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State-of-the-Art Review

Pregnancy and COVID-19: pharmacologic considerations

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ABSTRACT

In this review, we summarize evidence regarding the use of routine and investigational pharmacologic interventions for pregnant and lactating patients with coronavirus disease 2019 (COVID-19). Antenatal corticosteroids may be used routinely for fetal lung maturation between 24 and 34 weeks' gestation, but decisions in those with critical illness and those < 24 or > 34 weeks' gestation should be made on a case-by-case basis. Magnesium sulfate may be used for seizure prophylaxis and fetal neuroprotection, albeit cautiously in those with hypoxia and renal compromise. There are no contraindications to using low-dose aspirin to prevent placenta-mediated pregnancy complications when indicated. An algorithm for thromboprophylaxis in pregnant patients with COVID-19 is presented, which considers disease severity, timing of delivery in relation to disease onset, inpatient vs *outpatient status, underlying comorbidities and contraindications to the use of anticoagulation. Nitrous oxide may be administered for labor analgesia while using appropriate personal protective equipment. Intravenous remifentanil patient-controlled analgesia should be used with caution in patients with respiratory depression. Liberal use of neuraxial labor analgesia may reduce the need for emergency general anesthesia which results in aerosolization. Short courses of non-steroidal anti-inflammatory drugs can be administered for postpartum analgesia, but opioids should be used with caution due to the risk of respiratory depression. For mechanically ventilated pregnant patients, neuromuscular blockade should be used for the shortest duration possible and reversal agents should be available on hand if delivery is imminent. To date, dexamethasone is the only proven and recommended experimental treatment for pregnant patients with COVID-19 who are mechanically ventilated or who require supplemental oxygen. Although hydroxychloroquine, lopinavir/ritonavir and remdesivir may be used during pregnancy and lactation within the context of clinical trials, data from non-pregnant populations have not shown benefit. The role of monoclonal antibodies (tocilizumab), immunomodulators (tacrolimus), interferon, inhaled nitric oxide and convalescent plasma in pregnancy and lactation needs further evaluation.*

INTRODUCTION

By early 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was responsible for over 85 million cases of coronavirus disease 2019 (COVID-19) and almost 2 million deaths globally[1]. In certain regions of the world, up to 15% of pregnant women were found to have a positive result on polymerase chain reaction testing for SARS-CoV-2 upon admission for delivery[2]. While pregnant women do not appear to be at substantially higher risk of severe manifestations from COVID-19 compared with non-pregnant adults[3], the disease has resulted in severe maternal morbidity and mortality in both high- and low-resource settings[4,5]. Obstetrics is an essential service and the provision of routine obstetric care must continue through pandemics to ensure optimal maternal and fetal health. The COVID-19 pandemic has sparked controversies surrounding the use of certain pharmacologic interventions in pregnancy. As a result, numerous professional societies have issued

practice statements and guidelines regarding the use of those medications in pregnant and postpartum women with COVID-19. The aim of this review is to summarize published evidence and critically appraise international guidelines in order to provide an expert opinion regarding pharmacologic considerations unique to the care of pregnant and postpartum women with COVID-19.

The first section focuses on the impact of COVID-19 on the use of medications for pregnancy care. This includes medications administered routinely in pregnancy, such as antenatal corticosteroids for fetal lung maturation, magnesium sulfate ($MgSO_4$) for fetal neuroprotection and eclampsia prophylaxis/treatment, and low-dose aspirin for prevention of placenta-mediated complications. Anesthetic considerations will also be discussed, including the use of nitrous oxide and regional analgesia to avoid the administration of general anesthesia in emergency situations. We also assess the role of thromboprophylaxis in pregnant women with COVID-19. The second section describes the impact of pregnancy on the use of medications that may be given specifically in the setting of COVID-19. This includes guidance on the use of medications during mechanical ventilation, and the safety of experimental medications for COVID-19 during pregnancy and lactation. As such, this review serves as a guide for healthcare professionals and researchers in various healthcare disciplines caring for pregnant and postpartum women during the COVID-19 pandemic.

