



# Managing COVID-19 in pregnant women

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**Principles of management of COVID-19 in the general population apply in pregnancy with few exceptions. Clinical inertia can lead to preventable morbidity and mortality. COVID-19 vaccines are safe and should be recommended at any stage of pregnancy.** <https://bit.ly/3Rj8nWr>

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## COVID-19 in pregnancy

Pregnant women are no more likely to contract coronavirus disease 2019 (COVID-19) than the background population and two-thirds of those testing positive are asymptomatic [1, 2]. Risk factors for severe infection reflect those outside pregnancy and include being unvaccinated, aged >35 years, having a body mass index >25 kg·m<sup>-2</sup>, having a medical comorbidity, being in the Black, Asian and Minority Ethnicity (BAME) population, and socioeconomic deprivation [1]. Pregnant women who develop moderate/severe disease are more likely to require hospitalisation and critical care admission, particularly in the third trimester [1].

Physiology in normal pregnancy changes to meet an increase in oxygen demand [3]. There is a 15% increase in metabolic rate, 20% increase in oxygen consumption and 40–50% increase in minute ventilation, mostly due to an increase in tidal volume as respiratory rate remains unchanged. Mechanical adaptations include diaphragmatic elevation due to the enlarging uterus, which results in decreased functional residual capacity [3]. Coupled with altered immunity and physiological vascular and haemodynamic changes, women appear to compensate substantially, but deterioration can occur precipitously [4]. A modified early warning score in maternity (Modified Early Obstetric Warning Score; MEOWS) is used to identify women at risk of deterioration and prompt early escalation. Target oxygen saturations in pregnancy are 94–98% [5].

A standard approach to investigation is recommended, including use of radiological investigations when indicated. Clinical judgement should be applied in making treatment decisions as scoring systems, such as the International Severe Acute Respiratory and Emerging Infections Consortium Coronavirus Clinical Characterisation Consortium (ISARIC4C) Mortality and Deterioration Scores [6], are not validated in pregnancy. The D-dimer assay has no role in the investigation of venous thromboembolism (VTE) in pregnancy but may be included in the standard COVID-19 admission and surveillance laboratory panel as screening for a hyperinflammatory state.

Women should be cared for by a multidisciplinary team (MDT) inclusive of obstetric physicians, respiratory physicians, virologists, obstetricians, midwives and critical care specialists. Pharmacological treatment options are rapidly expanding as further evidence-based therapies emerge. Data have shown that only 25% of pregnant women received standard treatment, even in the context of severe COVID-19 illness necessitating intensive care [7, 8]. Many of the standard therapies used in the treatment of COVID-19 are appropriate for use in pregnancy. A paucity of safety data for COVID-19 therapies in pregnancy have led to undertreatment [9, 10]. Management in pregnancy must reflect, as closely as possible, management outside pregnancy. When uncertainty exists, urgent advice should be sought through maternal medicine networks if delays in care and associated maternal morbidity and mortality are to be minimised.

## Severity of COVID-19 disease

Mild disease refers to asymptomatic or symptomatic illness (cough, fever, sore throat, nasal congestion, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, altered taste and smell) without dyspnoea or



abnormal chest imaging [7]. Two-thirds of pregnant women will be asymptomatic. Women with mild disease should be offered surveillance in the community, considered for eligibility for pre-emptive treatment (table 1) and VTE risk assessed (figure 1).

Moderate COVID-19 disease is defined by clinical or radiological evidence of lower respiratory tract involvement with preserved oxygenation (oxygen saturation  $\geq 94\%$  on room air) [7]. Severe disease is characterised by hypoxaemia (oxygen saturation  $< 94\%$  on room air or a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ( $P_{aO_2}/F_{IO_2}$ )  $< 300$  mmHg), a respiratory rate  $> 30$  breaths·min<sup>-1</sup>, or lung infiltrates  $> 50\%$  [7]. Critical COVID-19 disease is characterised by respiratory failure, septic shock and/or multiple organ dysfunction [7]. The delta variant has been implicated in the majority of moderate, severe and critical COVID-19 disease [4].

