

# COVID-19 in pregnancy

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Accepted on 23 October 2024.

## Key content

- COVID-19 is known to be associated with significant morbidity for pregnant women and their babies.
- This susceptibility to adverse clinical outcomes may be associated with the unique physiological characteristics of the pregnant host.
- Public health measures recommended for the management and prevention of critical COVID-19 in pregnancy and lactation evolved during the 2020 pandemic; some decisions were controversial.
- We highlight lessons learnt and considerations for future pandemic preparedness.

## Learning objectives

- To outline the pathology of COVID-19 in pregnancy, including placental involvement.

- To summarise current evidence-based management and signpost to resources updates.
- To discuss the role of vaccines to reduce morbidity and mortality for existing and novel SARS-CoV-2 viral strains.

## Ethical issues

- Sustained international collaborative strategies are crucial to ensure global equity for access to treatment and vaccines for communicable diseases.

**Keywords:** clinical trials / COVID-19 / pregnancy / SARS-CoV-2 variants / vaccines

Please cite this paper as: Greer O, Saeed Z, Woon EV, Singh N, Johnson M, Shah N. COVID-19 in pregnancy. *The Obstetrician & Gynaecologist* 2025;27:43–56. <https://doi.org/10.1111/tog.12960>

## Introduction

The World Health Organization (WHO) declared the COVID-19 pandemic in March 2020, recognising this as a global public health emergency. A key milestone, this led to the implementation of a diverse range of public health strategies worldwide.<sup>1</sup> Commentary and analysis, abundant both within and outwith the scientific literature, have focused on the clinico-pathogenesis and socioeconomic impacts of the pandemic.<sup>2–4</sup> Many researchers directed their efforts towards uniquely vulnerable groups at risk of developing adverse clinical outcomes, including pregnant women, who were disproportionately affected during the pandemic with high morbidity and mortality rates.<sup>5–7</sup> In this review, we summarise current understanding of the impact of the SARS-CoV-2 virus and pandemic on pregnant and recently pregnant women and the recommended management.

## Clinical manifestations of SARS-CoV-2 infection

Early characterisation of clinical outcomes following SARS-CoV-2 infection in pregnant women demonstrated the high risk of morbidity and mortality.<sup>8,9</sup> Compared to some other respiratory viral pandemics, case fatality rates (CFRs) for COVID-19 in this group were greater.<sup>8</sup> In the United Kingdom, COVID-19 was associated with a CFR of 2.64 (95% CI 1.82–3.71) per 100 000 maternities, which was considerably greater than the CFR of 1.13 (95% CI 0.75–1.65) observed during the H1N1 influenza pandemic in 2009–2010.<sup>10,11</sup>

Given similar findings across the population, a UK-wide policy of ‘lockdowns’ was implemented to control viral transmission, with restructuring of healthcare provision to focus on emergency care.<sup>12</sup> Accordingly, the use of

telemedicine and highly focused triage, based on clinical severity, was widespread.<sup>13</sup> Public health messaging also played an important role, encouraging severely ill and 'at risk' groups to seek medical attention.<sup>14</sup>

Over time, sequential 'waves' of new dominant viral variants of concern (VoC) with altered transmissibility and pathogenicity circulated.<sup>15</sup> Notably, Vousden et al. reported increased hospital admissions of pregnant women with moderate or severe COVID-19 coinciding with dominance of specific SARS-CoV-2 variants.<sup>15–17</sup> Evaluation of illness severity was key to triage for admission and escalation of care and the WHO developed a classification tool, which included alerts for high-risk groups, including pregnant women.<sup>18</sup> In fact, at its peak, severe infection in pregnancy was associated with an increase in crude numbers of admissions and referrals of pregnant women to ITU (4-fold) and

extracorporeal membrane oxygenation (ECMO) centres (3-fold) across the United Kingdom.<sup>19</sup>

### Symptoms and illness severity

Several studies observed that symptomatology in pregnancy was similar to that of the general population, with comparable risk factors for severe disease (advanced *maternal* age, BMI >35 kg/m<sup>2</sup> and non-Caucasian ethnicity).<sup>8,9,20</sup> Cough, fever, myalgia and (although not pathognomonic) anosmia and dysgeusia were synonymous with a diagnosis of COVID-19 (Figure 1; Figure S1); however, many remained asymptomatic and were identified through individual or institutional screening. In a meta-analysis of 293 152 pregnant and recently pregnant women, the reported prevalence of SARS-CoV-2 was 9% (95% CI 7–10%) (Figure 1).<sup>20</sup>

