection will have normal or even high platelet counts, COVID-19 can be associated with thrombocytopenia.*[143]* It was previously suggested that when aspirin has been prescribed as prophylaxis for pre-eclampsia or SGA, it should be discontinued for the duration of the infection as this may increase the bleeding risk in women with thrombocytopenia.*[144]* Results from the RECOVERY trial,*[145]* however, have concluded that, in general, prescribing 150 mg aspirin daily to hospitalised patients with COVID-19 can increase the likelihood of being discharged home alive within 28 days (RR 1.06, CI 1.02–1.1). The trial also noted the rate of thromboembolic events was lower in the group allocated to aspirin, but there was an increase in the risk of a major bleeding event. The decision to stop aspirin prophylaxis during an acute illness with COVID-19 should therefore be balanced by the risk of bleeding versus the evidence for improved outcomes, but it seems reasonable for this to be continued in most cases. LMWH thromboprophylaxis during pregnancy should be discontinued when the woman's platelet count falls below 50 x 10^9/l and their further care should be discussed with a haematologist.

Myocardial injury as demonstrated by abnormal cardiac biomarkers and bradycardia may be common among pregnant women with severe or critical COVID-19.*[146]* Early involvement of an MDT to investigate for potential myocardial injury is essential if this is suspected.*[147]* Further details of investigation and management is available in the NICE rapid guideline on managing COVID-19.*[147]*

Increased rates of iatrogenic preterm birth are associated with severe COVID-19 infection in pregnancy (section 1.6). Antenatal corticosteroids are well established as being beneficial in preterm labour, or if iatrogenic preterm birth is anticipated.*[53]* Magnesium sulfate therapy is recommended for neuroprotection of the neonate, and should be offered to women up to 29^{+6} weeks of gestation and considered up to 33^{+6} weeks of gestation.*[53]* The administration of steroids and magnesium sulfate to women who are severely unwell with COVID-19 should be considered by an MDT.

For non-specialist anaesthetists and physicians involved in the care of pregnant women with COVID-19 and other medical conditions, useful information is available from the Royal College of Anaesthetists guideline *Care of the critically ill woman in childbirth; enhanced maternal care* and the Royal College of Physicians' *Acute care toolkit 15: Managing acute medical problems in pregnancy*.

Prone positioning of patients with moderate to severe acute respiratory distress syndrome (ARDS) can improve respiratory function and has been recommended for the care of patients with COVID-19.*[140]* There is some evidence on the use of prone positioning in pregnancy;*[148]* and guidance from the Intensive Care Society in the UK*[149]* advises that it is relatively contraindicated in the second and third trimesters of pregnancy. However, a review article*[150]* on prone positioning for pregnant women who are unwell with COVID-19 provides advice, guidance and an algorithm on how this can be undertaken successfully in the second and early third trimesters.

The level of personal protective equipment (PPE) required by healthcare professionals caring for a woman with COVID-19 who is undergoing a caesarean birth should be determined by national and local guidance.

4.3 What therapies should be offered to pregnant, or recently pregnant, women with COVID-19?

Strong recommendation

Recommendation	Evidence Level	Strength	Rationale for the recommendation
Oxygen, IV fluids, and venous thrombo-prophylaxis should be considered under 'Good Practice Points' as below.	3	D	Adequate early oxygen therapy is essential.[30] There is a UK NHS consensus statement for COVID-19 patients on the criteria for considering, and referring to, an ECMO centre.[151]
Maternal corticosteroid therapy should be given for 10 days or up to discharge, whichever is sooner, for women who are unwell with COVID-19 and requiring oxygen supplementation or ventilatory support. Suggested steroid regimens: • **If steroids are not indicated for fetal lung maturity, oral prednisolone 40 mg daily (or oral methylprednisolone 32 mg daily), or IV hydrocortisone 80 mg twice daily, for 10 days or until discharge, whichever is sooner. IV methylprednisolone is an alternative especially for ICUs more familiar with this preparation (e.g. 1 mg/kg twice daily for 5–7 days, weaned to 1 mg/kg once daily for 5–7 days).** • **If steroids are indicated for fetal lung maturity, intramuscular dexamethasone 12 mg twice (24 hours apart), immediately followed by oral prednisolone 40 mg once a day, or IV hydrocortisone 80 mg twice daily, to complete a total of 10 days or until discharge, whichever is sooner.** • **Short courses of steroids, such as the course described in the RECOVERY trial (dexamethasone 6 mg once a day for up to 10 days), are considered safe in breastfeeding.**	1+	A	There is a significant reduction in 28-day mortality for individuals with COVID-19 requiring oxygen who were given corticosteroid therapy.
For women meeting the criteria (hypoxic with systemic inflammation), the use of tocilizumab should be strongly considered. **It is recommended that any decision to treat with anti-IL6 agents should be taken by an MDT, including obstetric and infection specialists, and given if the benefits outweigh the risks.**	1+	A	The interleukin-6 receptor antagonist (anti-IL6) tocilizumab has been shown to improve outcomes, including survival, in hospitalised patients with hypoxia (oxygen saturation below 92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein at or above 75 mg/l). Although data for the use of tocilizumab in pregnancy in this situation are limited, there is currently no evidence that tocilizumab is teratogenic or fetotoxic.
Strongly consider treatment with neutralising monoclonal antibodies (nMABs) in pregnant and breastfeeding women if they are symptomatic, hospitalised with COVID-19 infection, and have no SARS-CoV-2 antibodies.	1+	A	The decision about which preparation to offer may depend on the variant; the most up-to-date information can be found at the Medicines and Healthcare products Regulatory Agency (MHRA) Central Alerting System.
Sotrovimab (Xevudy), a nMAB, is	1+	A	It is likely the counselling for, and the administration

recommended for symptomatic pregnant women who have recent-onset PCR-confirmed SARS-CoV-2 infection, who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19 infection.			of, sotrovimab will need direct involvement of secondary care. The Summary of Product Characteristics (SmPC) states that sotrovimab may be used during pregnancy where the expected benefit to the mother justifies the risk to the fetus. Updated information can be found at the MHRA Central Alerting System.
Remdesivir, an antiviral, may be considered in pregnant women with COVID-19 in community and hospital settings.	**3**	**D**	Clinicians should be aware that the fetal risk profile of remdesivir is largely unknown. See SmPC for further information.

Rationale

Adequate early oxygen therapy is essential.*[30]* There is evidence that ECMO is either not being considered or being inappropriately discounted*[30]* and there is now a UK NHS consensus statement for COVID-19 patients on the criteria for considering, and referring to, an ECMO centre.*[151]*

There is no evidence to guide prophylactic LMWH dosing in obstetric patients with COVID-19, i.e. whether to prescribe the usual prophylactic dose, a higher prophylactic dose or a therapeutic dose. There is some evidence to guide dosing in other groups of patients,*[152][153]* which may not translate to an obstetric population, and this is also summarised in the NICE *COVID-19 rapid guideline: managing COVID-19*.*[147]*

The interim results of the RECOVERY trial demonstrated a significant reduction in 28-day mortality for individuals with COVID-19 requiring oxygen who were given corticosteroid therapy (age-adjusted rate ratio 0.83, 95% CI 0.75–0.93; $P < 0.001$).*[154]* The RECOVERY trial protocol for pregnancy recommends oral prednisolone 40 mg once daily and, in women unable to take oral medicine, IV hydrocortisone 80 mg twice daily instead of dexamethasone treatment.*[155][156][157]* Unlike dexamethasone, prednisolone and hydrocortisone are extensively metabolised in the placenta with minimal transfer to the fetus.