SEARCH STRATEGY AND SELECTION CRITERIA

MEDLINE, EMBASE, the Cochrane Library databases, CINAHL and Scopus were searched from inception until 14 May 2020, using medical subject heading (MeSH) terms and free-text search terms related to 'coronavirus infection', 'pregnancy' and 'breastfeeding'. This was supplemented with targeted searches of general medical and obstetric journals for publications related to routine, off-label and experimental medications used in COVID-19 patients either for symptomatic relief or in the context of clinical trials, and discussions with international experts. In addition, we reviewed product monographs of all drugs and conducted targeted literature searches involving the use of each drug in pregnant women. Finally, clinical practice recommendations were summarized from pregnancy guidelines of international societies, and ongoing trials were reviewed from three clinical trial registries: www.clinicaltrials.gov, Australian New Zealand Clinical Trials Registry (ANZCTR) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). Given the limited experience with the management of COVID-19, research letters, editorials, commentaries, opinion pieces and special communications were included. No language restrictions were applied.

PHARMACOLOGIC CONSIDERATIONS: IMPACT OF COVID-19 ON DELIVERY OF PREGNANCY CARE

Medications administered routinely to pregnant and postpartum women

Administration of medications for prevention or treatment of certain maternal and fetal conditions is an integral part of routine obstetric care. The use of three categories of medications generated debate during the COVID-19 pandemic: (1) antenatal corticosteroids; (2) $MgSO_4$; and (3) non-steroidal anti-inflammatory drugs (NSAIDs). Practice recommendations are summarized in Table 1.

Antenatal corticosteroids

There is strong evidence to support the use of a single course of antenatal corticosteroids (betamethasone or dexamethasone) in women at risk of preterm birth between 24 and 34 weeks of gestation. Antenatal corticosteroids have been shown to reduce the risk of perinatal death, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, need for respiratory support and neonatal intensive care unit (NICU)

Table 1 Recommendations for use in pregnant and postpartum patients with COVID-19, of medications administered routinely in pregnancy

Medication	*Recommendation(s)*
Antenatal corticosteroids for fetal lung maturation	• Continue to administer when indicated for fetal lung maturation. • There is insufficient evidence to strongly recommend use after 34 weeks of gestation. • Risks and benefits should be weighed carefully in women with critical illness.
Magnesium sulfate	• Since respiratory muscle weakness is a potential side effect of magnesium sulfate, it should be used judiciously in women with established respiratory distress.
NSAIDs	• There are insufficient data available to recommend against use of low-dose aspirin for prevention of placenta-mediated complications. • There are no COVID-19-specific contraindications to use of indomethacin as a tocolytic. • There are no contraindications to use of NSAIDs for postpartum analgesia.

NSAIDs, non-steroidal anti-inflammatory drugs.

admission, even in the current era of advanced neonatal care[6]. More recent evidence suggests that the benefits of antenatal corticosteroids might extend to infants born at 22–24 weeks' gestation[7] and between 34 + 0 and 36 + 6 weeks' gestation[8]. However, not all guidelines recommend their administration at extremes of prematurity.

Corticosteroids were associated with an increased risk of mortality in a systematic review of 30 studies examining their use as an adjunctive treatment for influenza[9]. However, this study included only one randomized controlled trial (RCT) and the certainty of the available evidence from observational studies was deemed to be low, because of the potential for confounding by indication. Furthermore, the doses used were 4–10 times higher than the typical dose administered in pregnancy for fetal lung maturation. So far, there is no evidence from the current or previous (e.g. severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus) coronavirus outbreaks that a single course of corticosteroids given for fetal lung maturation causes maternal complications[10]. Moreover, a weak recommendation has been issued for the use of corticosteroids in patients with acute respiratory distress syndrome, based on indirect evidence[11], and more recently, evidence from RCTs has suggested that a course of corticosteroids may be beneficial for certain patients with COVID-19 pneumonia (see section below about use of corticosteroids in COVID-19 patients).

Professional societies continue to support the use of antenatal corticosteroids when indicated for fetal lung maturation among women with COVID-19[10,12–18]. However, the risks and benefits of corticosteroids should be carefully weighed in women with critical illness, and their administration should not delay urgent delivery[15,16]. Given the lack of robust evidence, several societies have recommended against their use after 34 weeks[10,12,16,17].