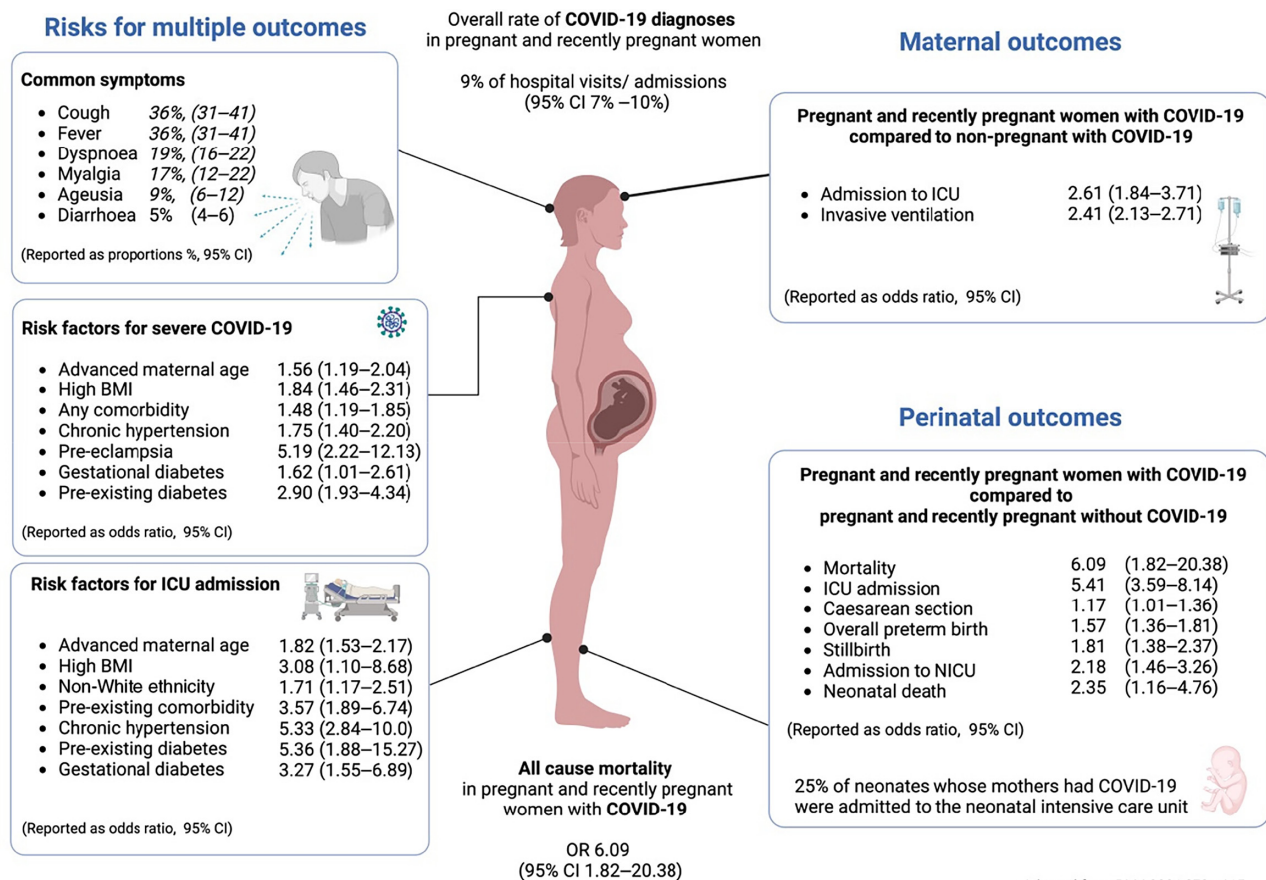


**Figure 1.** An overview of the clinical manifestations of COVID-19 in pregnant and recently pregnant women. The proportion of pregnant and recently pregnant participants reporting symptoms associated with COVID-19 is highlighted in the top left box. Characteristics of pregnant and recently pregnant women with SARS-CoV-2 infection that were associated with an increased odds ratio of developing severe COVID-19, or requiring ICU admission are outlined in the left middle and bottom boxes of this figure respectively. Comparison of outcomes for pregnant and recently pregnant women versus non-pregnant women with COVID-19 is outlined on the top right hand side of the figure. Comparison of outcomes for pregnant and recently pregnant women with COVID-19 versus those without COVID-19, is outlined on the bottom right-hand side of this figure.<sup>20</sup> Created with [BioRender.com](https://www.biorender.com).

## Outcomes for mother and baby

### Birth outcomes

Numerous systematic reviews have shown increased maternal morbidity associated with SARS-CoV-2 infection, but in an analysis of 52 systematic reviews, Allotey et al. was the only one considered to be at low risk of bias.<sup>9,20–22</sup> This study compared pregnant and puerperal with non-pregnant women infected with SARS-CoV-2 and reported an increased risk of admission to the intensive care unit (ICU) (OR 2.61, 95% CI 1.84–3.71) or invasive ventilation (OR 2.41, 95% CI 2.13–2.71).<sup>20</sup> Reported maternal mortality rates were between 0% and 11% with an increased risk of death in pregnant women with COVID-19 compared to those without the disease (OR 6.09 95% CI 1.82–20.38).<sup>20,22</sup> In the United Kingdom, MBRRACE reported 33 maternal deaths attributable to COVID-19 (occurring at the height of the pandemic during the 2019–2021 triennium) contributing to 13.7% of all direct and indirect deaths and a further 12 women died between 6 weeks and 1 year after delivery (causing 3.9% of all late maternal deaths).<sup>11</sup>

Other risks included pre-term delivery (OR 1.57 95% CI 1.36–1.81) and Caesarean section (OR 1.17, 95% CI 1.01–1.36) (Figure 1).<sup>20,22</sup> As for the neonates born to infected mothers, there was an increased risk both of admission to the neonatal intensive care unit and of neonatal death (OR 2.35 95% CI 1.16–4.76) with MBRRACE reporting that, during the 2019–2021 triennium in the United Kingdom, 4.8% of neonatal deaths in babies born  $\geq 24$  weeks' gestation were born to mothers positive for SARS-CoV-2 (prematurity is likely to be a significant contributor).<sup>20,22,23</sup>

### Pregnancy loss

In a systematic review and meta-analysis of pregnancy loss in the first and second trimester ( $<24$  weeks of gestation), van Baar et al. evaluated 18 233 women (120 studies) with suspected or confirmed SARS-CoV-2 and were unable to demonstrate an association with miscarriage in the first or second trimester.<sup>21</sup>

In addition, regarding stillbirth, Allotey et al. reported an OR of 1.81 (95% CI 1.38–2.37) when compared to that in non-infected women (overall rates reported were 0.4%, 95% CI 0.2–0.6%) and data from MBRRACE in 2021, reported 11.9% of total stillbirths in the United Kingdom were associated with a positive SARS-CoV-2 test in either the mother or the baby.<sup>20,23</sup> It is important, however, to note the absence of evidence to support a causal link, as well as the infrequency of transplacental viral infection and poor access to maternity care, following organisational changes made during the pandemic, may have contributed.<sup>24</sup> However, as more pathogenic strains emerged (e.g. during the Delta wave), the rates of stillbirths also increased. As such, an alternative hypothesis is the effect of placental injury from viral infection or inflammation.<sup>20,24</sup>

### Long COVID

It is defined by WHO as a continuation, or new onset, of symptoms 3 months after initial SARS-CoV-2 infection that lasts for at least 2 months without an alternative diagnosis; it is reported to affect 1 in 10 patients.<sup>27</sup> Presentation is diverse with prominent symptoms including breathlessness, fatigue and a reduction in pre-morbid cognition with potentially a significant impact on quality of life.<sup>25–28</sup> Hypotheses for its multi-systemic nature include reactivation of dormant virus, persisting inflammation and microvascular thrombotic events, with comparisons made with post-viral sequelae associated with other common viral infections, such as Epstein–Barr Virus.<sup>25,29</sup> Unfortunately, treatment options remain limited.