While the neonatal benefits of antenatal corticosteroids (betamethasone and dexamethasone) are well-established when administered to women at risk of imminent preterm birth (NICE NG25),*[53]* exposure to repeat doses of steroids may be associated with adverse neonatal outcomes.*[158]* It is, therefore, recommended that if corticosteroids are not indicated for fetal lung maturity, oral prednisolone 40 mg once a day, or IV hydrocortisone 80 mg twice daily, should be administered for 10 days or up to discharge, whichever is sooner. If steroids are indicated for fetal lung maturity, intramuscular dexamethasone 12 mg twice (24 hours apart), immediately followed by oral prednisolone 40 mg once a day, or IV hydrocortisone 80 mg twice daily, to complete a total of 10 days or until discharge, whichever is sooner. Methylprednisolone is commonly used in the intensive care setting and may be used for those more familiar with its administration. A reasonable dose would be oral methylprednisolone 32 mg daily, or it may be given IV (e.g. 1 mg/kg twice daily for 5–7 days, weaned to 1 mg/kg once a day for 5–7 days).

The WHO*[159]* has recommended the use of anti-IL-6 agents, tocilizumab or sarilumab, for patients with severe or critical COVID-19 infection. Corticosteroids should be used alongside anti-IL-6 agents in patients meeting the severity criteria. Anti-IL-6 agents reduce mortality (OR 0.86, 95% CI 0.79–0.95)*[160]* and the need for mechanical ventilation (OR 0.72, 95% CI 0.57–0.90).*[161]* Tocilizumab is given as single IV infusion of 8 mg/kg of actual body weight, up to a maximum of 800 mg. Sarilumab is most commonly given at 400 mg as single IV infusion consistent with the REMAP-CAP trial.*[154][161][162][163][164][165]* Drug registries*[166][167]* on the use of tocilizumab in pregnancy have limited numbers and show no evidence of harm. Eligibility criteria have been published by the MHRA for advice on the use of anti-IL-6 agents and can be found in detail by accessing their Central Alerting System, which is regularly updated. Dose scheduling and exemptions can also be accessed using this link. Tocilizumab is excreted in very low levels in breast milk.*[168]* Any decision to treat pregnant or postnatal women with anti-IL6 agents should be taken by an MDT and, when feasible, in discussion with the woman.

Comparable efficacy between tocilizumab and sarilumab has been demonstrated in several international clinical trials.*[169][165][170]* When tocilizumab is unavailable or cannot be used, it is reasonable to consider using sarilumab in severe cases of COVID-19.*[171]* There has been no research examining the safety of sarilumab in pregnancy or during breastfeeding. Decisions to use sarilumab should be made with multidisciplinary input, and ideally within the context of a clinical trial.

There is a question around the timing of BCG vaccination for the babies of women who have received tocilizumab. The advice is that women who have been taking biologics throughout pregnancy are advised to defer BCG vaccination until the baby is aged 6 months because of a theoretical possibility of neonatal or infant immunosuppression and many clinicians will, entirely appropriately, wish to adhere to this advice. There is limited evidence for the recommendation, however, and there are data to suggest that babies born to these women are able to mount a good immune response. Tocilizumab is only used as a short dose, is therefore very unlikely to affect the baby, and delay in BCG immunisation may cause more harm than good. It therefore seems

reasonable, if the clinician considers that the benefits of administration to outweigh the risks of delay and after an informed discussion with the parents, to offer BCG immunisation at the usual time after birth. Note that nMAB's (below) are not an immunosuppressant and maternal administration does not require any changes to the infant vaccine schedule.

nMABs are synthetic antibodies that bind to the spike protein of SARS-CoV-2, preventing subsequent entry of the virus into the host cell and its replication. This effectively 'neutralises' the virus particle.*[172]* Data on the safety of monoclonal antibodies in pregnancy have been evaluated in earlier cohort and registry studies,*[173]* indicating that exposure in pregnancy is not associated with an increased risk for adverse pregnancy outcomes when compared to unexposed pregnancies with the same underlying medical diseases.*[174]* This is supported by a consensus report on immunosuppressives and biologics during pregnancy and lactation, with no evidence of elevated adverse pregnancy outcomes or malformation risks,*[175]* a small observational series' of tocilizumab in pregnant women with COVID-19 and a cohort study of 944 women who received nMABs for COVID-19 infection in pregnancy.*[176][177]*

There are two nMABs with conditional marketing authorisation for use in the UK in the treatment of COVID-19. These are Ronapreve® and sotrovimab. Although there are no specific data for sotrovimab in pregnant women, it is recommended that both Ronapreve® and sotrovimab may be used during pregnancy.*[172][178]*

Results from the RECOVERY trial*[177]* indicated that Ronapreve® reduced the relative risk of mortality by 20% (24% in the treatment group versus 30% in those who received standard care alone) in hospitalised patients with COVID-19 who had not mounted an antibody response of their own to the virus (were seronegative/anti-S antibody negative) at the time of treatment. The RECOVERY trial included women who were pregnant or breastfeeding, with no serious adverse events reported. The cohort study mentioned above concluded that nMAB treatment in pregnancy was associated with similar 28-day COVID-19-associated outcomes and possibly more non-COVID-19-related hospital admissions compared to no nMAB treatment. As the randomised trials demonstrated benefit, however, and there were no safety concerns in this study, it seems reasonable to continue offering nMAB's in the context of pregnancy. Current use of Ronapreve is limited as evidence has shown it has significantly decreased efficacy against the Omicron variant.*[179]*

Interim analysis of the COMET-ICE trial, which studied sotrovimab administered intravenously to non-hospitalised patients with mild-to-moderate disease and at least one risk factor for disease progression, showed a relative risk reduction in hospitalisation or death at day 29 by 85% in patients treated with sotrovimab compared with placebo.*[180]* The final analysis of this study has shown a relative risk reduction in hospitalisation or death at day 29 by 79% in patients treated with sotrovimab compared with placebo.*[181]* It is also licensed third line for the treatment of patients in hospital with COVID-19. Sotrovimab use in breastfeeding is not well studied and caution may be appropriate. As it is a large protein molecule, however, the amount in breast milk is likely to be very low and it is also likely to be partially broken down in the infant's gastrointestinal tract.*[182]*

Given that there is no clear view as to how nMABs should be given to pregnant women in the community and the relative rarity of this situation, it seems most appropriate administration should be through secondary care and involve the most experienced team members available (e.g. a maternity COVID-19 champion, a clinician with maternal medicine experience, or an obstetrician working jointly with a physician experienced in COVID-19 treatment).

Eligibility criteria have been published by the MHRA for advice on the use of nMABs in hospital/community settings and can be found in detail by accessing their Central Alerting System, which is regularly updated. Dose scheduling and exemptions can also be accessed using this link.

Remdesivir (Veklury®), an IV antiviral medication, has conditional marketing authorisation in the UK. Eligibility criteria for its use can be accessed via the MHRA Central Alerting System. The evidence demonstrates that administering to non-hospitalised patients with risk factors for disease progression within 7 days of COVID-19 symptom onset, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28.*[183]* To date, there have been limited data on remdesivir use in pregnant women. A recent study has treated 41 pregnant patients with remdesivir for COVID-19 and concluded that early administration was associated with improved clinical outcomes, including lower rates of ICU admission, decreased length of hospitalisation, and decreased progression to critical disease in pregnant individuals hospitalised with COVID-19. No adverse outcomes were reported in this small study.*[184]* Given that further studies are needed, remdesivir should ideally be avoided in pregnancy and while breastfeeding unless clinicians believe the benefits of treatment outweigh the risks to the individual.*[172]* Since the safety of remdesivir in pregnancy is largely unknown it should be:

- considered on an individual basis for those who are stable but not improving
- considered more strongly in those who are deteriorating.