Magnesium sulfate

$MgSO_4$ has been shown to be effective for prophylaxis and treatment of seizures in pre-eclampsia at any gestational age[19], and for fetal neuroprotection (decreasing the risk of cerebral palsy) when administered to women at imminent risk for preterm birth[20], especially before 30 weeks of gestation. Although $MgSO_4$ may be associated with an increased risk of maternal respiratory muscle weakness, no risk of respiratory failure has been demonstrated[21]. Several professional societies support the use of $MgSO_4$ when indicated in pregnant women with COVID-19[10,12,15]. An individual-patient assessment of risks and benefits must be performed when using $MgSO_4$, particularly in women with hypoxia[12]. Alternate dose regimens for neuroprotection could be considered on an individual basis, such as a single 4 g intravenous bolus dose of $MgSO_4$[22]. Moreover, prophylaxis with $MgSO_4$ for women with pre-eclampsia can be safely withheld in the absence of severe features[12]. As per routine practice, the dose of $MgSO_4$ should be adjusted in patients with acute kidney injury, which may be a feature of COVID-19.

Low-dose aspirin for prevention of placenta-mediated conditions

Aspirin at doses of 75–162 mg inhibits the production of cyclooxygenase isoenzyme 1, leading to decreased platelet production of thromboxane A_2, a potent vasoconstrictor[23]. As a result, antenatal low-dose aspirin is recommended as primary and secondary prophylaxis for placenta-mediated complications of pregnancy, including pre-eclampsia, fetal growth restriction and preterm birth[19,23]. Human pathogenic coronaviruses, including SARS-CoV-2, bind to target cells through angiotensin-converting enzyme 2 (ACE2)[24]. Given possible increased expression of ACE2 in patients taking ibuprofen, concerns were initially raised about the use of NSAIDs in patients with COVID-19[25]. However, a rapid systematic review conducted by WHO showed that the use of NSAIDs is not associated with severe adverse events, increased acute healthcare utilization, decreased long-term survival or reduced quality of life in patients with COVID-19[26]. As such, the known benefits of pre-eclampsia prevention appear to outweigh the hypothetical risks of adverse outcomes of SARS-CoV-2 infection related to the usage of low-dose aspirin[27]. Accordingly, the International Federation of Gynaecology and Obstetrics (FIGO) and the American College of Obstetricians and Gynecologists (ACOG) have stated that there are insufficient data available to recommend against the use of low-dose aspirin for prophylaxis against placenta-mediated complications of pregnancy[15,17].

Indomethacin for prevention of preterm birth

Indomethacin is a tocolytic that can be used to suppress preterm labor in order to facilitate administration of antenatal corticosteroids or transfer to a tertiary center[28]. Although the administration of a single course of indomethacin for the purpose of tocolysis is unlikely to lead to serious maternal adverse events in the context of COVID-19 and pregnancy, its use is associated with an increased risk of neonatal morbidity, including severe intraventricular hemorrhage, necrotizing enterocolitis and periventricular leukomalacia[29]. Indomethacin can also cause reversible premature closure of the ductus arteriosus if administered after 32 weeks' gestation[28]. When possible, alternate tocolytics should be used.

Thromboprophylaxis in pregnant patients with COVID-19

High rates of thrombotic complications have been reported in patients with severe and critical COVID-19[30]. These events are the result of at least two mechanisms: pulmonary microvascular thrombosis (immunothrombosis) and hospital-associated venous thromboembolism (VTE)[31]. Since pregnancy is a prothrombotic state, the possibility of an increased risk of thrombosis in pregnant women with COVID-19 has become an area of

concern. However, published data do not suggest that pregnant women have an increased risk of thrombotic complications related to COVID-19[4,32].