## Pathophysiology

### The virus

The structure of SARS-CoV-2 is characterised by a core RNA genome complexed with nucleocapsid protein (NP) enveloped by a membrane (Figure 2).<sup>30,31</sup> The membrane of the virion is embedded with three proteins: membrane protein (M), small membrane protein (E) and spike protein (S). The key receptor identified to facilitate its entry into host cells is angiotensin-converting enzyme 2 (ACE-2)<sup>30–32</sup> and entry via ACE-2 can occur in a transmembrane serine protease 2 (TMPRSS2) dependent or independent manner.<sup>33</sup> Upon entry, the viral genome is integrated into the host DNA and transcribed and translated for the creation of more virions.<sup>34</sup>

### Susceptibility in pregnancy

ACE-2, a key enzyme of the renin–angiotensin–aldosterone (RAA) system (RAS), modulates vascular function. It is ubiquitously expressed in many human tissues, including lungs and blood vessels and, notably, expressed in the placenta (decidual stroma, perivascular cells, cytotrophoblasts and syncytiotrophoblasts).<sup>50,51</sup> ACE-2 converts angiotensin (Ang) II to Ang I, resulting in vasodilatory, anti-angiogenic and anti-proliferative effects.<sup>52</sup> RAS also regulates other vasodilators, including prostaglandin E2, nitric oxide and bradykinin; the net effect is a low-resistance peripheral vascular system.<sup>53–55</sup>

Interestingly, the effects of SARS-CoV-2 infection share similar mechanisms with pre-eclampsia with a shift from Ang I to Ang II predominance (here due to engagement of spike with the ACE-2 receptor) that results in vasoconstriction.<sup>35,36</sup> Since ACE-2 receptors are also expressed by endothelial cells, viral infection leads to endothelial injury causing systemic inflammation and a pro-coagulable state which explains the clinical manifestations of vascular thrombosis and stroke observed in patients with COVID-19.<sup>36–39</sup> Thirdly,

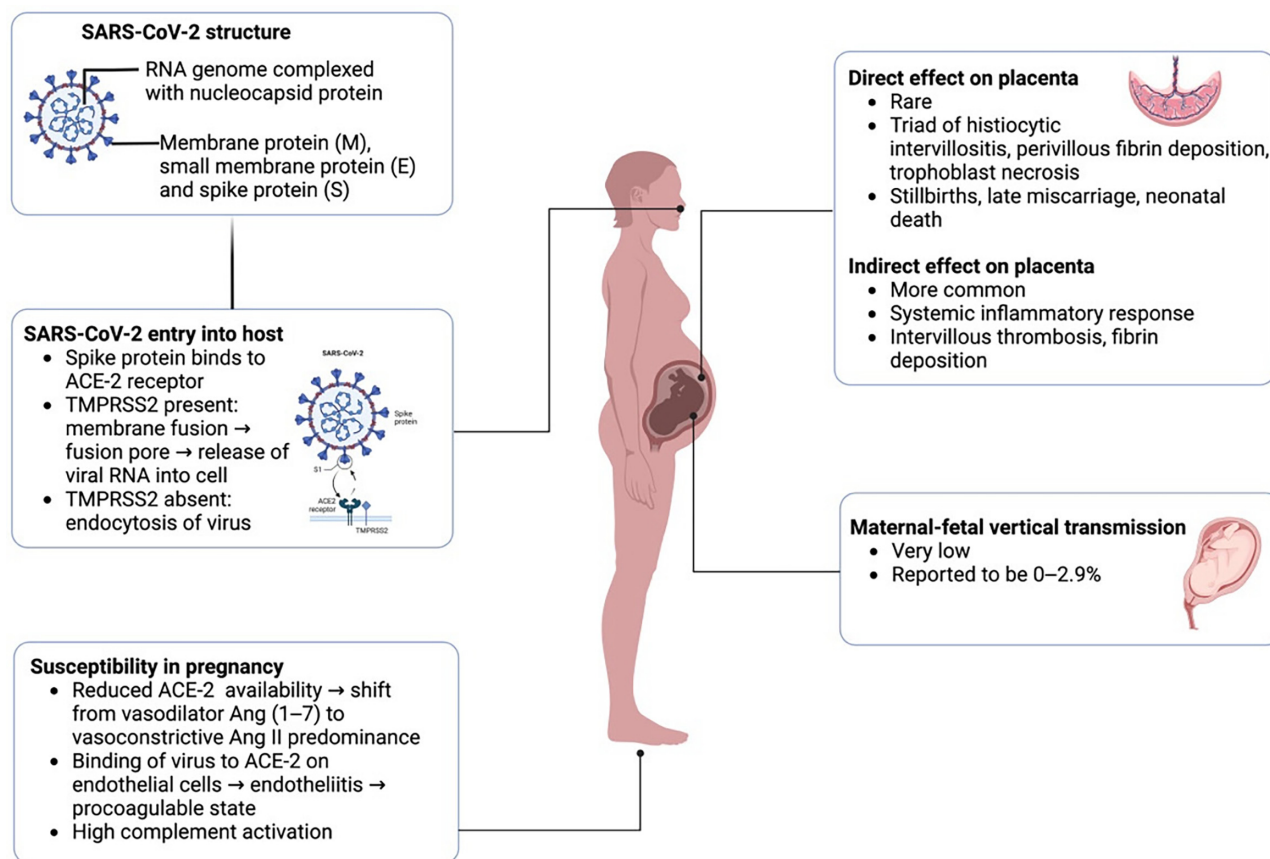


**Figure 2.** An overview of the pathophysiology of COVID-19 in pregnancy: Structure of SARS-CoV-2, mode of entry of virus into host, direct and indirect effects of SARS-CoV-2 on placenta and systemic effects of SARS-CoV-2 infection on the pregnant mother.<sup>32–49</sup> Created with BioRender.com.