In breastfeeding women with COVID-19, the use of remdesivir should be restricted to women where benefit has been reported (hospitalised patients requiring oxygen therapy, especially early in disease course, and not in patients who are mechanically ventilated).*[185]* Any decision to treat with remdesivir should be taken by an MDT and, when feasible, in discussion with the woman.

Molnupiravir is an oral antiviral medicine which has demonstrated a relative risk reduction of 30% in the composite primary outcome of hospitalisation or death at day 29 during the phase 3 MOVe-OUT trial in at-risk, non-hospitalised adult patients with mild–moderate COVID-19.*[186]* A relative risk reduction of 30% was seen in the composite primary outcome of hospitalisation or death at day 29 (6.8% in the molnupiravir group versus 9.7% in the placebo group, *P* = 0.0218). Eligibility criteria required that all patients had laboratory-confirmed mild–moderate COVID-19, with symptom onset within 5 days of study randomisation, and to have a significant risk factor (e.g. obesity, diabetes or heart disease). Molnupiravir is not recommended in pregnancy, however, until further studies have established its efficacy and safety. Pregnant women who have received molnupiravir at any stage in their pregnancy should be discussed with UKTIS for further advice (www.uktis.org, 0344 892 0909 Mon-Fri 9am–5pm) and follow-up as per MHRA advice.

Results from the RECOVERY*[187]* trial have demonstrated that Olumiant (baricitinib), an anti-inflammatory medication which is a selective and reversible Janus kinase (JAK) 1 and 2 inhibitor, reduces the risk of death (CI 0.77–0.98) when given to hospitalised patients with severe COVID-19. However, animal studies have shown reproductive toxicity, adverse effects on bone development and teratogenicity in rats and rabbits. It is therefore contraindicated in pregnancy, and women of child bearing age should use effective contraception for at least 1 week after treatment. It is unknown if baricitinib/metabolites are excreted in human milk although animal studies have shown evidence of milk excretion. Risks to newborns/infants from breast feeding cannot therefore be excluded and a decision must be made whether to discontinue breast feeding or to discontinue baricitinib therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Further information can be accessed via the MHRA Central Alerting System (CAS).

Paxlovid (nirmatrelvir/ritonavir) is an inhibitor of CYP3A and is an antiviral medication licensed for treatment of patients in hospital with COVID-19. Results from the EPIC HR trial indicate that the dual oral antiviral nirmaltrelvir/ritonavir resulted in a relative risk reduction of hospitalisation or death by 89% (within 3 day of symptom onset) compared to placebo in non-hospitalised high-risk adults with COVID-19.*[181][188]* Although safety in pregnancy has not been established, ritonavir has been used safely for treatment of HIV in pregnancy. In circumstances such as in women who are clinically vulnerable or have reduced antibody protection (e.g. the non-vaccinated population), or in women with severe disease where other established treatments have been ineffective, its use could be acceptable.*[189]* It is nonetheless important to recognise that MHRA do not recommended this in pregnancy. It may also reduce the efficacy of combined hormonal contraceptives and women should be advised to use an alternative method or additional barrier method during treatment and for one complete menstrual cycle after stopping nirmaltrevir/ritonavir. Further information can be accessed via the MHRA Central Alerting System (CAS).

A review of the literature on ivermectin does not show benefit for ivermectin in either hospital or community settings, and it should only be considered as part of a clinical trial.*[147]*

Good practice statement

Good Practice Points

- If there is clinical uncertainty about whether to offer a therapy to a pregnant woman, advice should be sought through maternal medicine networks.
- Oxygen should be titrated to target saturations to 94–98% using escalation through nasal cannula, face mask, venturi mask, non-rebreather mask, non-invasive positive airway pressure (e.g. CPAP), intubation and IPPV, and ECMO as appropriate. Referrals to the NHS ECMO service should be made for pregnant or postpartum women using the same criteria as for other adult patients, i.e. if worsening severe respiratory failure despite appropriate conventional ventilatory support, or for women in whom lung-protective ventilation cannot be achieved because of the severity of hypoxaemia or hypercapnia, or significant air-leak (e.g. barotrauma or bronchopleural fistula).
- Proning should be strongly considered. Although evidence is limited there are reports that this is feasible (with appropriate padding).
- Caution should be applied to IV fluid management:
    - Hourly fluid input/output charts should be used to monitor fluid balance in women with moderate to severe symptoms of COVID-19.
    - The aim should be to maintain a neutral fluid balance.
    - When required, boluses in volumes of 250–500 ml should be employed and an assessment for fluid overload made before proceeding with further fluid resuscitation.
- Antibiotics should be commenced at presentation if there is clinical suspicion of bacterial infection or sepsis, with an early review and rationalisation of antibiotics if COVID-19 is confirmed. Even when COVID-19 is confirmed, clinicians should remain open to the possibility of another coexisting condition. There should be no delay in the administration of therapy that would usually be given in maternity care (e.g. IV antibiotics in woman with fever and prolonged rupture of membranes).
- All pregnant women should be assessed for risk of VTE and, where indicated, prescribed thromboprophylaxis with LMWH unless there is a contraindication (see section 3). The dose of LMWH should be considered on an individual basis and discussed with the MDT. Therapeutic doses of LMWH should be employed when VTE is suspected until objective testing can be undertaken.
- Thrombocytopenia may be associated with severe COVID-19. For women with thrombocytopenia (platelets less than 50×10^9/l), aspirin and LMWH thromboprophylaxis should be discontinued and haematology advice sought. The use of mechanical aids (such as intermittent pneumatic compression) should be used if LMWH therapy is contraindicated or paused secondary to thrombocytopenia.
- Molnupiravir is not recommended in pregnancy until further studies have established its effectiveness and safety.
- Baricitinib is not recommended in pregnancy or breast feeding.
- Paxlovid (nirmatrelvir/ritonavir) is contraindicated in pregnancy and women of childbearing potential not on effective contraception.
- Hydroxychloroquine, lopinavir/ritonavir and azithromycin have been shown to be ineffective in treating COVID-19 infection and should not be used for this purpose.
- Pregnant women should be offered the opportunity to enrol, if they are eligible, in clinical trials (such as the RECOVERY trial).

5 Postnatal care

Routine postnatal care for women in accordance with NICE guideline [NG194] *Postnatal care.[190]*

5.1 How should neonatal care be structured for a baby whose mother is positive for COVID-19?

Summary points

- Women with suspected or confirmed COVID-19 should remain with their baby and be supported to practise skin-to-skin/ kangaroo care if the newborn does not require additional medical care at this time.
- Babies born to SARS-CoV-2-positive women should be cared for as per guidance from the British Association of Perinatal Medicine (BAPM).

There are limited data to guide the neonatal care of babies of women who tested positive for SARS-CoV-2 in the third trimester.*[188]* A prospective cohort study*[191]* in the UK investigating SARS-CoV-2 infection in the first 28 days of life found neonatal infection is uncommon (66 babies with confirmed SARS-CoV-2 infection [incidence 5.6/10 000 livebirths, 95% CI 4.3–7.1], of whom 28 [42%] had severe neonatal SARS-CoV-2 infection [incidence 2.4/10 000 livebirths, 95% CI 1.6–3.4]), and infection with neonatal admission following birth to a woman with perinatal SARS-CoV-2 infection was unlikely; consequently, this study supported guidance to avoid separation of women and their babies.

The RCPCH/BAPM and the RCM have provided separate guidance on this topic,*[192][193]* with accompanying FAQs produced by BAPM, as well as various COVID-19 resources on newborn life support from the Resuscitation Council.