Low molecular weight heparin (LMWH) is the drug of choice for thromboprophylaxis in pregnant women with COVID-19. Its utility, however, is established only for the treatment of VTE, and LMWH may have little or no effect for immunothrombosis. This explains why thrombotic events have been described in those on prophylactic, and even therapeutic, LMWH, and suggests that the thrombotic risk from immunothrombosis is unlikely to be lowered by increasing the dose of LMWH. Thus, other treatments should be considered, such as anticytokine and antiviral therapy in carefully selected patients within a clinical trial setting[31]. Decisions about initiation and duration of prophylactic anticoagulation in the context of pregnancy and COVID-19 should be made by a multidisciplinary team including hematologists, internists/intensivists and obstetricians, and must consider disease severity, the timing of delivery in relation to disease onset, whether the patient is admitted to the hospital or self-isolating at home, the underlying prothrombotic risk secondary to comorbidities and the presence of major bleeding from obstetric or non-obstetric causes, including coagulopathies. We have recently reviewed the published literature and international guidelines and made clinical practice recommendations for antepartum and postpartum thromboprophylaxis in ambulatory and inpatient pregnant women with COVID-19 (Table 2). In summary, based on published literature, there is insufficient evidence to recommend the use of intermediate or therapeutic doses of LMWH, which may increase bleeding risk without reducing thrombotic risk in pregnant patients with COVID-19. There is also insufficient evidence to comment on the role of low-dose aspirin in thromboprophylaxis or that of anticytokine and antiviral agents in preventing immunothrombosis. These unanswered questions should be addressed in clinical trials.

Intrapartum analgesia and anesthesia

Intrapartum analgesia

Neuraxial labor analgesia. Neuraxial analgesia is the first choice for intrapartum analgesia in pregnant women with COVID-19[33]. Concerns about the risk of meningitis or encephalitis in the context of active viremia remain theoretical[34]. Thrombocytopenia has been described in certain cohorts of patients with COVID-19, and, as such, a platelet count should be available to confirm eligibility for the procedure. The platelet cut-off for neuraxial analgesia should be determined by the clinical context, keeping in mind that the risk of clinical deterioration with general anesthesia is far greater than the risk of epidural hematoma with thrombocytopenia[35]. Preprocedure ultrasound assistance can be considered to facilitate epidural insertion[36], while

Table 2 Clinical recommendations on thromboprophylaxis (TP) for pregnant and postpartum women with confirmed or suspected COVID-19 (reproduced from D'Souza *et al.*[31])

	Isolating at home			*Inpatient*		
	Low-risk pregnancy and low risk for VTE	*Risk factors for VTE and not receiving TP*	*Receiving TP*	*Hospitalized for non-COVID-19-related reason, but asymptomatic or minor symptoms such as anosmia*	*Pneumonia requiring supplementary oxygen but not ventilation*	*Pneumonia requiring mechanical ventilation*
Antepartum	Encourage hydration and mobilization	Conduct risk assessment and consider TP on individual basis	Continue TP	Conduct risk assessment and consider TP on individual basis	Give TP (LMWH)	Give TP (LMWH); dose according to local critical care protocol
Peripartum	Not applicable	Follow local policy for interruption of anticoagulation prior to delivery	Follow local policy for interruption of anticoagulation prior to delivery	Follow local policy for interruption of anticoagulation prior to delivery	Follow local policy for interruption of anticoagulation prior to delivery	Follow local policy for interruption of anticoagulation prior to delivery
Postpartum (while in hospital)	Usual care	Conduct risk assessment and consider TP on individual basis	Continue usual TP	Conduct risk assessment and consider TP on individual basis	Give TP (LMWH)	Give TP (LMWH); dose according to local critical care protocol
Postpartum (upon discharge)	Usual care; encourage hydration and mobilization	Usual care and consider TP on individual basis; encourage hydration and mobilization	Decision based on primary indication for TP; encourage hydration and mobilization	Conduct risk assessment and consider TP on individual basis; encourage hydration and mobilization	Conduct risk assessment and consider extended TP on individual basis; encourage hydration and mobilization	Conduct risk assessment and consider extended TP on individual basis; encourage hydration and mobilization

LMWH, low molecular weight heparin; VTE, venous thromboembolism.

following current guidelines for cleaning and preparing equipment[37]. An early epidural placement may reduce the need for general anesthesia in case of conversion to Cesarean delivery[3,36]. Although no pharmacologic changes in regular dosing have been recommended, a modified epidural infusion regimen (local anesthetic concentration, adjuvants and/or pump settings) may be considered in order to minimize in-person contact with patients with COVID-19[36]. While neuraxial procedures are not considered to be aerosol-generating medical procedures (AGMP), healthcare providers should use droplet precautions and the patient should wear a surgical mask[36].