complement activation exacerbates endothelial injury and thrombotic vascular damage.<sup>56</sup>

### Effect of SARS-CoV-2 on the placenta

Direct infection of the placenta has not been universally agreed in the literature and, although some case reports and small case series have reported SARS-CoV-2 in placental tissue (syncytiotrophoblast and fetal endothelium) this has not been shown in larger case series.<sup>40,57–68</sup> Furthermore, although the placenta expresses both ACE-2 receptor and TMPRSS2, their co-expression, which is required for its canonical entry, remains uncommon.<sup>69</sup> Moreover, ACE-2 receptor expression in the placenta diminishes with advancing gestation.<sup>41</sup> Despite this, systemic inflammation, endothelial injury and thrombosis are still seen in placental tissue in the absence of virus.<sup>40–45</sup> In fact, placentitis, rather than fetal infection, may be the cause of stillbirths or late miscarriages.<sup>70</sup>

### Vertical transmission

The likelihood of materno-fetal vertical transmission is low, with studies reporting approximate rates of 0.9%–2.8%.<sup>46–49</sup> True in-utero infection, determined by spike-specific IgM in cord blood, has been suggested to be in the range of 0%–7.7%, with detectable viral genome in cord blood in 0%–2.9% of cases.<sup>7,47,71</sup> Postnatally, WHO recommends breastfeeding as there is little evidence to suggest that breastfeeding and maternal bonding increase the risk of vertical transmission.<sup>72</sup>

## The host immune response

### The innate response

Early in the pandemic, ‘cytokine storm’, due to dysregulated innate cellular responses, was put forward as a driver of severe infection, as seen during severe bacterial sepsis. Ordinarily, innate pro-inflammatory immune responses

follow viral antigen exposure and, as the infection is controlled, a counter-release of anti-inflammatory cytokines suppresses the inflammatory response limiting indiscriminate injury to 'bystander' tissues. However, with persisting viral replication, this process is disrupted and disordered inflammatory signalling predominates, leading to damage to surrounding infected *and* non-infected tissues, causing organ injury. Pregnancy may increase susceptibility to this type of tissue injury due to immune modifications that favour inflammation. This includes a rapid increase in the production and release of pro-inflammatory cells, such as monocytes and neutrophils, as well as plasmacytoid dendritic cells (key secretors of antiviral type I interferons).<sup>73–77</sup> During the H1N1 (influenza A virus) pandemic of 2009–2010, Kay et al. characterised antigen-specific in vitro responses of natural killer (NK) cell responses to H1N1 and found an increase in activated cells producing pro-inflammatory molecules (e.g. MIP-1 $\beta$ ) and markers of cytotoxicity (CD107a) in pregnancy.<sup>78,79</sup> However, during SARS-CoV-2 infection, Habel et al. did not detect a significant difference in the frequency of monocytes or key pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$  or IL-6 in the peripheral blood of infected pregnant women.<sup>80</sup> Additionally, they saw no significant difference in the activation status of peripheral natural killer (NK) or  $\gamma\delta$ T cells, both with antiviral properties.<sup>80</sup> It is important to note, however, that none of the pregnant participants in this study had a diagnosis of critical COVID-19.

### The adaptive response—T cells

Lymphopenia has been widely described as a feature of severe COVID-19.<sup>7,81–83</sup> An associated reduction in frequencies of CD4<sup>+</sup> and CD8<sup>+</sup> T cells and important subsets needed for antigen-specific responses has been proposed as a cause for the increased risk of adverse clinical outcomes seen in some.<sup>73,74</sup> However, this has not been replicated during leucocyte phenotyping in mild or convalescent infection. Interestingly, T-cell activation status or cytokine secretion (IFN $\gamma$ , TNF $\gamma$  or CD107a) and recall responses following stimulation using SARS-CoV-2 peptides have not been shown to be impaired in pregnancy.<sup>84,85</sup>

### cT<sub>FH</sub> and B-cell immunology in pregnancy

T follicular helper cells (T<sub>FH</sub>) are a specialised subset of effector CD4 T cells, found in lymphoid tissue, that induce B-cell activation and differentiation into class-switched and antibody-secreting long-lasting plasmablasts and memory B cells (Figure S2).<sup>86–88</sup> They are needed for humoral immunity and dysregulation of T<sub>FH</sub> can negatively affect pregnancy outcomes.<sup>89–94</sup> As evaluation of T<sub>FH</sub> requires invasive lymph node drainage for sampling, circulating variants of T<sub>FH</sub> (cT<sub>FH</sub>) and their subsets are often used for ex vivo research. While our understanding is that proportions of activated

(ICOS<sup>+</sup>) cT<sub>FH</sub> may increase in pregnancy, driven by oestrogen, other groups have shown comparable cT<sub>FH</sub> activation between pregnant and non-pregnant cohorts.<sup>95–98</sup> cT<sub>FH</sub> subsets can be divided into three distinct groups that resemble the T-helper subsets (Th1, Th2 and Th17) and are referred to as T<sub>FH</sub>1 (Th1)-like, T<sub>FH</sub>2 (Th2)-like and T<sub>FH</sub>17 (Th17)-like.<sup>90,99</sup> The expansion of circulating T follicular helper (cT<sub>FH</sub>) populations post SARS-CoV-2 vaccination in healthy individuals (not specifically pregnancy) appears to be biased towards Th1- and Th17-like subsets, which are associated with improved humoral responses (both antiviral and antibody).<sup>100</sup>