5.2 What should women and families be advised regarding infant feeding if they have COVID-19?

Summary points

- Breastfeeding should continue to be recommended to all women.
- Individualised support, advice and guidance on breastfeeding should be offered to all women who wish to breastfeed. Remote support for breastfeeding should be signposted to all women.
- Women and their families should be informed that infection with COVID-19 is not a contraindication to breastfeeding.
- Women and their families should be supported to make a fully informed choice on how to feed their baby. The potential risks and benefits of feeding the baby near individuals with suspected or confirmed COVID-19 should be discussed.
- When a woman is not well enough to care for her own infant or where direct breastfeeding is not possible, the woman should be supported to express her breast milk by hand or using a breast pump, and/or offered access to donor breast milk. It is entirely appropriate for a woman to choose formula milk to feed her baby.
- The following RCPCH/BAPM precautions should be taken to limit viral spread to the baby:
  - Wash hands before touching the baby, breast pump or bottles.
  - Avoid coughing or sneezing on the baby while feeding.
  - Consider wearing a face covering or fluid-resistant face mask while feeding or caring for the baby.
- Babies should not wear masks or other face coverings as they risk suffocation.
- When women are expressing breast milk in hospital, a dedicated breast pump should be used. Follow recommendations for pump cleaning after each use.
- Adhere strictly to sterilisation guidance for babies who are bottle-fed with formula or expressed milk.
- Consider asking someone who is not infected with COVID-19 to bottle feed the baby expressed breastmilk or formula.
- Breastfeeding is not a contraindication for vaccination against COVID-19, see section 2 for more detailed advice.

Throughout the pandemic, international organisations including WHO and UNICEF have continued to support breastfeeding.*[194][196]* Breastfeeding has many advantages for the woman and her infant and does not need to be discontinued during COVID-19 infection nor before or following vaccination of the woman. General advice on supporting women through their infant feeding journey can be found in the NICE guideline *Postnatal care* (NG194).*[190]*

A systematic review*[195]* has established the presence of antibodies against SARS-CoV-2 in breastmilk, both when the woman contracts the disease and after the vaccine against the virus has been administered. Although there is a transmission of antibodies against SARS-CoV-2 through breastmilk this appears to be passive transmission rather than because of neonatal infection: SARS-CoV-2 RNA has been found in breastmilk, but not viable viruses. This review also supported recommendations to continue breastfeeding during mild–moderate maternal COVID-19 illness, as breastmilk may provide specific immune benefits to infants. The main risk of breastfeeding is postulated to be the close contact between the baby and the woman, who is likely to share infective respiratory droplets.

Specific recommendations on minimising the risk of COVID-19 transmission when feeding babies has been developed by the BAPM and RCM.*[193][197]* The NHS has general guidance on sterilising bottles in order to protect babies against infections.

Face coverings are not appropriate for babies. The UK government advice for using face coverings is directed towards adults and children aged 11 and over.*[198]*

5.3 What are the general considerations for postnatal care for women and babies following COVID-19?

Summary points

- Postnatal care should be provided as per NICE guideline [NG194] *Postnatal care*.
- Following childbirth, effective contraception should be discussed with and offered to all women prior to discharge from maternity services.
- Women and their families should be given clear advice about careful hand hygiene and infection control measures when caring for and feeding their baby.
- Families should be guided on how to identify signs of illness in their newborn or worsening of the woman's symptoms and should be provided with appropriate contact details if they have concerns or questions about their baby's wellbeing. NHS leaflets, providing this information, are also available.
- Women should be advised that, if they or their babies require readmission for postnatal obstetric or neonatal care for suspected or confirmed COVID-19, they should contact their local unit ahead of arrival.
- Women who have recently given birth and test positive for COVID-19 should receive all recommended advice, guidance and support in relation to their postnatal physical and mental health, and wellbeing and care of their newborn baby. This includes necessary in-person assessments using appropriate PPE.
- In-person home or clinic appointments should be offered to allow an overall assessment of the physical and psychological health and wellbeing of the woman and her baby.
- In some areas, and where appropriate, some postnatal care may need to be via telephone or video link, but considerations should be made upon individual circumstances. This should be discussed with women and families.
- For advice about neonatal BCG vaccination, following maternal immunotherapy for the treatment of COVID-19 infection in pregnancy, see section 4.3.

Wherever possible, it is advised that postnatal care for women be carried out in full as per the NICE guideline *Postnatal care* (NG194). Contraceptive advice can be found through the Faculty of Sexual and Reproductive Health (FSRH) who have a specific guideline on contraception in the postnatal period.*[199]*

The BAPM has also published guidelines on the neonatal care of babies born to women with COVID-19.*[193]*

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Appendices

Appendix I: Explanation of grades and evidence levels

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of Recommendation

A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good Practice Points

GPP	Recommended best practice based on the clinical experience of the guideline development group.*

*on the occasion when the guideline development group find there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. These are marked in the guideline, and are indicated by **ü**. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

Appendix II: Summary of key studies and meta-analysis on maternal and pregnancy outcomes

Key studies summary on the effect of COVID-19 on pregnancy and maternal outcomes

Key studies of maternal and perinatal outcomes are summarised in tables 1 and 2. The largest study is the Preg-Cov-19 systematic review.[19] These tables list studies published October 2020 - January 2022, forming the RCOG meta-analyses presented below. Case series with less than 20 cases have been excluded

Study	Country	Population		Effect of COVID-19 on pregnancy		
Allotey et al. 2020[1] PregCOV-19 Systematic Review (updated 29/11/20)	30 countries	**COVID-19** Approx. 1000 pregnant women with COVID-19	**Control** Approx. 5000 pregnant women without COVID-19	**COVID-19** 12.4% preterm (147/1184) 0.9% stillbirth (9/1039)	**Control** 7.8% preterm (572/7365) 0.5% stillbirth (26/4755)	**aOR** 1.47 (1.14–1.91) 2.84 (1.25–6.45)
Vousden et al. 2021[2] UKOSS update	UK	COVID-19 1148 pregnant women with COVID-19 hospitalised for any reason (722 symptomatic)	Control Historical control of 694 pregnant women from 2018	Overall 15.6% preterm (156/1003) 1.1% stillbirth (11/1019) Symptomatic COVID 19% preterm birth (76% iatrogenic) (120/623) 49% caesarean section *Asymptomatic COVID* 9% preterm birth (36/380) 40% caesarean section	Control 9% preterm birth (63/702) 0.3% stillbirth (2/705) 29% caesarean section	
Jering et al. 2021[3]	USA	COVID-19 6380 pregnant women with COVID	Control 400 066 pregnant women without COVID	COVID-19 7.2% preterm birth (322) 28.9% caesarean birth 8.8% pre-eclampsia 0.5% stillbirth (34)	Control 5.8% preterm (16137) 27.5% caesarean 6.8% pre-eclampsia 0.3% stillbirth (1289)	aOR (95%CI) 1.17 (1.06–1.29) 1.07 (1.02–1.13) 1.21 (1.11–1.33)
Crovetto et al. 2021[4]	Barcelona, Spain	COVID-19 317 pregnant women with COVID-19 (detected by antibody or PCR)	Control 1908 pregnant women without COVID-19	COVID-19 13.6% pregnancy complication 11.4% preterm (20/176) 0.6% perinatal death (1/178) Symptomatic COVID 16.9% preterm birth (12/71) 19.2% intrapartum fetal distress	Control 14% pregnancy complication 7.2% preterm (81/1128) 0.5% perinatal death (6/1160) Control 7.2% preterm birth (81/1128) 9.1% intrapartum fetal distress	Risk difference 0.4% (4.1 to 4.1) 4.2% (0.03 to 9.9) 0.1% (0.7 to 2.7)
Molenaar 2021[5]	NY, USA	COVID-19 (not acute) 105 women who were seropositive for SARS-COV-2 but PCR negative at birth	Control 591 women who were seronegative for SARS-CoV-2 and PCR negative at birth	COVID-19 7.6% preterm (8) 8.6% SGA (9)	Control 6.3% preterm (37) 7.3% SGA (43)	aOR 1.08 (0.46–2.54) 1.19 (0.53–2.65)