Nitrous oxide for labor and delivery. Nitrous oxide is a non-flammable gas commonly used for analgesia and general anesthesia. However, evidence on whether it constitutes an AGMP is currently lacking[38]. The British Columbia Center for Disease Control (BCCDC) and the Royal College of Obstetricians and Gynaecologists (RCOG) have recommended using a microbiological filter to prevent contamination of the gas inhalation system[10,39]. Given concerns regarding aerosolization, the Society for Maternal-Fetal Medicine (SMFM) and the Society for Obstetric Anesthesia and Perinatology (SOAP) in the USA have advocated to suspend the use of nitrous oxide[12,40], while others, such as the Society of Obstetricians and Gynaecologists of Canada (SOGC), have not recommended against its use[18]. Based on current evidence, nitrous oxide may be administered on a case-by-case basis while using appropriate personal protective equipment.

Patient-controlled analgesia. Remifentanil intravenous patient-controlled analgesia is an analgesic alternative to labor epidurals. Nevertheless, there are important considerations in patients with respiratory symptoms, such as the increased risk of respiratory depression, as well as vomiting, which could potentially generate aerosols[41]. Remifentanil should be used on a case-by-case basis and in the absence of respiratory compromise.

Postpartum analgesia

Initial concerns about the use of NSAIDs for postpartum analgesia in patients with SARS-CoV-2 infection have been allayed by WHO's rapid systematic review, as detailed above[26]. NSAIDs can be used for analgesia in postpartum women with COVID-19. Acetaminophen is another safe medication for postpartum analgesia. Opioids should be used with caution because of the risks of respiratory depression.

Pharmacologic strategies for the management of postdural puncture headache should be implemented prior to considering an epidural blood patch. Concerns have been raised regarding injection of blood in the epidural space in the setting of ongoing viremia[42]. However, providers can proceed with epidural blood patch in cases of debilitating and severe headache. Nasal sphenopalatine ganglion block should be discouraged as it is a potential AGMP[33].

Anesthesia for Cesarean delivery

Neuraxial techniques. In order to avoid tracheal intubation and extubation (AGMP) during general anesthesia, neuraxial anesthesia remains the first choice for Cesarean delivery. Both spinal and epidural anesthesia are adequate options depending on the clinical context (elective, emergency or intrapartum Cesarean section). Only essential drugs and equipment should be available in the operating room in order to prevent contamination and wastage. The dosing regimen should be given according to standard of care, while minimising the risk of conversion to general anesthesia. Importantly, significant intraoperative hypotension was reported in pregnant women with COVID-19[43]. As such, an adequate prophylactic strategy, such as a phenylephrine infusion, is strongly recommended[44].

General anesthesia. Recommendations and guidelines for managing the airway during general anesthesia in patients with COVID-19 should be followed rigorously to minimize aerosols, which can increase the potential for human-to-human viral transmission[45]. Proper pre-oxygenation and stable hemodynamics should be ensured to maintain optimal placental perfusion. Moreover, rapid neuromuscular block (rocuronium 1.2 mg/kg or succinylcholine 1 mg/kg) and strategies to maximize first-pass success, such as video laryngoscopy, should be performed to prevent coughing and limit aerosolization[45,46].

IMPACT OF PREGNANCY ON PHARMACOLOGIC MANAGEMENT OF PATIENTS WITH COVID-19

Mechanical ventilation

The mainstay of COVID-19 therapy remains optimal supportive care. Optimal mechanical ventilation of the pregnant patient with respiratory failure may require analgesic, sedative and neuromuscular blocking medications. The current critical care approach to sedation is to minimize the use of sedative drugs, because of benefit to the mother and fetus. The optimal analgesic and sedative intensive care unit (ICU) regimen during pregnancy is unknown. Some drugs are described under the section 'intrapartum analgesia and anesthesia' above, but safety considerations differ when comparing short-term to long-term use in the ICU. A recent US Food and Drug Administration (FDA) drug safety announcement[47] suggested that long-term maternal sedation may pose potential risk to fetal neurodevelopment, although this report did not specifically mention ICU sedation. The ACOG has challenged this statement, identifying the lack of clinical evidence[48].