Research on antibody secreting cells (ASCs) is limited in pregnancy and animal models have shown inconclusive results.<sup>101,102</sup> In pregnant mice, influenza infection induced lower antibody neutralising titres within the first 8 weeks of infection, but this resolved and no change was observed in ASC frequency during later pregnancy.<sup>101</sup> However, plasmablast metabolism and post-translational modifications were downregulated without affecting long-term antibody function. In humans, Habel et al., analysed B-cell activation in COVID-19 pregnant and non-pregnant women and found comparable frequencies of ASCs during acute and convalescent infection.<sup>95</sup>

### Vaccine efficacy and immunogenicity in pregnancy

Currently, in the United Kingdom, only mRNA vaccines for SARS-CoV-2 have been licensed for use in pregnancy and these have proven to be extremely effective at reducing severe disease. Between December 2020 and August 2021, hospitalisation rates among vaccinated pregnant women were 28 per 100 000 infections (>14 days post-double dose) versus 1807 in the unvaccinated, giving a vaccine effectiveness of 83% (CI 76%–89%).<sup>103</sup> Data from large cohorts of vaccinated and unvaccinated pregnant women in the United Kingdom and United States ( $n = 186\,990$ ,  $n = 106\,428$ , respectively) have shown that vaccination is protective against adverse maternal-fetal outcomes.<sup>104,105</sup> Participants in these retrospective datasets either completed a vaccination course pre-pregnancy or received a second dose or booster in pregnancy. As both a primary vaccination (two doses) or a single booster, mRNA vaccines have been shown to generate robust anti-spike IgG and neutralising antibody responses in pregnancy irrespective of gestation.<sup>106–109</sup> Moreover, mRNA vaccines have shown a neonatal benefit with time-dependent transfer of IgG and neutralising antibodies to the neonate that persists through early infancy.<sup>106,107,110</sup> For antibody transfer, vaccination should ideally occur more than 9 days before birth.<sup>107</sup> It is also important to appreciate that mRNA vaccines work by transfecting antigen-presenting cells that present antigen to cytotoxic and helper T cells, typically in lymph nodes local to the injection sites which induces the desired protective

immune response.<sup>111,112</sup> There is no evidence to suggest that mRNA vaccines or their components are significantly transferred to the placenta or fetus during pregnancy; ex vivo work using placentas from vaccinated women and human placental explant models have observed minimal or no uptake of mRNA vaccines.<sup>113,114</sup>

Other vaccines developed during the pandemic include inactive vaccines that are able to induce a more diverse immune response; this is particularly evident in T-cell responses (i.e. IFN $\gamma$  and IL-2 cytokine responses to spike, membrane and NP).<sup>115</sup> Clinically, this seems to provide a protective effect, as patients who respond to a broader range of T-cell epitopes generally experience milder symptoms.<sup>116,117</sup> This is partly due to a wider T-cell receptor (TCR) repertoire and a higher chance of cross-recognition of a greater number of epitopes.<sup>118</sup> Inactive vaccines have been more commonly used in low- and middle-income countries (LMICs) due to less restrictive storage and transport requirements and lower cost. Data from observing their use in pregnancy following inadvertent vaccination have shown that they induce effective neutralising antibodies (after two doses) with no safety concerns.<sup>100,119</sup> Vaccine effectiveness (85%) is also comparable to their mRNA counterparts.<sup>120</sup> However, total spike IgG and spike-specific T-cell responses are still better with mRNA vaccines which, despite a B-cell receptor (BCR) and TCR repertoire that is skewed towards immunodominant epitopes (spike), are still able to protect against existing and emerging VOCs.<sup>115,121–123</sup> Nonetheless, although other vaccine technologies (adenovirus vector and recombinant protein with adjuvant) generate comparable seroprotective antibodies and spike-specific  $cT_{FH}$ , mRNA vaccines generate longer-lived receptor binding domain (RBD)-specific memory B cells.<sup>124</sup>

During the initial roll out of COVID-19 vaccines, pregnant women were typically excluded from the initial vaccine trials. However, inadvertent pregnancies occurring in participants provided observational safety data to support their rollout to pregnant women during the pandemic.<sup>125</sup> One of the biggest challenges has been poor vaccine uptake in not only pregnant women but also among non-pregnant women of reproductive age. In the United Kingdom alone during the 2022–2023 winter period, influenza vaccine and autumn SARS-CoV-2 booster uptake were 35% and 13.1%, respectively.<sup>126,127</sup> Much vaccine hesitancy is due to concerns surrounding safety, perceived effectiveness and trust.<sup>128</sup> This is despite a strong body of evidence to support a lack of any safety concerns for pregnant women receiving a COVID-19 vaccine and clear benefits.<sup>129,130</sup> Certainly, as healthcare workers, it is everyone's responsibility as part of good antenatal and preconception care, to discuss and recommend all indicated vaccines pre and during pregnancy.

## Management

### Acute care

At the start of the pandemic, in the absence of tried and tested viral-specific therapies, pillars of treatment broadly included:

1. Supportive interventions to maintain optimal organ function;
2. Surveillance for features of end-organ dysfunction; and
3. Therapy to minimise systemic inflammation.