Metz et al. 2021[6]	USA	1219 pregnant women with COVID-19, split by severity: • 47% asymptomatic • 27% mild • 14% moderate • 8% severe • 4% critical		Severe/critical COVID 41.8% preterm birth	Asymptomatic COVID 11.9% preterm birth	aRR (95% CI) 3.53 (2.42–5.14)
Savirón-Cornudella et al. 2021[7]	Spain	COVID-19 65 pregnant with COVID (by Ab or PCR), all asymptomatic or mild infection	Control 1146 pregnant women without COVID-19	COVID-19 0% stillbirth (0)	Control 0.2% stillbirth (2)	*P*-value 0.944
Abedzadeh-Kalahroudi 2021[8]	Iran	COVID-19 56 women with COVID-19	Control 94 pregnant women with COVID-19	COVID-19 16.1% fetal distress 34.5% preterm (19) 3.6% perinatal death (2)	Control 4.3% fetal distress 12.8% preterm (12) 0% perinatal death (0)	RR 3.84 (1.24–11.90) 2.70 (1.42–5.14) 8.48 (0.41–173.53)
Trahan 2021[9]	Canada	COVID-19 45 pregnant women with COVID-19	Control 225 pregnant women without COVID-19	COVID-19 16% preterm (7)	Control 9% preterm (21)	*P* = 0.28
Zgutka 2021[10]	NY, USA	COVID-19 62 pregnant women with COVID-19	Control 124 pregnant women without COVID-19	COVID-19 18.3% preterm (11)	Control 8.1% preterm (10)	*P* = 0.04

Katz 2021[11]	USA	COVID-19 490 pregnant women with COVID-19 (176 [35.9%] symptomatic)	Control 964 pregnant women without COVID-19	COVID-19 14.8% preterm (73) symptomatic	Control 10.2% preterm (98)	aOR (95% CI) 1.47 (1.03–2.09) 2.08 (1.29–3.36)
Martinez-Perez 2021[12]	Spain	COVID-19 246 pregnant women with COVID-19	Control 763 pregnant women without COVID-19	COVID-19 13.8% preterm (34) 1.2% stillbirth (3)	Control 6.7% preterm (51) 0.1% stillbirth (1)	aOR or *P* 2.12 (1.32–3.36) 0.047
Hcini 2021[13]	French Guiana	COVID-19 137 pregnant women with COVID-19	Control 370 pregnant women without COVID-19	COVID-19 5.1% stillbirth (7) 0.8% preterm < 34 weeks (1)	Control 1.1% stillbirth (4) 3.4% preterm < 34 weeks (12)	RR 4.7 (1.4–15.9) RR not given
Villar 2021[14]	18 countries	COVID-19 706 pregnant women with COVID-19	Control 1424 pregnant women without COVID-19	COVID-19 22.5% preterm (159) 17% severe perinatal morbidity and mortality index (120)	Control 13.6% preterm (194) 7.9% severe perinatal morbidity and mortality index (113)	RR 1.59 (1.30–1.94) 2.14 (1.66–2.75)
Adhikari 2020[15]	USA	COVID-19 252 pregnant women with COVID-19	Control 3122 pregnant women without COVID-19	COVID-19 11% preterm (27) 0% stillbirth (0)	Control 11% preterm (328) 0.6% stillbirth (18)	RR 1.02 (0.70–1.48) 0.33 (0.02–5.48)

Soto-Torres 2021[16]		COVID-19 106 pregnant women with COVID-19	Control 103 pregnant women without COVID-19	COVID-19 20.8% preterm (35/40 weeks of gestation) (22/106)	Control 8.8% preterm (35/40 weeks of gestation) (9/103)	OR 2.37 (1.14–4.91)
Gurol-Urganci 2021[17]	UK	COVID-19 3527 pregnant women with COVID-19	Control 338 553 pregnant women without COVID-19	COVID-19 12.1% preterm 0.85% stillbirth	Control 5.8% preterm 0.34% stillbirth	aOR 2.17 (1.96–2.42) 2.21 (1.58–3.11)
Aabakke et al. 2021[18]	Denmark	COVID-19 418 pregnant women with COVID-19	Control 82 262 pregnant women without COVID-19	COVID-19 4.7% preterm (13) 2 stillbirth	Control 5.4% preterm (2539) 0.3% stillbirth (134)	OR 0.85 (0.49–1.49)
Tadas et al. 2021[19]	India	COVID-19 181 pregnant women positive at delivery	Control 181 pregnant women without COVID-19 at delivery	COVID-19 7 stillbirth	Control 7 stillbirth	*P* value 1
Akbar et al. 2021[20]	Indonesia	COVID-19 62 pregnant women with COVID-19 at delivery	Control 79 pregnant women without COVID-19 at delivery	COVID-19 12.06% preterm birth (7)	Control 6.49% preterm (5)	*P* value 0.25
Papageorghiou et al. 2021[21]	18 countries	COVID-19 725 pregnant women with COVID-19 during pregnancy	Control 1459 pregnant women without COVID-19 at enrolment	COVID-19 21.0% preterm birth (152)	Control 13.1% preterm birth (191)	

Teixeira et al. 2021[22]	Brazil	COVID-19 26 pregnant women with COVID-19	Control 73 pregnant women without COVID-19	COVID-19 26.9% preterm (7)	Control 13.7% preterm (10)	*P* value 0.139
Saadia et al. 2021[23]	Pakistan	COVID-19 48 pregnant women with COVID-19	Control 46 pregnant women without COVID-19	COVID-19 2.1% preterm labour (1)	Control 0% preterm labour (0)	
Ruggiero et al. 2021[24]	Italy	COVID-19 28 pregnant women with COVID-19 at delivery	Control 287 pregnant women without COVID-19 at delivery	COVID-19 7.1% preterm (2)	Control 7.7% preterm (22)	*P* value 1.00
Timircan et al. 2021[25]	Romania	COVID-19 101 pregnant women admitted with COVID-19	Control 938 pregnant women without COVID-19 on admission	COVID-19 15% preterm (15)	Control 8% preterm (75)	*P* value 0.095
Karasek et al. 2021[26]	California, USA	COVID-19 8957 pregnant women with COVID-19 at delivery	Control 231 200 pregnant women without COVID-19 at delivery	COVID-19 11.8% preterm (1060)	Control 8.7% preterm (19 999)	OR 1.4 (1.3–1.4)
Hill et al. 2021[27]	New Jersey USA	COVID-19 218 pregnant women with asymptomatic COVID-19 at delivery	Control 413 pregnant women with no COVID-19 at delivery	COVID-19 23% preterm (50)	Control 11.4% preterm (48)	