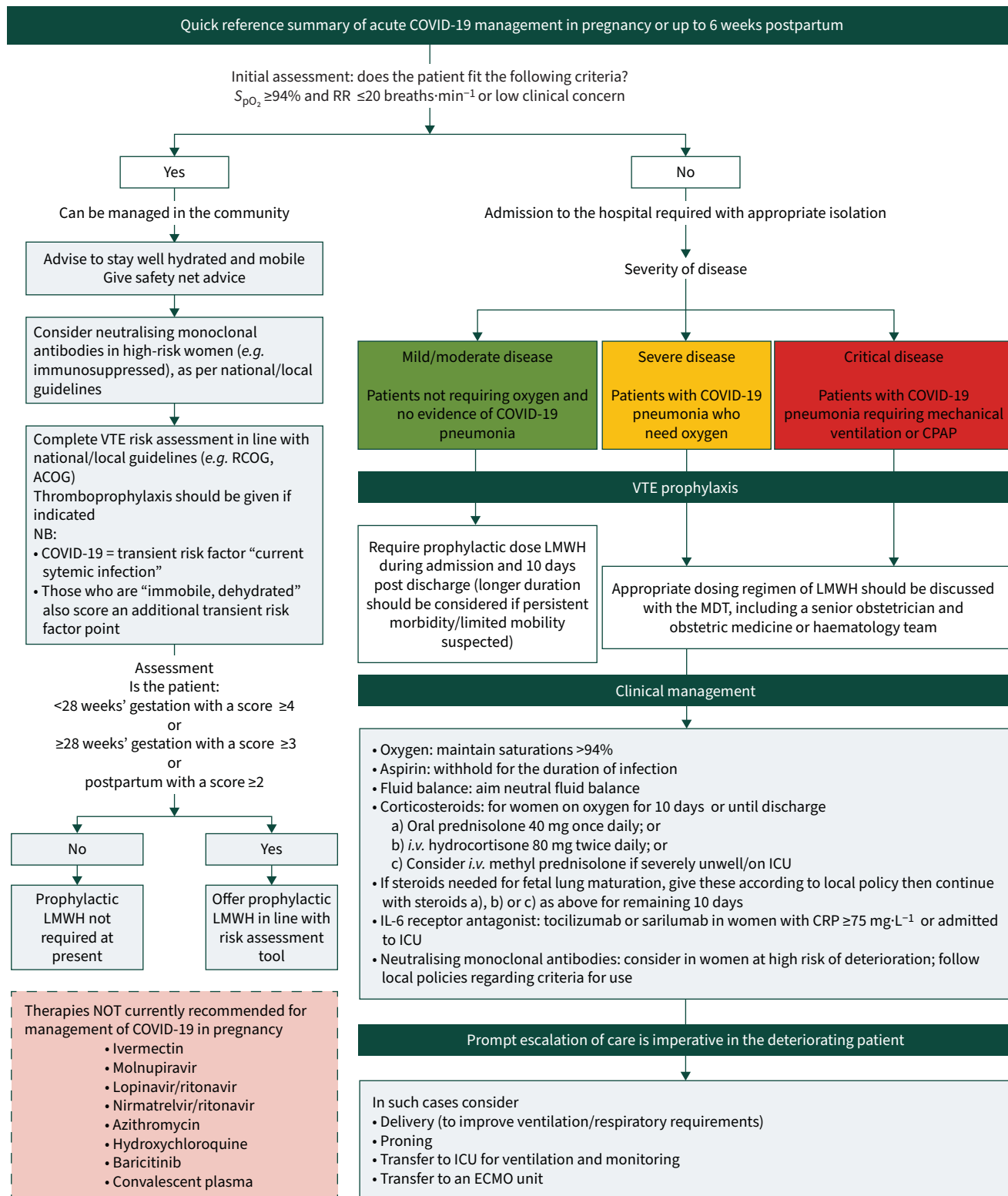
Subtle changes in condition should be observed and care escalated in those showing signs of deterioration, manifested by increased work of breathing, respiratory rate  $> 20$  breaths·min<sup>-1</sup>, desaturation on exertion or oxygen saturation of  $< 94\%$  on room air. There should be a low threshold for referral for critical care in pregnant women. Escalation to critical care is recommended when  $F_{IO_2}$  exceeds 35% [1].

Prone is not contraindicated in pregnancy and can be facilitated by optimising maternal position and supportive padding [19]. The UK Obstetric Surveillance System (UKOSS) reported that 11% of hospitalised pregnant women with COVID-19 have required intensive care unit admission, with  $< 1\%$  requiring extracorporeal membrane oxygenation (ECMO) [2, 20]. It is important to note that mechanical ventilation and referral for ECMO should not be withheld in pregnancy [4, 19].