### Supportive care

Oxygen delivery and the monitored administration of intravenous fluids, in line with the management of sepsis, are key to maintaining adequate organ oxygenation as well as perfusion, in the face of poor oral fluid intake and high insensible losses exacerbated by pyrexia.<sup>131</sup>

### Critical care

As per RCOG guidance, urgent multidisciplinary (MDT) input is required for the unwell woman with COVID-19, including those requiring oxygen, with a respiratory rate  $\geq 20$  breaths per minute or a heart rate  $\geq 110$  beats/min.<sup>131</sup> Oxygen delivery is recommended to maintain oxygen saturations between 94% and 98%, and to achieve this, escalation of the mode of oxygen delivery, that is, via nasal cannula or face mask, may be required.<sup>131</sup> In the severest cases, urgent escalation to high dependency or intensive care is required and current guidance outlines physiological thresholds which should trigger a critical care review and plan of care (Table 1).<sup>131,132</sup> As always, an individualised approach is required and escalation for review by the critical care team may be indicated before these thresholds have been reached.

The WHO published technical advice on the management of COVID-19 (adapted from existing guidance for critical viral respiratory illness) which it continues to update in accordance with the developing evidence.<sup>133,134</sup> For pregnant and lactating patients, appropriate modifications to the recommendations have been made to accommodate for known physiological adaptations of pregnancy as well as consideration of teratogenic or fetotoxic drugs (with overt clarification, where data are limited).<sup>131</sup> Current UK guidance for pregnancy has been developed from best practice and the results of efficiently implemented clinical trials (Figure 3).<sup>131,135,136</sup>

While most randomised therapeutic trials for COVID-19 explicitly excluded pregnant and lactating women two international randomised controlled trials (RCTs), RECOVERY and SOLIDARITY, were adapted to include pregnant and lactating women.<sup>137–139</sup> Despite this, pregnancy-specific data have yet to be published and management decisions are based on prior knowledge of

**Table 1.** RCOG Coronavirus infection in pregnancy guidance for physiological thresholds prompting urgent escalation for critical care input in the unwell woman with suspected or confirmed COVID-19<sup>116</sup>

| Respiratory                                                             | Renal                                                                                                                   | Central nervous system                       |
|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| RR rapidly rising or increasing to $\geq 25$ bpm despite oxygen therapy | Reduction in urine output <sup>a</sup>                                                                                  | Altered mentation, e.g. somnolence, delirium |
| Increasing O <sub>2</sub> requirements or FiO <sub>2</sub> $> 35\%$     | Acute kidney injury (serum creatinine $> 77 \mu\text{mol/L}$ in the absence of pre-existing renal disease) <sup>a</sup> |                                              |

<sup>a</sup>Wiles et al.<sup>132</sup> comment that acute kidney injury and oliguria are difficult to define in pregnancy as threshold criteria are based on the non-pregnant and do not account for gestational variation or physiological changes in the peripartum period.  
bpm = breaths per minute; FiO<sub>2</sub> = fraction of inspired oxygen; RR = respiratory rate.

the pharmacokinetic, teratogenic and fetotoxic profiles of the drug and administered following risk–benefit evaluation.<sup>135,136,140</sup> Accordingly, in the RECOVERY trial, women in pregnancy were only recruited to treatment arms with an acceptable safety profile.<sup>135</sup>

For the SOLIDARITY trial (where known drugs were repurposed to evaluate their efficacy in the management of COVID-19), pregnancy was not definitively excluded.<sup>139</sup> One such drug, remdesivir (an antiviral), has been accepted for use in the latest version of the RCOG ‘COVID-19 in pregnancy’ guidance with emphasis on a MDT decision to balance maternal benefit with unknown fetal risks.<sup>131,141,142</sup> In non-pregnant cases, remdesivir (vs. control) did not reduce mortality in ventilated participants (RR 1.13 [0.89–1.42],  $p = 0.32$ ) although there was evidence of a reduction in mortality for spontaneously ventilating patients requiring oxygen (RR 0.87 [0.76–0.99],  $p = 0.03$ ) as well as a reduction in the composite outcome of death/progression to ventilation (RR 0.84 [0.75–0.93],  $p = 0.001$ ).<sup>142</sup> Remdesivir is currently indicated for hospitalised patients, either requiring low-flow oxygen or for those who are immunocompromised and have a diagnosis of COVID-19 pneumonia, as well as for patients in the community (but only for those with a risk of progression to severe disease).<sup>143</sup> In pregnancy, its safety profile remains to be established with reporting to the UK teratology information service (UKTIS) encouraged.<sup>144,145</sup>

Of the pregnancy-approved treatment arms in the RECOVERY trial, corticosteroids, tocilizumab and

sotrovimab have subsequently been approved for severe COVID-19 or for those at risk of progression to severe disease.<sup>131</sup>

Given ongoing research and developments in the evidence for therapeutics, treatment recommendations continue to evolve. We therefore strongly recommend referring to living guidance updates, as cited throughout this manuscript.<sup>131,146</sup>

## Steroids

Oral and intravenous corticosteroids are used in pregnancy for the management of a range of maternal medical conditions from severe asthma to autoimmune conditions, such as systemic lupus erythematosus and are recommended in COVID-19 for the same indications as in the general population.<sup>147</sup> The current body of evidence does not support a high overall risk of orofacial/cardiac anomalies, miscarriage, fetal growth restriction (FGR) or stillbirth with short courses of low-dose steroids, and the association with pre-term birth may be confounding, although it is acknowledged that considerable study heterogeneity exists and that high-quality robust studies are required.<sup>147</sup>