Chinn et al. 2021[28]	USA (499 centres)	COVID-19 18 715 pregnant women with COVID-19 at delivery	Control 850 364 pregnant women without COVID-19 at delivery	COVID-19 16.4% preterm (3072)	Control 11.5% preterm (97 967)	
Cuñarro-López et al. 2021[29]	Spain	COVID-19 1347 pregnant women with COVID-19	Control 1347 pregnant women without COVID-19	COVID-19 11.1% preterm birth (149)	Control 6.0% preterm (81)	*P* value 0.001
Son et al. 2021[30]	USA	COVID-19 7432 pregnant women with COVID-19	Control 613 264 pregnant women pre COVID-19 pandemic	COVID-19 0.4% stillbirth (26) 8.5% preterm (631)	Control 0.4% stillbirth (366) 6.9% preterm (7669)	
Overtoom et al. 2021[31]	Netherlands	COVID-19 289 pregnant women with COVID-19 Subgroup: 70 pregnant women with symptomatic COVID-19	Control 183 413 pregnant women pre-pandemic	COVID-19 9.7% preterm (28) 18.6% preterm (13)	Control 6.7% preterm (12 352)	OR 1.01 (0.68–1.49) 2.02 (1.11–3.69)
Blitz et al. 2021[32]	New York, USA	COVID-19 2473 pregnant women with COVID-19 in pregnancy	Control 29 077 pregnant women without COVID-19	COVID-19 8.5% preterm (211)	Control 7.1% preterm (2067)	

Lankford et al. 2021[33]	Maryland USA	COVID-19 261 pregnant women with COVID-19 at birth (all caesarean births)	Control 12 046 pregnant women without COVID-19 at birth (all caesarean births)	COVID-19 8.8% preterm (23) 3.1% stillbirth (8)	Control 4.5% preterm (546) 0.8% stillbirth (96)	*P* value 0.001 < 0.001
Harel et al. 2021[34]	Israel	COVID-19 172 pregnant women with COVID-19 at delivery	Control 2299 pregnant women without COVID-19 at delivery	COVID-19 2.9% preterm (5)	Control 4.3% preterm (98)	*P* value 0.39
DeSisto et al. 2021[35]	USA (736 hospitals)	COVID-19 18 094 pregnant women with COVID-19 at delivery (pre-Delta) 3559 pregnant women with COVID-19 at delivery (Delta period)	Control 1 058 651 pregnant women without COVID-19 at delivery (pre-Delta) 169 330 pregnant women without COVID-19 at delivery (Delta period)	COVID-19 1.0% stillbirth (177) 2.7% stillbirth (96)	Control 0.6% (6806 stillbirth) 0.6% stillbirth (1075)	Adjusted RR 1.47 (1.27–1.71) 4.04 (3.28-4.97)
DeSisto et al. 2021 (overall)[35]	USA (736 hospitals)	COVID-19 21 653 pregnant women with COVID-19 at delivery	Control 1 227 981 pregnant women without COVID-19 at delivery	COVID-19 1.3% stillbirth (273)	Control 0.6% stillbirth (7881)	
Budhram et al. 2021[36]	South Africa	COVID-19 148 pregnant women admitted for COVID-19	Control 382 pregnant women admitted for other medical indication (no COVID-19)	COVID-19 33.1% preterm (49) 3.4% stillbirth (5)	Control 31.7% preterm (121) 5.2% stillbirth (20)	

Gupta et al. 2021[37]	India	COVID-19 70 pregnant women with COVID-19 at delivery	Control 116 pregnant women without COVID-19 at delivery	COVID-19 17% preterm (12)	Control 12% preterm (14)	*P* value 0.096
Epelboin et al. 2021[38]	France	COVID-19 874 pregnant women with COVID-19 at birth	Control 234 771 pregnant women with no COVID-19 at birth	COVID-19 16.7% preterm (146)	Control 7.1% preterm (17 215)	OR 2.64 (2.21–3.16)
Khoiwal et al. 2021[39]	India	COVID-19 60 pregnant women with COVID-19 at admission	Control 60 pregnant women without COVID-19 at admission	COVID-19 31.7% preterm (19)	Control 30% preterm (18)	
Vera von Bargen et al. 2021[40]	Chile	COVID-19 68 pregnant women with COVID-19 at delivery	Control 633 pregnant women	COVID-19 23.52% preterm (16)	Control 8.68% preterm (55)	*P* value 0.0002
Vizheh et al. 2021[41]	Iran	COVID-19 254 pregnant women with COVID-19	Control 345 pregnant women without COVID-19	COVID-19 21.65% preterm (55)	Control 13.0% preterm (45)	*P* value 0.043
Regan et al. 2021[42]	USA	COVID-19 2655 pregnant women with COVID-19 in pregnancy	Control 75 628 pregnant women without COVID-19	COVID-19 7.8% preterm birth (199) 0.5% stillbirth (14)	Control 6.6% preterm (4431) 0.6% stillbirth (387)	Hazard ratio 2.37 (1.89–2.98) 1.55 (0.52–4.61)
Zgutka et al. 2021[10]	USA	COVID-19 60 pregnant women with COVID-19 at birth	Control 124 pregnant women without COVID-19 at birth	COVID-19 18.3% preterm (11)	Control 8.1% preterm (10)	
Ali et al. 2021[43]	Pakistan	COVID-19 90 pregnant women with COVID-19	Control 90 pregnant women without COVID-19	COVID-19 22.2% preterm (20)	Control 11.1% preterm (10)	
Akyıldız et al. 2021[44]	Turkey	COVID-19 101 pregnant women with COVID-19 at birth	Control 101 pregnant women without COVID-19 at birth	COVID-19 28.7% preterm (29)	Control 10.9% (11)	*P* value 0.01
Lucovnik et al. 2021[45]	Slovenia	COVID-19 193 pregnant women with COVID-19 in pregnancy	Control 1124 pregnant women without COVID-19 at birth	COVID-19 5.7% preterm (11) 0.5% stillbirth (1)	Control 3.1% preterm (35) 0.4% stillbirth (4)	OR 0.85 (0.46–1.60) 1.41 (0.16–12.56)

Table 2: Summary of key studies relevant for the effect of COVID-19 on maternal outcomes

The table below only includes studies with a comparison group (non-pregnant individuals with COVID-19).

Study	Country	Population		Effect of COVID-19 on pregnant women		
Allotey et al. 2020[1] PregCOV-19 Systematic Review (updated 29/11/2020)	30 countries	*Pregnant* 34 047 pregnant women with COVID-19	*Not pregnant* 567 075 non-pregnant women with COVID-19	*Pregnant* 1.8% ICU (616) 0.6% ventilation (270)	*Not pregnant* 1.7% ICU (9568) 0.6% ventilation (3280)	*aOR* 2.13 (1.54–2.95) 2.59 (2.28–2.94)
Zambrano et al. 2020[46] CDC Report	USA	*Pregnant* 23 434 pregnant women with symptomatic COVID-19	*Not pregnant* 386 028 non-pregnant women aged 15-44 with symptomatic COVID-19	*Pregnant* 1.05% ICU 0.29% invasive ventilation 0.07% ECMO 0.15% death	*Not pregnant* 0.39% ICU 0.11% invasive ventilation 0.03% ECMO 0.12% death	*aRR (95% CI)* 3.0 (2.6–3.4) 2.9(2.2–3.8) 2.4(1.5–4.0) 1.7(1.2–2.40)
Martinez-Portilla et al. 2020[47]	Mexico	Pregnant 5183 pregnant women with symptomatic COVID-19 admitted to hospital	Not pregnant 5183 matched non-pregnant women aged 15–49 with symptomatic COVID-19	Pregnant 1.5% death 13% ICU 8.1% intubated	Not pregnant 0.8% death 7.4% ICU 8.6% intubated	OR (95% CI) 1.84 (1.30–2.61) 2.25 (1.86–2.71) 0.93 (0.70–1.25)
DeBolt et al. 2020[48]	UK	Pregnant 38 pregnant women with severe or critical COVID-19	Not pregnant 94 non-pregnant women aged 23–50 with severe or critical COVID-19	Pregnant 39.5% ICU 26.3% invasive ventilation	Not pregnant 17% ICU 10.6% invasive ventilation	aOR (95% CI) 5.2 (1.5–17.5) 3.3 (0.5–21.1)