**TABLE 1** Pharmacological therapy used in the treatment of COVID-19 in pregnancy

Class	Drug	Duration	Indication	Evidence base
Corticosteroid	Prednisolone 40 mg once daily, or hydrocortisone 80 mg twice daily, or methylprednisolone 1 mg·kg <sup>-1</sup> twice daily for 5–7 days followed by once daily for 5–7 days	For 10 days or until discharge from hospital (individualised in the ICU setting)	Oxygen saturation $< 94\%$ on room air or need for supplemental oxygen	Significant reduction in 28-day mortality [11]
IL-6 receptor antagonist	Tocilizumab 8 mg·kg <sup>-1</sup> or sarilumab 400 mg	Administered once only by intravenous infusion	CRP $\geq 75$ mg·L <sup>-1</sup> and oxygen requirement or admission to critical care	Reduction in 60-day mortality; possible reduced progression to intubation [12]
Neutralising monoclonal antibody	Casirivimab and imdevimab	Patients hospitalised with COVID-19: 2.4 g as a combined single intravenous infusion Patients with hospital-onset COVID-19: 1.2 g as a combined single intravenous infusion	Delta variant; SARS-CoV-2 IgG negative	Reduction in 28-day mortality in patients admitted to hospital who were seronegative at baseline [13]
Neutralising monoclonal antibody	Sotrovimab 500 mg	Administered as a single intravenous infusion over 30 min	Non-hospitalised patients with mild to moderate disease who are considered very high risk for disease progression [14]	Reduces the risk of hospitalisation or death by 70–85% [1, 15]
Neutralising monoclonal antibody	Tixagevimab 300 mg <i>i.m.</i> and cilgavimab 300 mg <i>i.m.</i>	Administered as separate, consecutive intramuscular injections	Not routinely given; the MHRA supports its use where the expected benefits outweigh the potential risks [16]	Pre-exposure immunoprophylaxis in adults who have an increased risk of an inadequate response to vaccination, increased risk of exposure, or both [16]
Antiviral	Remdesivir	3-day course <i>i.v.</i> : 200 mg on day 1 and 100 mg on days 2 and 3	Not routinely recommended; may be considered in women who are deteriorating despite standard management and have a non-omicron genotype	Reduces the risk of hospitalisation or death by 85–90% [17, 18]

ICU: intensive care unit; IL: interleukin; CRP: C-reactive protein; MHRA: Medicines and Healthcare products Regulatory Agency.



**FIGURE 1** Approach to clinical management of women with COVID-19 who are pregnant or up to 6 weeks postpartum.  $S_{pO_2}$ : oxygen saturation measured by pulse oximetry; RR: respiratory rate; CPAP: continuous positive airway pressure; VTE: venous thromboembolism; RCOG: Royal College of Obstetricians and Gynaecologists; ACOG: American College of Obstetricians and Gynecologists; LMWH: low molecular weight heparin; MDT: multidisciplinary team; ICU: intensive care unit; CRP: C-reactive protein; ECMO: extracorporeal membrane oxygenation. Reproduced and modified from [4] with permission.

## Pharmacological management of COVID-19 in pregnancy

### *Corticosteroids*

The RECOVERY trial has demonstrated that dexamethasone significantly reduces mortality in patients admitted to hospital with an oxygen requirement [11]. Prednisolone, hydrocortisone or methylprednisolone are the preferred corticosteroids for treatment of COVID-19 pneumonia in pregnancy because repeated doses of dexamethasone have been associated with neurocognitive and neurosensory disorders in childhood [21]. When maturation of the fetal lung in preterm delivery is the desired outcome, intramuscular dexamethasone and betamethasone are the agents of choice, as they are synthesised to resist metabolism and readily cross the placenta. The corticosteroid being given for COVID-19 pneumonia should be omitted on the days in which intramuscular dexamethasone or betamethasone is being given (figure 1). Blood glucose monitoring should be performed twice daily in all women receiving corticosteroid therapy due to the risk of steroid-induced gestational diabetes.

### *Interleukin-6 receptor antagonists*

The interleukin (IL)-6 receptor antagonists tocilizumab or sarilumab are indicated in women with hypoxia (oxygen saturation <94% on room air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein  $\geq 75 \text{ mg}\cdot\text{L}^{-1}$ ) or in those admitted to critical care [12].

*In utero* exposure to biological agents for immunomodulation may have adverse consequences upon infants who receive live vaccines, including a predisposition to neonatal infection [22]. With COVID-19, however, because such therapy is short-term, current guidance recommends offering the bacille Calmette–Guérin (BCG) vaccination after informed discussion with the mother, particularly if the IL-6 receptor antagonist was given early in pregnancy [1].