Low-dose corticosteroids are recommended for the treatment of severe/critical disease given evidence of a reduction in 28-day mortality (age-adjusted rate ratio 0.83; 95% CI 0.75–0.93;  $p < 0.001$ ). Evidence of benefit was seen in patients requiring oxygen both with and without mechanical ventilation.<sup>146,148</sup> Of note, high-dose steroids were found to be detrimental and increased the risk of death in patients either on simple oxygen or on no oxygen at all.<sup>111</sup> The RECOVERY trial evaluated the clinical response using dexamethasone and as such, it is the suggested treatment option in the general population.<sup>146,148</sup> However, as a fluorinated corticosteroid, greater transplacental passage occurs and so, where imminent pre-term delivery (for acceleration of fetal lung maturity) is not required, its use should be postponed for postnatal (including lactating) women.<sup>131,149,150</sup> Despite strong evidence of benefit if given to mothers of neonates born between 22 and 35 weeks of gestation, repeated courses or prolonged doses of fluorinated corticosteroids are associated with higher levels of fetal drug exposure and concerns regarding an increased association with neurodevelopmental delay.<sup>151,152</sup> The literature suggests that this is more of a concern with steroid use in late preterm and term infants, and when assessed at 5 years.<sup>153,154</sup> However, longer term effects may not be as significant and judicious use is advised, while further research is needed.<sup>155</sup> Unfluorinated corticosteroids, therefore, are the preferred alternatives during the antenatal period, as placental metabolism results in as little as approximately 10% of the drugs reaching the fetus. As such, the recommended treatment options in pregnancy are oral prednisolone, methylprednisolone (PO/IV) or hydrocortisone (IV).<sup>131,136,147</sup>

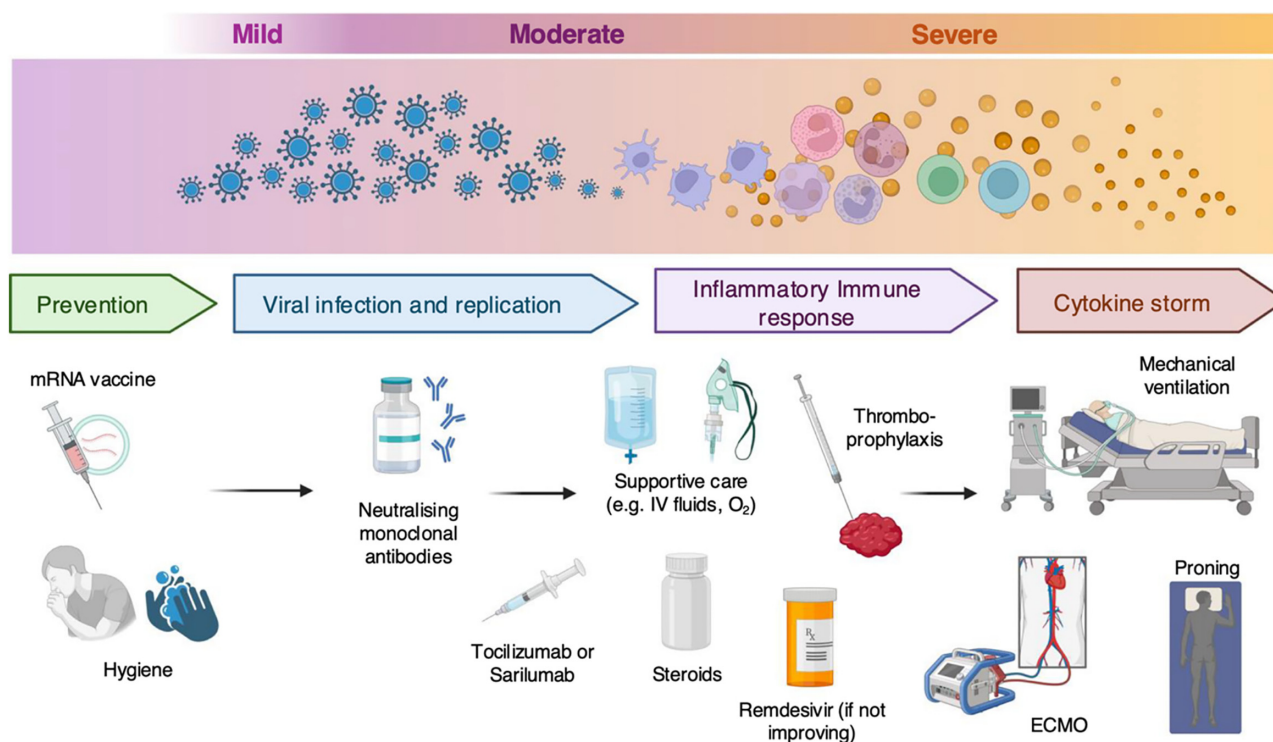


**Figure 3.** The progression of COVID-19 and treatment methodologies. Stages of infection begin with mild to moderate and severe illness. Treatment spans the progression of illness and inflammatory immune responses that are associated with worsening disease. For pregnant women in particular, that are considered high risk for severe complications, prevention strategies are key and these include vaccination. For moderate and severe illness: Neutralising monoclonal antibodies should be considered in women who are hospitalised with symptomatic infection who do not have SARS-CoV-2 antibodies (e.g. Ronapreve® IV) or who are in the community with very high-risk factors (e.g. sotrovimab); supportive care with oxygen where required to maintain saturations >94%, and careful fluid balance. Steroid treatment: If not required for preterm delivery then use oral prednisolone, methylprednisolone or IV hydrocortisone; but if needed for preterm delivery use dexamethasone IM, then continue oral prednisolone/IV hydrocortisone; use tocilizumab or sarilumab in women with hypoxia; consider remdesivir for those who are not improving, or who are deteriorating; remember to give thromboprophylaxis; for ICU care patients who may need mechanical ventilation, proning up to at least 28 weeks is recommended.<sup>131</sup> Created with BioRender.com.