Badr et al. 2020[49]	France	Pregnant 83 pregnant women (≥ 20 weeks) with COVID-19	Not pregnant 107 non-pregnant women of reproductive age with COVID-19	Pregnant 11.08% ICU 10.16% invasive ventilation	Not pregnant 2.38% ICU 1.67% invasive ventilation	
Oakes et al. 2021[50]	USA	Pregnant 22 pregnant women with symptomatic COVID-19	Not pregnant 240 non-pregnant women aged 13–45 with symptomatic COVID-19	Pregnant 31.8% severe COVID (NCPERET criteria) 13.6% severe COVID (WHOOSCI criteria)	Not pregnant 7.1% severe COVID (NCPERET criteria) 2.5% severe COVID (WHOOSCI criteria)	aRR (95% CI) 3.59(1.49–7.01) 5.65 (1.36–17.31)
Lokken et al. 2021[51]	USA	Pregnant 240 women with COVID-19	Not pregnant 34 902 adults (male and female) aged 20–39	Pregnant 10% hospitalisation for COVID-19 1.25% death	Not pregnant 2.8% hospitalisation for COVID-19 0.091% death	RR (95% CI) 3.5 (2.3–5.3) 13.6 (2.7–43.6)
Artymuk et al. 2021[52]	Siberia, Russia	Pregnant 8485 women with COVID-19	Not pregnant General population (496 170)	Pregnant 5933 per 100 000 incidence 3.57% ICU 0.48% mechanical ventilation	Not pregnant 1960 per 100 000 incidence 2.24% ICU 1.05% mechanical ventilation	
Behrens 2021[53]	USA	Pregnant 43 women with COVID	Not pregnant 1265 women with COVID aged 16–51	Pregnant 0% deaths (0)	Not pregnant 3% deaths (39)	
Vizheh 2021[54]	Iran	Pregnant 110 pregnant women with COVID	Not pregnant 234 non-pregnant women with COVID	Pregnant 9.1% ICU (10) 5.5% death (6)	Not pregnant 8.1% ICU (18) 5.1% death (12)	*P* value 0.76 0.80

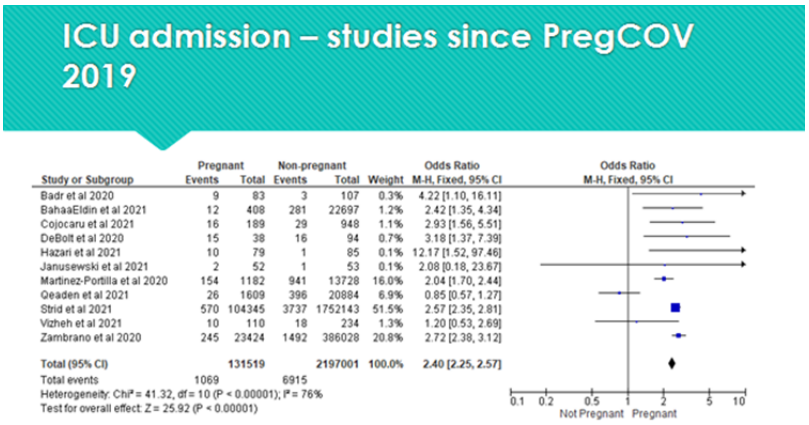
Qeadan 2021[55]		Pregnant 1609 pregnant women with COVID-19	Not pregnant 20 884 non-pregnant women with COVID aged 18–44	Pregnant 1.6% ventilation (26) 0.2% death (4)	Not pregnant 1.9% ventilation (396) 0.5% death (100)	*P* value 0.48 0.26
Crossette-Thambiah et al. 2021[56]	UK	Pregnant 36 pregnant women admitted with COVID-19	Not pregnant 36 propensity matched women admitted with COVID-19	Pregnant 8% mechanical ventilation (3) 0% deaths (0)	Not pregnant 31% mechanical ventilation (11) 0% deaths (0)	*P* value 0.03
Cojocaru et al. 2021[57]	USA (multiple centres)	Pregnant 189 pregnant women with COVID-19	Not pregnant 948 women aged 18–45 with COVID-19	Pregnant 8.5% ICU (16) 5.3% mechanical ventilation (10) 0.5% death (1)	Not pregnant 3.1% ICU (29) 1.8% mechanical ventilation (17) 0.2% death (2)	*P* value < 0.001 0.008 0.4
Scheler et al. 2021[58]	Brazil	Pregnant 4853 pregnant or postpartum women with ARDS secondary to severe COVID-19	Not pregnant 42 915 women aged 15–49 with ARDS secondary to severe COVID-19	Pregnant 7.8% deaths (377)	Not pregnant 13.9% deaths (5946)	OR (95% CI) 0.52 (0.47–0.58)
Knobel et al. 2021[59]	Brazil	Pregnant 2265 pregnant women with acute respiratory symptoms of COVID-19	Not pregnant 21 910 non-obstetric women of reproductive aged 10–45 with acute respiratory symptoms of COVID-19	Pregnant 6.7% deaths (152) 18.7% ICU admission (424) 7.4% mechanical ventilation (168)	Not pregnant 13.0% death (2,848) 24.4% ICU admission (5346) 10.7% mechanical ventilation (2344)	*P* value > 0.0001 > 0.0001 > 0.0001
Serra et al. 2021[60]	Brazil	Pregnant 3372 pregnant women hospitalised with acute respiratory symptoms of COVID-19	Not pregnant 37 268 non-obstetric women of reproductive age hospitalised with acute respiratory symptoms of COVID-19	Pregnant 21.1% ICU (574/2721) 8.0% invasive ventilation (209/2598) 6.2% deaths (181/2904)	Not pregnant 27.3% ICU (8014/29 368) 12.5% invasive ventilation (3536/28 199) 14.1% deaths (4534/32 081)	OR (95% CI) 0.71 (0.65–0.78) 0.42 (0.36–0.48) 0.40 (0.34–0.47)
Hazari et al. 2021[61]	United Arab Emirates	Pregnant 79 pregnant women	Not pregnant 85 non-pregnant women with COVID-19	Pregnant 12.6% ICU (10) 8% ventilation (6) 1% death (1)	Not pregnant 1.2% ICU (1) 1% ventilation (1) 0% death (0)	*P* value 0.003 0.03
Januszewski et al. 2021[62]		Pregnant 52 pregnant women admitted with COVID-19	Not pregnant 53 non-pregnant women of reproductive age admitted with COVID-19	Pregnant 0% ventilation (0) 3.9% ICU admission (2)	Not pregnant 1.9% ventilation (1) 1.9% ICU admission (1)	*P* value 0.32 0.547