### *Neutralising monoclonal antibodies*

Neutralising monoclonal antibodies have been demonstrated in the RECOVERY trial to be effective, particularly in patients who had not developed innate immunity to COVID-19 [13]. Safety data are lacking in pregnancy. However, they are specifically directed towards viral proteins and therefore harm to the fetus is unlikely. To enable generation of safety data, reports of use in pregnancy should be made to a teratology information service or national registry.

Casirivimab and imdevimab (Ronapreve) should be considered in women who do not have SARS-CoV-2 IgG antibodies and are hospitalised with symptomatic COVID-19 infection due to the delta variant [23–25]. Emerging evidence indicates that the casirivimab and imdevimab preparation has significantly decreased efficacy against the omicron variant [26].

Data have shown that sotrovimab administered to non-hospitalised patients with mild/moderate disease, with at least one risk factor for disease progression, resulted in a relative risk reduction in hospitalisation or death by 85% [15]. Women considered highest risk include those with trisomy 21, solid or active metastatic cancer, haematological malignancy or stem cell transplant, chronic kidney disease stage 4–5 or renal transplant, chronic liver disease Child Pugh B–C or liver transplant, solid organ transplant, immune deficiencies, poorly controlled HIV infection, or active or unstable immune-mediated inflammatory disorders (*e.g.* inflammatory bowel disease, myasthenia gravis, multiple sclerosis) on B-cell depleting therapies, biologics, corticosteroids (equivalent to  $\geq 10 \text{ mg}\cdot\text{day}^{-1}$  of prednisolone for  $\geq 28$  days), cyclophosphamide, tacrolimus or ciclosporin. Such women, with ongoing symptoms within 5 days of a positive test, who are in the community or admitted to hospital for another reason, can be offered sotrovimab as pre-emptive treatment [14].

The long-acting neutralising antibody combination of tixagevimab and cilgavimab has been demonstrated in the PROVENT trial to be efficacious as pre-exposure immunoprophylaxis in non-pregnant adults with increased risk of inadequate response to vaccination, increased risk of exposure, or both, without safety concerns [16]. Safety data within pregnancy are lacking, and as both are human IgG they have potential to cross the placenta. However, no off-target binding was detected in a cross-reactive binding assay using a protein array enriched for human embryo-fetal proteins. Thus, the Medicines and Healthcare products Regulatory Agency supports its use in pregnancy where the expected benefits outweigh the potential risks to the fetus [27].

### *Other therapies*

Rapid advances have been made in the development of evidence-based therapies for managing COVID-19, most of which are appropriate to use in pregnancy on a benefit/risk basis. There is little evidence to

support this, as pregnant women are a traditionally poorly represented group in clinical trials of medications [28].

The PRINCIPLE trial has demonstrated that inhaled budesonide can reduce the recovery time for COVID-19-positive patients being managed in primary care [29]. Inhaled corticosteroids can safely be used in pregnancy and should therefore not be avoided where indicated [30].

Numerous antiviral medications have been proposed and trialled for the treatment of COVID-19 [4]. Remdesivir was the first drug licensed for treatment of COVID-19 and reduces time to recovery in hospitalised patients [17]. Although there have been no serious safety signals, limited data exist for pregnancy safety, and remdesivir is not routinely recommended in pregnancy, but may be considered after a multidisciplinary discussion in women who are deteriorating despite standard management and have a non-omicron genotype [18].

Nirmatrelvir plus ritonavir (Paxlovid), a protease inhibitor, has been shown to significantly reduce hospital admission and mortality in a selected, high-risk, non-pregnant population, when given in the first 3 days from symptom onset, without evident safety concerns [31]. 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 might be acceptable [4].

Molnupiravir is a ribonucleoside that has broad antiviral activity against RNA viruses and is not currently recommended in pregnancy.

Baricitinib is an oral selective Janus kinase (JAK) 1/2 inhibitor with anti-inflammatory properties. In non-pregnant adults, baricitinib, combined with standard care including dexamethasone, was associated with reduced mortality in hospitalised patients with COVID-19 [32]. However, the safety of JAK inhibitors has not been established in pregnancy; therefore, treatment with baricitinib is currently not recommended for COVID-19 in pregnancy [33].

Varying outcomes have been reported for the use of convalescent plasma in COVID-19. However, neither the RECOVERY trial (which included pregnant women) nor the REMAP-CAP trial demonstrated benefit and thus convalescent plasma is not currently routinely used either in or outside pregnancy [34].

Antibiotics should not routinely be used unless there is evidence to support the presence of secondary bacterial superinfection.