Sedation

Opioids and benzodiazepines are commonly used drugs in the ICU, and there are risks of infant sedation

and neonatal abstinence syndrome. However, most will not require NICU admission or medication if born at term. Case reports describe the use of propofol during mechanical ventilation with no significant harm other than hypotension with an associated decrease in uteroplacental perfusion. A report on propofol infusion in two pregnant women undergoing prolonged neurosurgical procedures describes development of acidosis, but atypical of propofol infusion syndrome[49]. Dexmedetomidine, a sedative alpha-2 receptor agonist, has been used during Cesarean delivery and as an infusion in the ICU in a ventilated pregnant woman[50]. This drug crosses the placenta and can induce uterine contractions[51].

Neuromuscular block

Non-depolarizing neuromuscular blocking agents cross the placenta in variable amounts; the fetal–maternal drug concentration ratio of atracurium, vecuronium, rocuronium and pancuronium varies between 0.07 and 0.26[51]. Little is known about the fetal effects of neuromuscular block infusion during pregnancy. While an older report described fetal paralysis and neonatal arthrogryposis following 10-day administration of d-tubo-curarine (as well as several sedatives)[52], a more recent report described good outcomes after a 10-h infusion of pancuronium during the third trimester[51]. Prolonged infusion of neuromuscular-blocking agents should be avoided or used with caution. Neuromuscular blockade should be used for the shortest duration possible and reversal agents should be available to hand if delivery is imminent.

Corticosteroids

According to the preliminary results of the Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial, in which 2104 patients hospitalized with COVID-19 were assigned to receive dexamethasone (6 mg once a day, oral or intravenous) for up to 10 days and 4321 to receive usual care, 482 (22.9%) patients in the dexamethasone group and 1110 (25.7%) in the usual-care group died within 28 days after randomization (age-adjusted rate ratio, 0.83 (95% CI, 0.75–0.93); $P < 0.001$)[53]. It should be mentioned that the lower 28-day mortality was only noted among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. Although six pregnant participants were included in the study, pregnancy-specific conclusions could not be drawn due to the small size of the pregnant subgroup. Based on the findings of this study, the National Institutes of Health have recommended in their COVID-19 treatment guidelines the use of dexamethasone in pregnant women with COVID-19 who are mechanically ventilated or who require supplemental oxygen, given the potential benefit of decreased maternal mortality and the low risk of fetal adverse effects associated with this short course of therapy[54]. While it is unclear whether clinical benefits were the result of a corticosteroid class effect, clinicians could consider a non-fluorinated corticosteroid (e.g. prednisolone and hydrocortisone) at equivalent doses in order to minimize fetal exposure to dexamethasone.

Experimental drugs for COVID-19 in the setting of clinical trials

A number of antivirals and host-directed therapies have been repurposed and are being studied for COVID-19[55]. Although primarily intended for the treatment of other conditions, these drugs have the potential to prevent viral replication, minimize serious morbidity and offer symptomatic relief to patients with COVID-19[56]. These and several other agents are currently under study, with over 3000 clinical trials registered on the International Clinical Trials Registry Platform for COVID-19. The magnitude of clinical research for patients with COVID-19 is both commendable but also concerning, due to the risk of unnecessary duplication and the risk of several studies being underpowered. Further, as only a minority of studies include pregnant women, there is also a risk that the data are not generalizable to the pregnant and postpartum population[57,58].

A summary of available information on the safety of the most widely studied experimental drugs in pregnant and lactating women is presented in Table S1. The risk during pregnancy has been described in terms of teratogenicity (congenital malformations) and other toxicity (fetal/neonatal loss, prematurity and concerns about growth and development). An attempt has been made to summarize the highest-quality data available, but in the absence of such data, information has been extrapolated from case reports and animal studies.