### Tocilizumab

Tocilizumab, an IL-6 antagonist used in the treatment of rheumatoid arthritis, has been shown to improve in-hospital survival in critically ill patients (median adjusted cumulative OR 1.64, 95% credible interval 1.14–2.35) as well as to reduce the duration and need for mechanical ventilation and the duration of hospital stay when compared to standard care.<sup>156–158</sup>

### Sotrovimab

Sotrovimab has been included in the latest RCOG guidance and was an active arm of the RECOVERY trial.<sup>131,146,159</sup> It is a synthetic neutralising human monoclonal antibody that binds to the SARS-CoV-2 spike receptor binding protein to block viral entry.<sup>160</sup> The optimal administration is within 5 days of symptom onset with a reported relative risk reduction of 85% (97.24% CI, 44–96;  $p = 0.002$ ) for hospitalisation or death.<sup>160–162</sup>

### Extracorporeal membranous oxygenation (ECMO)

Pregnancy is not a contraindication for treatment by ECMO and early escalation to units providing the service is recommended for clinically deteriorating pregnant and puerperal patients. Data specific to COVID-19 are limited but viral-specific outcomes have been reported to be superior in pregnancy and the puerperium to that of non-pregnant women.<sup>163</sup> In a retrospective cohort study, O'Neil et al. reported a statistically significant difference for age, immunocompromise and diabetes mellitus between pregnant and non-pregnant cohorts and survival analysis demonstrated an overlap propensity score-weighted odds ratio of 1.18 (95% CI 1.10–1.27).<sup>163</sup> For those who meet the admission criteria for a range of pathologies, good outcomes for mother and baby have been reported, and a meta-regression analysis demonstrated maternal and fetal pooled

survival data of 77.2% (95% CI: 64.1–88.4%) and 69.1% (95% CI: 44.7–89.8%), respectively.<sup>164–166</sup>

## Adjunctive care

Prone positioning has been used by intensivists in both awake and mechanically ventilated patients as supportive management for patients with acute hypoxaemic respiratory failure.<sup>167,168</sup> It is understood to optimise oxygenation by helping to equilibrate transpulmonary pressures, to alleviate cardiac and diaphragmatic pressures on lung parenchyma and facilitate recruitment of collapsed dorsal alveoli, thus improving ventilation: perfusion matching.<sup>167,169</sup> In addition to evidence of often short-term respiratory physiological improvement of respiratory physiological parameters, such as  $\text{PaO}_2/\text{FiO}_2$ , there is some evidence for improved clinical outcomes.<sup>170</sup> A multi-centre randomised trial (total  $n = 1121$ ) of awake prone positioning reported a reduction in endotracheal intubation (HR 0.75 [0.62–0.91]  $p = 0.0038$ ) when compared to standard care but the impact on mortality is not evident, and there are no robust data for pregnancy.<sup>171</sup> However, it has been acknowledged that advanced gestation will impact its practical use, so placing patients in the left lateral decubitus position has been recommended by the WHO and RCOG for patients with moderate to severe acute distress syndrome.<sup>131,134,172</sup> Tolcher et al. proposed an algorithm to guide prone positioning in both the awake and intubated pregnant patient (Supplementary material—Appendices 1–3). Furthermore, they proposed step-by-step guides to perform the procedure in both cases.<sup>173</sup>

An increased incidence of pulmonary embolism has been reported in patients with severe COVID-19 with subsequent recommendations to treat patients with prophylactic LMWH.<sup>134</sup> The recommendation was extended to include women in pregnancy, already a known risk factor for VTE, if severely ill or admitted to hospital.<sup>131,174</sup>

## Delivery as treatment

Ultimately, a decision for delivery of the baby may be a necessary step in management for maternal benefit and, particularly at pre-term gestations, this decision should be multidisciplinary. Pulmonary pathophysiology resulting from SARS-CoV-2 infection may be compounded by a reduction in functional residual capacity associated with diaphragmatic elevation in advanced pregnancy.<sup>175,176</sup> Given this, it has historically been considered that optimal mechanical ventilation may be achieved following delivery. Interestingly, however, in a prospective multi-centre cohort study ( $n = 91$ ), Vasquez et al. recruited pregnant and puerperal women requiring mechanical ventilation and evaluated the respiratory parameters pre and post-delivery. They reported no significant change in the

majority of respiratory parameters except for an increase in the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen concentration ( $\text{PaO}_2:\text{FiO}_2$ ) from within a 2-h period prior to delivery to 24 h after delivery ( $p = 0.025$ ).<sup>177</sup>

Notwithstanding the prerequisite of individualised care, there is a lack of data to support guidance on the optimal timing of delivery in critically ill pregnant women for maternal benefit, while balancing neonatal outcomes and further research in this area is welcome.

## Ethical considerations

During the COVID-19 pandemic, rapid strategic changes were made to clinical research and the delivery of healthcare.<sup>178</sup> Much was commendable, contributing to the identification of life-saving therapies and, most notably, the development of a highly effective vaccine.<sup>178</sup> Such developments were facilitated by mobilisation of significant national and international communication and collaboration, which should be a key lasting legacy of the pandemic.<sup>178,179</sup>

However, there have been some unwanted effects of organisational changes made within healthcare, for example, the suspension of non-urgent and elective work, while trying to maintain specialist areas such as cancer services, albeit with variable success.<sup>178,180</sup> In addition, restructuring in services such as gynaecology resulted in a transition to virtual care, notably for patients requiring benign gynaecological and early pregnancy care, sexual health and contraception.<sup>131</sup> Importantly, there has been recognition of the potential adverse impact of these changes on specialty training and thus delivery of patient care in the short and long-term.<sup>181,182</sup>

Globally, health care inequities became glaringly apparent. Despite likely under-reporting, due to variability in availability of testing, it is likely that disproportionate mortality occurred in LMICs, an international failure compounded by a lack of multilateralism in the distribution of vaccines.<sup>183</sup> International organisations such as WHO and the EU have prepared strategies to mitigate the effects of a future inevitable pandemic but much work is required to address existing global health inequalities.<sup>178,183,184</sup>

## Author contributions

OG conceived and designed the objectives of the review. OG, ZS and EVW are joint first authors having contributed equally to the primary literature research and initial draft of the manuscript. NS made a significant contribution to the critical revision of the final draft. The remaining authors edited and revised the manuscript critically for

important intellectual content. All authors approved the final version.

## Conflict of interest statement

There are no conflicts of interest.

## Supporting Information

Additional supporting information may be found in the online version of this article at <http://wileyonlinelibrary.com/journal/tog>

**Figure S1.**

**Figure S2.**

**Data S1.**

**Infographic S1.**

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