### ***Venous thromboembolism prophylaxis***

COVID-19 infection is a transient risk factor for VTE in pregnancy (figure 1) [35]. Women considered appropriate for outpatient management should undergo VTE risk assessment and be prescribed prophylaxis accordingly. Women admitted to hospital with COVID-19 should be given thromboprophylaxis using weight-adjusted and risk-appropriate doses of low molecular weight heparin (LMWH) during their inpatient admission and for at least 10 days post-discharge unless contraindicated [1, 35].

Discussion with the MDT should occur if delivery is imminent as the last dose of LMWH should be withheld for 12 h in prophylaxis and 24 h in treatment of VTE, prior to spinal and epidural procedures.

### **Maternal and fetal monitoring**

A standard approach to monitoring pregnant women should be undertaken with the use of MEOWS, with close observation paid to the work of breathing. The standard surveillance blood investigations should be performed. There should be a low threshold for computed tomography pulmonary angiography in cases of clinical deterioration, as risk of VTE remains high despite prophylactic LMWH. There should be increased surveillance for steroid-induced gestational diabetes. In women who are given IL-6 receptor antagonists, monitoring for secondary infection is required as immune response may be blunted. The INTERCOVID study demonstrated higher rates of pre-eclampsia and preterm birth in women infected with COVID-19 [36].

Fetal monitoring is provided at a woman's bedside *via* cardiotocography. This is recommended twice daily in hospitalised women or prompted by reduction in fetal movements [1]. A growth ultrasound scan should also be performed to assess for fetal growth restriction, informing timing of delivery. Hospitalised women

who have recovered from a period of severe or critical illness with COVID-19 should be offered a fetal growth scan 2 weeks after recovery.

### Mode and timing of delivery

Mode and timing of delivery should be an MDT decision [1]. In women with severe/critical disease requiring mechanical ventilation, delivery is typically offered particularly if >34 weeks gestation, usually *via* emergency Caesarean section. There is no evidence of benefit to improvement in ventilation, maternal or fetal outcomes if delivery is performed before 34 weeks. Critically unwell women should be offered continuous electronic fetal monitoring during delivery.

In cases in which preterm birth is expected, magnesium sulphate therapy should be administered for fetal neuroprotection until 29+6 weeks gestation. Administration of corticosteroids for fetal lung maturation should be given prior to 35 weeks gestation.

All efforts should be made to facilitate early bonding with skin-to-skin contact and breastfeeding.

### Follow-up

Follow-up, usually 6 weeks after hospital discharge, is recommended to ensure resolution of disease and absence of features of long COVID. Oxygen saturations should be measured and a chest radiograph reviewed. Persistent fatigue, dyspnoea, anxiety and depression are often reported among patients who were treated for severe/critical COVID-19 pneumonia [37]. A mental health screen should be performed and perinatal mental health support considered. COVID-19 vaccination should be strongly recommended 28 days following infection in unvaccinated patients.

### COVID-19 vaccination

At least 275 000 pregnant women have been vaccinated in the UK and USA with no adverse safety signals reported. No pregnant woman with COVID-19 who has received two doses of the vaccine has developed severe/critical illness requiring hospitalisation or intensive care [38]. As such, vaccination is endorsed at any stage in pregnancy [1, 4]. Most evidence exists for the mRNA vaccines and these are thus preferred in pregnancy.

Maternal deaths from COVID-19 continue to occur in unvaccinated women, with highest death rates attributable to the delta variant [4]. With the emergence of the omicron variant, a booster vaccine is recommended 3 months following the second dose, to confer additional protection [1].

There has been notable vaccine hesitancy, with many women preferring to delay vaccination until after pregnancy due to unsubstantiated concerns about infertility, harm to the fetus and vaccine-induced thrombotic thrombocytopenia, which is not only rare but idiosyncratic. Vaccination rates amongst pregnant women, particularly in those of younger age and amongst BAME populations remain low despite good evidence supporting an association between vaccination and lower odds of adverse outcomes in COVID-19 of any severity in pregnancy. Vaccines are available, effective in pregnancy and without adverse consequences towards mother or fetus. Women should not postpone vaccination until after they have given birth and should be signposted to relevant patient information at every opportunity [39].

### Key points

- The principles of management of COVID-19 in the general population apply in pregnancy with few exceptions.
- Clinical inertia in the investigation and treatment of COVID-19 in pregnancy can lead to preventable morbidity and mortality.
- COVID-19 vaccines are safe and should be recommended at any stage of pregnancy or when breastfeeding.

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