Drug transfer into breast milk and safety in lactation depends primarily upon the medication's molecular weight, protein binding, half-life, fat solubility, maternal plasma concentration and neonatal oral bioavailability[59]. The most useful and accurate measure of exposure is the relative infant dose (RID), which provides a weight-based approximation of the neonatal dose as a percentage of the maternal dose[59]. This is calculated as ((infant dose in mg/kg per day)/(maternal dose in mg/kg per day)), and expressed as a percentage of the mother's dose. It has been recommended that a RID of more than 10% should be the theoretical level of concern for most medications[60]; however, this level should be considered relative, and each situation should be evaluated individually, according to the overall toxicity of the medication[59].

The most common drugs for COVID-19 that are currently being investigated in pregnant women are hydroxychloroquine (HCQ), lopinavir/ritonavir, remdesivir and tocilizumab[55,56]. HCQ is an antimalarial drug and is used for the treatment of autoimmune disease. It interrupts the glycosylation of cellular receptors of SARS-CoV-2 and has demonstrated activity against SARS coronaviruses in laboratory studies[61,62]. A number of recently published randomized trials have, however, shown no benefit to the use of HCQ over routine care, for post-exposure prophylaxis[63] or in non-hospitalized[64,65]

and hospitalized[66] patients. Lopinavir/ritonavir is a combination of two protease inhibitors approved for the treatment of human immunodeficiency virus (HIV). It has demonstrated *in-vitro* activity against coronaviruses by inhibiting the enzyme 3-chymotrypsin-like protease. Although a recent trial was not able to show benefit in patients with COVID-19 over usual care[67], a combination of lopinavir/ritonavir, interferon beta-1b and ribavirin was found to be superior to lopinavir/ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild-to-moderate COVID-19[68]. Remdesivir is a novel broad antiviral nucleotide pro-drug which has been shown to inhibit replication of SARS coronaviruses *in vitro*. Results from published studies suggest that remdesivir use may shorten the time to clinical recovery in patients with COVID-19[69], although its overall clinical benefit remains unclear[70]. Tocilizumab is a humanized monoclonal antibody which inhibits the proinflammatory activity of interleukin-6 and may have a role in decreasing the cytokine release associated with organ damage in COVID-19. This drug is currently being investigated as part of a randomized trial[71]. High-dose inhaled nitric oxide (160–200 ppm) has demonstrated antimicrobial effects against bacteria and viruses (including SARS-CoV), and is used as an adjunct treatment for acute respiratory distress syndrome and pulmonary hypertension. A case series of pregnant patients with severe COVID-19 treated with high-dose nitric oxide demonstrated improvement in hypoxemia and tachypnea with no adverse neonatal effects[72].

A number of other therapies are also being investigated for the management of patients with COVID-19. While the mechanisms of action of antivirals and certain immunomodulators are apparent, those of some other medications are quite varied. Recombinant human interferon α1b and α2b stimulates immune responses during viral infections. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers might prevent viral entry, as ACE2 is a co-receptor for SARS-CoV-2 entry into human cells[73]. In addition to treating superimposed bacterial infection, the macrolide antibiotic azithromycin has immunomodulatory and anti-inflammatory effects.

Although many of these medications are considered safe for use during pregnancy and lactation, most clinical trials exclude women who are pregnant or lactating[57,58], due to concerns regarding the effect of these medications on mothers and fetuses. Since pregnant women do not lack the capacity to make an informed choice about participating in research[74], data outlined in Table S1 could serve to inform consent and facilitate enrollment in trials. As only corticosteroids have been shown to definitively improve mortality in patients with COVID-19, we encourage pregnant and lactating women to consider participating in clinical trials if they are eligible and if supporting safety data are available for the investigational agent to better inform further management options.

CONCLUSIONS

The vast majority of common antepartum, intrapartum and postpartum pharmacologic interventions can be used in women with COVID-19. So far, the well-established benefits of most medications are not outweighed by theoretical concerns associated with their use in the setting of COVID-19. Decisions to administer interventions deemed at higher risk should be made on a case-by-case basis, while taking the patient's unique context and preferences into account. The safety data summarized herein can be used to obtain informed consent in trials investigating therapies for COVID-19. In turn, this could facilitate increased representation of pregnant and postpartum women in clinical trials for COVID-19.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Available evidence on use of experimental medications in pregnancy and breastfeeding