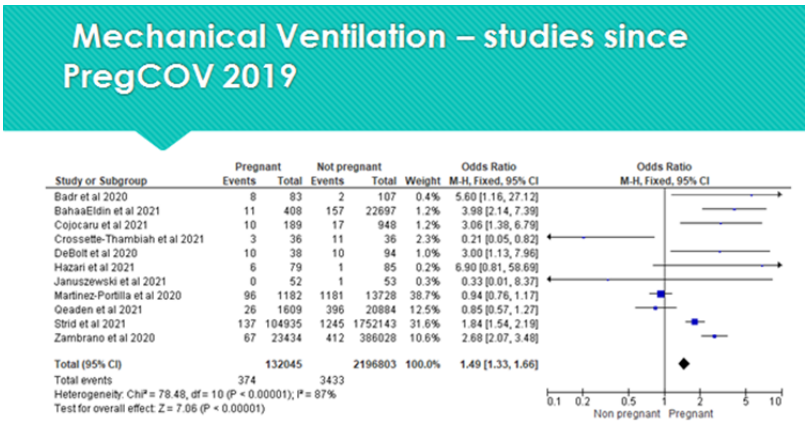
Strid et al. 2021[63] Pre-Delta Delta	USA	Pregnant 89 435 pregnant women with COVID-19 14 910 pregnant women with COVID-19	Not pregnant 1 491 870 non-pregnant women aged 15–44 with COVID-19 260 273 non-pregnant women aged 15–44 with COVID-19	Pregnant 0.51% ICU (455) 0.12% invasive ventilation or ECMO (111) 0.11% death (94) 0.77% ICU(115) 0.18% invasive ventilation or ECMO (27) 0.34% death (50)	Not pregnant 0.21% ICU (3115) 0.07% invasive ventilation or ECMO (1013) 0.09% death (1400) 0.24% ICU (622) 0.09% invasive ventilation or ECMO (232) 0.18% death (478)	RR (95% CI) 2.44 (2.18–2.72) 1.83 (1.45–2.30) 1.12 (0.89–1.41) 3.23 (2.61–3.99) 2.03 (1.32–3.12) 1.83 (1.34–2.48)
Leung et al. 2021[64]	Brazil	Pregnant 7235 pregnant women admitted for COVID-19	Not pregnant 90 477 non-pregnant women aged 15–45 admitted for COVID-19	Pregnant 29.2% ICU (2113) 48.4% ventilated (3500)	Not pregnant 26.6% ICU (24 038) 60.1% ventilated (54 379)	*P* value < 0.001 < 0.001
BahaaEldin et al. 2021[65]	Egypt	Pregnant 408 pregnant women with COVID-19	Not pregnant 22 697 non pregnant women aged 18–49 with COVID-19	Pregnant 2.9% ICU (12) 2.7% ventilated (11) 2.5% death (10)	Not pregnant 1.2% ICU (281) 0.7% ventilated (157) 1.5% death (348)	*P* < 0.001
Gonçalves et al. 2021[66]		Pregnant 9370 pregnant women with acute respiratory symptoms of COVID-19	Not pregnant 399 970 non-pregnant women aged 10–45 with acute respiratory symptoms of COVID-19	Pregnant 26.5% ICU (2226/8407) 11.1% death (1031/9270)	Not pregnant 36.7% ICU (127 070/345 822) 38.4% death (153 457/399 970)	

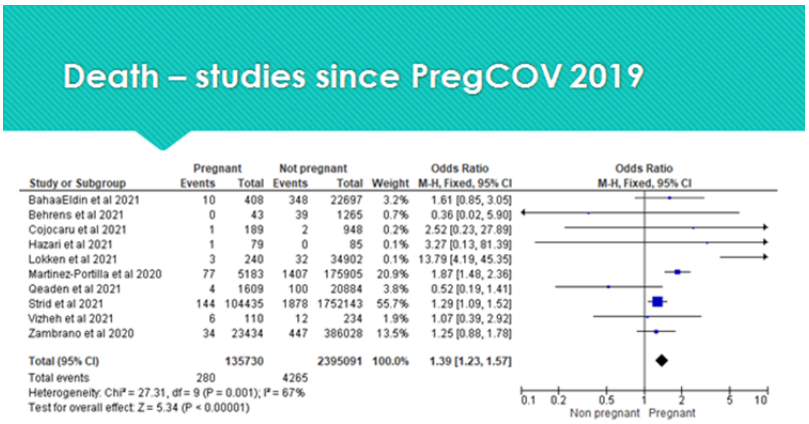
Meta-analysis of the effect of COVID-19 on pregnancy outcomes

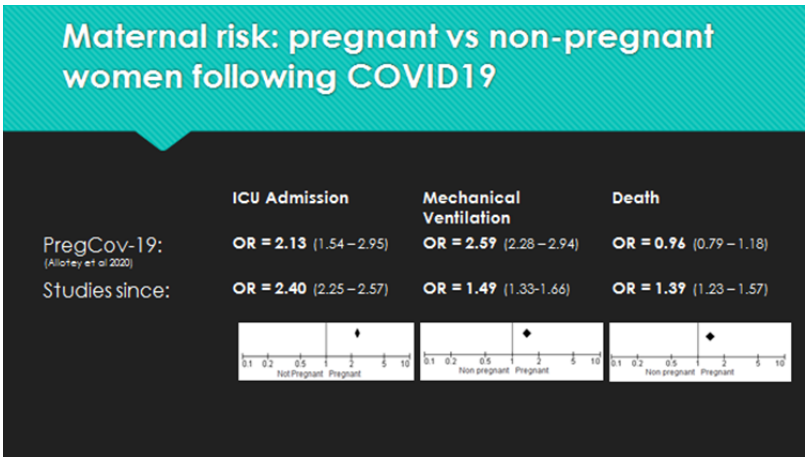
Meta-analysis of the maternal effects of COIVD-19

Meta-analysis of the maternal effects of COVID-19 (ICU admission, mechanical ventilation and death) was performed using data from the studies in Table 2 (above) published following the Feb 2021 update of the PregCOV-19 Systematic Review, using the online Cochrane Revman software (Shea and Karia et al., unpublished). The results of this meta-analysis are compared with the results of the latest online update of the PregCOV-19 Systematic Review from May 2022.[19]









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Appendix III: What to consider when counselling a pregnant woman for vaccination

Counselling may cover the following points.

The options available to the pregnant woman:

- To receive vaccination against COVID-19 now.
- To decline the vaccine, with the option of having it in future (either later in her pregnancy, or after the birth of her baby).
- To decline to have the vaccine altogether; this is a woman's individual choice.

2. The benefits of vaccination:

- Reduction in severe disease and hospital admission for a pregnant woman.
- Potential reduction in the risk of preterm birth associated with COVID-19.
- Potential reduction in transmission of COVID-19 to vulnerable household members.
- Potential reduction in the risk of stillbirth associated with COVID-19.

- Potential protection of the newborn from COVID-19 through passive antibody transfer.
- Potential reduction in the risk of developing long COVID.

3. The risks of vaccination (see section 2.3 for further detail):

- The vast majority of research and clinical experience relating to vaccinations in pregnancy has been with the Pfizer and Moderna vaccines.
- Minor local reaction (pain, redness or swelling at the injection site).
- Mild systemic adverse effects like fatigue, headache or myalgia, typically short-lived (less than a few days).
- Very rare thrombotic adverse events following use of the Oxford-AstraZeneca or Janssen vaccines, or very rare cardiac inflammation adverse events following the Moderna vaccines.
- There has been no evidence to suggest fetal harm following vaccination against COVID-19, and fetal harm is considered to be extremely unlikely based on evidence from other non-live vaccines. Risk of fetal harm cannot be precisely estimated until large-scale studies of vaccination in pregnancy have been completed.

4. The risks from COVID-19 to the woman and her fetus if the pregnant woman declines vaccination (see section 1 for further detail):

Maternal risks:

- Most women with COVID-19 in pregnancy will have no symptoms. Some women will develop critical illness from COVID-19.
- The risk of severe illness from COVID-19 is higher for pregnant women than for non-pregnant women, particularly in the third trimester.
- There is consistent evidence that pregnant women are more likely to be admitted to an ICU than non-pregnant women with COVID-19.

Fetal risks:

- Symptomatic maternal COVID-19 is associated with a two to three times greater risk of preterm birth.
- Although the overall risk of stillbirth is small, the risk is approximately doubled with SARS-CoV-2 infection.[19,51]

These risks should be personalised to each individual pregnant woman:

- Risk of exposure because of occupation: for example (and not limited to) healthcare and social workers, public-facing roles and education settings.
- Risk of severe illness: medical conditions (hypertension, diabetes), Black, Asian or minority ethnicity, BMI above 25 kg/m^2, aged 35 years and older, and being unvaccinated.

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